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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE

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GRANT APPLICATION

FOLLOW INSTRUCTIONS CAREFULLY

1. TITLE OF APPLICATION (Do not exceed 56 typewriter spaces)
Clinical Evaluation of Pion Radiotherapy

2. RESPONSE TO SPECIFIC PROGRAM ANNOUNCEMENT NO YES (If "YES," state RFA number and/or announcement title)

3. PRINCIPAL INVESTIGATOR (PROGRAM DIRECTOR)

3a. NAME (Last, first, middle) Moseley, Robert D., Jr., M.D. 3b. SOCIAL SECURITY NUMBER [REDACTED]

3c. MAILING ADDRESS (Street, city, state, zip code) 3d. POSITION TITLE

University of New Mexico
School of Medicine
Albuquerque, NM 87131

Professor & Chairman

3e. DEPARTMENT, SERVICE, LABORATORY OR EQUIVALENT

Department of Radiology

3f. TELEPHONE (Area code, number and extension) 3g. MAJOR SUBDIVISION

(505) 667-7115

School of Medicine

4. HUMAN SUBJECTS, DERIVED MATERIALS OR DATA INVOLVED? NO YES (If "YES," form NMS 506 required) 5. RECOMBINANT DNA RESEARCH SUBJECT TO NIH GUIDELINES NO YES

6. DATES OF ENTIRE PROPOSED PROJECT PERIOD (This application) 7. TOTAL DIRECT COSTS REQUESTED FOR PROJECT PERIOD (from page 5) 8. DIRECT COSTS REQUESTED FOR FIRST 12-MONTH BUDGET PERIOD (from page 4)

From: 1 December 1982 Through: 30 November 85

\$ 7,189,311

\$ 2,152,655

9. PERFORMANCE SITES (Organizations and addresses) 10. INVENTIONS (Competing continuation application only)

University of New Mexico
Department of Radiology
School of Medicine
Albuquerque, NM 87131

Have any inventions conceived or reduced to practice during the course of the project?
 NO YES - Previously reported
 YES - Not previously reported

Los Alamos National Laboratory
Los Alamos, NM 87545

11. APPLICANT ORGANIZATION (Name, address and congressional district)

University of New Mexico
Department of Radiology
School of Medicine
Albuquerque, NM 87131
Congressional District #1

12. ORGANISATIONAL COMPONENT TO RECEIVE CREDIT FOR INSTITUTIONAL GRANT (See instructions) 13. ENTITY IDENTIFICATION NUMBER

Code 01 Description School of Medicine

14. TYPE OF ORGANIZATION (See instructions)

Private Nonprofit
 Public (Specify Federal, State, Local): State

15. OFFICIAL IN BUSINESS OFFICE TO BE NOTIFIED IF AN AWARD IS MADE (Name, title, address and telephone number.) 16. OFFICIAL SIGNING FOR APPLICANT ORGANIZATION (Name, title, address and telephone number.)

Warren D. Baur
Comptroller, UNM Medical Center
University of New Mexico
Albuquerque, New Mexico 87131
(505) 277-4451

warren D. Baur
Comptroller, UNM Medical Center
University of New Mexico
Albuquerque, New Mexico 87131
(505) 277-4451

17. PRINCIPAL INVESTIGATOR PROGRAM DIRECTOR ASSURANCE: I agree to accept responsibility for the scientific conduct of the project and to provide the required progress reports if a grant is awarded as a result of this application. SIGNATURE OF PERSON NAMED IN 3a (In ink) DATE

18. CERTIFICATION AND ACCEPTANCE: I certify that the statements herein are true and complete to the best of my knowledge, and accept the obligation to comply with Public Health Service terms and conditions if a grant is awarded as the result of this application. I willfully issue certification if a criminal offense, U.S. Code, Title 18, Section 1001. SIGNATURE OF PERSON NAMED IN 16 (In ink) DATE

[Signature]
[Signature] Warren Baur 2-16-82

PMS-398 Rev. 5/80

FILE BARCODE



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DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE GRANT APPLICATION FOLLOW INSTRUCTIONS CAREFULLY	LEAVE BLANK		
	TYPE	ACTIVITY	NUMBER
	REVIEW GROUP	FORMERLY	
	COUNCIL BOARD (Month, year)	DATE RECEIVED	

1. TITLE OF APPLICATION (Do not exceed 56 typewriter spaces):
Clinical Evaluation of Pion Radiotherapy

2. RESPONSE TO SPECIFIC PROGRAM ANNOUNCEMENT NO YES (If "YES," state RFA number and/or announcement title)

3. PRINCIPAL INVESTIGATOR PROGRAM DIRECTOR

2a. NAME (Last, first, middle): **Moseley, Robert D., Jr., M.D.**

2b. SOCIAL SECURITY NUMBER: XXXXXXXXXX

2c. MAILING ADDRESS (Street, city, state, ZIP code):
**University of New Mexico
 School of Medicine
 Albuquerque, NM 87131**

3a. POSITION TITLE:
Professor & Chairman

3b. DEPARTMENT SERVICE, LABORATORY OR EQUIVALENT:
Department of Radiology

2d. TELEPHONE (Area code, number and extension):
(505) 667-7115

3c. MAJOR SUBDIVISION:
School of Medicine

4. HUMAN SUBJECTS, DERIVED MATERIALS OR DATA INVOLVED: NO YES (If "YES," form PHS 576 required)

5. RECOMBINANT DNA RESEARCH SUBJECT TO NIH GUIDELINES: NO YES

5. DATES OF ENTIRE PROPOSED PROJECT PERIOD (This application):
From: 1 December 1982 Through: 30 November 85

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8. DIRECT COSTS REQUESTED FOR FIRST 12-MONTH BUDGET PERIOD (from page 4): **\$ 2,152,655**

9. PERFORMANCE SITES (Organizations and addresses):
**University of New Mexico
 Department of Radiology
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 Have any inventions conceived or reduced to practice during the course of the project?
 NO YES - Previously reported
 YES - Not previously reported

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**University of New Mexico
 Department of Radiology
 School of Medicine
 Albuquerque, NM 87131
 Congressional District #1**

12. ORGANIZATIONAL COMPONENT TO RECEIVE CREDIT FOR INSTITUTIONAL GRANT (See instructions):
Code: 01 Description: School of Medicine

13. ENTITY IDENTIFICATION NUMBER:
1856000642A1

14. TYPE OF ORGANIZATION (See instructions):
 Private Nonprofit
 Public (Specify Federal, State, Local): **State**

15. OFFICIAL IN BUSINESS OFFICE TO BE NOTIFIED IF AN AWARD IS MADE (Name, title, address and telephone number):
**Warren D. Baur
 Comptroller, UNM Medical Center
 University of New Mexico
 Albuquerque, New Mexico 87131
 (505) 277-4451**

16. OFFICIAL SIGNING FOR APPLICANT ORGANIZATION (Name, title, address and telephone number):
**Warren D. Baur
 Comptroller, UNM Medical Center
 University of New Mexico
 Albuquerque, New Mexico 87131
 (505) 277-4451**

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SIGNATURE OF PERSON NAMED IN 3a (In ink): *[Signature]* DATE: *[Blank]*

18. CERTIFICATION AND ACCEPTANCE: I certify that the statements herein are true and complete to the best of my knowledge, and accept the obligation to comply with Public Health Service terms and conditions if a grant is awarded as the result of this application. A willfully false certification is a criminal offense (U.S. Code, Title 18, Section 1001).

SIGNATURE OF PERSON NAMED IN 16 (In ink): *Warren Baur* DATE: **2-16-82**

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ABSTRACT OF RESEARCH PLAN

NAME AND ADDRESS OF APPLICANT ORGANIZATION (Same as from I, page 1)

University of New Mexico School of Medicine
Albuquerque, New Mexico 87131

TITLE OF APPLICATION (Same as from I, page 1)

Clinical Evaluation of Pion Radiotherapy

Name, Title and Department of all professional personnel engaged on project, beginning with Principal Investigator/Program Director

Moseley, Robert D., Jr., M.D.	Chairman, Radiology	UNM Radiology
TBA	Radiation Oncologist	UNM Radiology
Gilman, Christopher, M.D.	Radiation Oncologist	UNM Radiology
Mettler, Fred, M.D.	Chief, Diagnostic Imaging	UNM Radiology
Seigel, Robert, M.D.	Neuroradiologist	UNM Radiology
Black, William C., M.D.	Chief, Oncologic Pathology	UNM Pathology
Kornfeld, Mario, M.D.	Neuropathologist	UNM Pathology
Anderson, Robert E., M.D.	Chairman, Pathology	UNM Pathology
Smith, A.R., Ph.D.	Chief, Clinical Physics, Los Alamos	UNM Radiology
Hilko, Robert, Ph.D.	Physicist	UNM Radiology
Bradbury, James N., Ph.D.	Group Leader, MP-3	LANL
Berardo, Peter, Ph.D.	Physicist	LANL
Paciotti, Michael, Ph.D.	Physicist	LANL
Wing, James	Engineer	LANL
Zink, Sandra, Ph.D.	Physicist	UNM Radiology

- see next page-

ABSTRACT OF RESEARCH PLAN: Concisely describe the application's specific aims, methodology and long-term objectives, making reference to the scientific disciplines involved and the health-relatedness of the project. The abstract should be self-contained so that it can serve as a succinct and accurate description of the application when separated from it. **DO NOT EXCEED THE SPACE PROVIDED.**

The primary objective of this program project is to conduct the necessary physical, biological, and clinical studies to evaluate the efficacy, potential benefit, and role of negative pi mesons (pions) in management of some types and stages of solid tumors not well managed by current methods or combinations thereof. The program is a joint effort of the University of New Mexico (UNM) and the Los Alamos National Laboratory (LANL) and utilizes negative pions produced by the 800-MeV proton linear accelerator at the Clinton P. Anderson Meson Physics Facility (LAMPF) in Los Alamos. Physicians throughout the nation are sending appropriate patients to this facility for pion radiotherapy. Phase I-II studies are in progress for patients with astrocytoma, Grade III or IV, unresectable carcinoma of the pancreas, and squamous carcinoma of the uterine cervix, Stage III and IV, and are planned for expansion to inoperable carcinoma of the esophagus and inoperable epidermoid carcinoma of the lung. Developmental and clinical physics activity is focused on dosimetry, calculational, and plotting techniques to achieve accurate dose distribution in a treatment volume of arbitrary size and location, with minimum damage to surrounding normal tissues, and development and implementation of technology for pion radiotherapy delivery. Biological studies are being conducted to measure the biological uniformity of pion beams routinely used in patient treatment and to measure acute and late effects of pions on normal and tumor tissues in experimental animals, and are proposed to assess mutagenicity and oncogenicity of pions and to determine whether there is a correlation between tumor differentiation and response to pion radiotherapy.

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LABORATORY ANIMALS INVOLVED. Identify by common names. If none, state "none"

Moseley, Robert D., Jr., M.D.
[REDACTED]

Name, Title, Department of Professional Personnel (continued):

van der Kogel, A.J., Ph.D.	Visiting Research Scholar	UNM Radiology
Raju, Mudundi, D. Sc.	Fellow	LANL
Tokita, N., M.D., Ph.D.	Staff Member	LANL
Davidson, Kincaid, M.S.	Program Manager	UNM Radiology

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DETAILED BUDGET FOR FIRST 12 MONTH BUDGET PERIOD
DIRECT COSTS ONLY

FROM 12/1/82 THROUGH 11/30/83

DOLLAR AMOUNT REQUESTED (omit cents)

PERSONNEL (Applicant organization only) (See instructions)		TIME EFFORT		SALARY	FRINGE BENEFITS	TOTALS
NAME	TITLE OF POSITION	%	Hours per year			
Moseley, Robert D., Jr., MD	Principal Investigator	15	6			
TBA	CoPrincipal Invest.	75	40			
Gilman, C., MD	Radiation Oncologist	100	40			
Mettler, F., MD	Diagnostic Radiolog.	5	2			
Seigel, R., MD	Neuroradiologist	2	3			
TBA	Chief Rad. Ther. Tech.	100	40			
TBA	CT Scan Technologist	100	40			
TBA	X-Ray Technologist	75	30			
TBA	Cast & Mold Tech.	75	30			
TBA	Chief Nurse	100	40			
TBA	Nurse	100	40			
TBA	Nurse	50	20			
TBA	Rad. Ther. Tech.	100	40			
FROM SUPPLEMENTAL PAGE						
SUBTOTALS				308,025	46,204	354,229

CONSULTANT COSTS (See instructions)

EQUIPMENT (Itemize)

SUPPLIES (Itemize by category)

SEE SUPPLEMENTAL PAGE

54,479

TRAVEL

DOMESTIC See supplemental page
FOREIGN

12,560

PATIENT CARE COSTS

INPATIENT
OUTPATIENT Grant reimbursement

(100,000)

ALTERATIONS AND RENOVATIONS (Itemize by category)

CONTRACTUAL OR THIRD PARTY COSTS (See instructions)

OTHER EXPENSES (Itemize by category)

Photographic services \$ 1,000
Communications 3,000
CT scan maintenance 62,190
Publication costs 1,100

67,290

TOTAL DIRECT COSTS (Also enter on page 1, item B)

\$ 388,558

Clinical Investigations: Radiation Oncology

PRINCIPAL INVESTIGATOR / PRINCIPAL DIRECTOR Robert O. Moseley, Jr., M.D.

DETAILED BUDGET FOR FIRST 12 MONTH BUDGET PERIOD
DIRECT COSTS ONLY

FROM 12/1/82 THROUGH 11/30/83

DOLLAR AMOUNT REQUESTED (in cents)

PERSONNEL (Applicant organization only) (See instructions)		TIME EFFORT		SALARY	FRINGE BENEFITS	TOTALS
NAME	TITLE OF POSITION	%	Months per Year			
Moseley, R. D., Jr., MD	Principal Investigator					
TBA	Co Principal Investigator					
Guevara, A.	Department Secretary	100	40			
Temporary Part Time	Patient Care Aide	65	26			
Temporary Part Time	Patient Care Aide	65	26			
Temporary Part Time	Patient Care Aide	65	26			
Temporary Part Time	Patient Care Aide	65	26			
(TO FIRST PAGE)				34,879	5,233	40,112

SUPPLIES

Supplies to maintain patients at LAMC apartments	2,000
Clinical supplies for 70 new patients @ \$205/pt	14,350
Immobilization, simulation and radiation treatment supplies for 70 new patients @ \$250/pt	17,500
Photographic supplies	3,848
CT scan supplies	15,781
Graphic supplies	1,000
Total Supplies	54,479

TRAVEL

Domestic - Los Alamos / Albuquerque M.D.'s	52 x \$128	6,656
Nurses & Techs	12 x 97	1,164
M.D. travel to collect follow-up data	4 x 300	3,200
2 Scientific meetings @ \$770		1,540
Total Travel		12,560

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BUDGET ESTIMATES FOR ALL YEARS OF SUPPORT REQUESTED
DIRECT COSTS ONLY

BUDGET CATEGORY TOTALS	1st BUDGET PERIOD (from page 4)	ADDITIONAL YEARS SUPPORT REQUESTED			
		2nd	3rd	4th	5th
PERSONNEL (Salary and fringe benefits.) (Applicant organization only)	354,229	389,652	428,617		
CONSULTANT COSTS					
EQUIPMENT					
SUPPLIES	54,479	59,927	65,920		
TRAVEL	DOMESTIC	12,560	13,816	15,198	
	FOREIGN				
PATIENT CARE COSTS	INPATIENT				
	OUTPATIENT	(100,000)	(110,000)	(121,000)	
ALTERATIONS AND RENOVATIONS					
CONTRACTUAL OR THIRD PARTY COSTS					
OTHER EXPENSES	67,290	74,019	81,421		
TOTAL DIRECT COSTS	388,558	427,414	470,156		
TOTAL FOR ENTIRE PROPOSED PROJECT PERIOD (Also enter on page 1, item 7)				→ \$ 1,286,128	

JUSTIFICATION (Use continuation pages if necessary): Briefly describe the specific functions of the personnel and consultants. For all years, justify any costs for which the need may not be obvious, such as equipment, foreign travel, alterations and renovations, and contractual or third party costs. For future years, justify any significant increases in any category. In addition, for COMPETING CONTINUATION applications, justify any significant increases over current level of support. If a recurring annual increase in personnel costs is anticipated, give percentage.

C

BUDGET JUSTIFICATION
CLINICAL INVESTIGATIONS: RADIATION ONCOLOGY

A. Salaries and Wages

Salary for TBA co-principal investigator, radiation oncologist is requested at 75 percent, because LANL participates in payment of his/her salary (approximately 25 percent) via a purchase agreement with UNM. A radiation oncologist, Dr. Gilman, will be based permanently at Los Alamos, and will travel to Albuquerque to work with follow-up pion protocol patients at the CRTC during periods between cycles. All CRTC radiation oncologists spend varying amounts of time in Los Alamos in at least one-day periods to participate in planning and conduct of the pion studies. The FTE complement of radiotherapy staff is high in relation to routine work for two reasons: (1) the optimal pion treatment day is 16 hours long, as opposed to 8 hours for conventional radiation; and (2) pion patient care requires far more time by the radiotherapists than does routine patient care in terms of daily observation of tumor and normal tissue responses and greatly increased complexity of treatment planning. It is anticipated that the LAMPF accelerator schedule will permit patient treatment over 24-30 weeks/year in Years 01-03, with early accession and carryover of patients receiving planned supplementary conventional irradiation up to 4-5 weeks preceding and following each treatment cycle. The accelerator and channel reliability factor during operation is approximately 85 percent for treatment day. While the accelerator is in its production cycle, the biomedical pion channel is used 24 hours per day, usually 14-16 hours for patient treatment and 8-10 hours for physics and biology experiments. The patient treatment hours can be extended as necessary in case of accelerator down time. Accelerator operations schedule is tailored to accommodate patients optimally, consistent with maintenance requirements. It should be noted that maximum cost effective operation is 36 weeks per year.

No funds are requested to support activity by the Diagnostic Imaging Section because the imaging studies performed are routine and customary, and reimbursement for services will be sought from third-party payers. Costs of CT scans and routine imaging studies are covered under Patient Costs, with factors applied to estimate cost recovery. Professional fees are budgeted under Patient Costs, Consultants, for those costs which cannot be recovered from third parties.

Salary is requested for two radiological technologists to perform simulation and treatment set-up, to perform orthodiagraphic and conventional port films, and to assist in fabrication of immobilization, collimation, bolus and other devices for pion patients. A 75 percent cast and mold room technologist has primary responsibility for fabricating custom casts, boluses, and collimators for wide-field and cone-down treatments. A radiological technologist is requested to operate the CT scanner for pion patients receiving pretreatment and follow-up diagnostic scans, as well as patients who are receiving scans during treatment to assess the need for modifications to their treatment plan. Salary levels for these positions are based on current experience with UNM staff and knowledge of the job market elsewhere.

A Chief Nurse is to be employed full-time to perform inventory control, development of nursing procedures, nursing care of follow-up patients, and nursing-related research including, for example, literature review and

development of appropriate nutritional management techniques for pion patients. One other nurse is to be employed full-time, while other nursing staff will be employed on a part-time basis, so that they work when patients are being treated and do not work when patients are not being treated (except for planning, restocking apartments, etc.). In addition to performing clinical nursing functions at the Biomedical Facility, these individuals perform home nursing care for patients at the outpatient apartment units next to the Los Alamos Medical Center and take on-call duty while patients are in Los Alamos.

Salary for 2.6 FTE patient set-up aides is requested to support operation of the prior immobilization and positioning (PIP) system, whereby one patient is set up as the previous patient is wheeled out after treatment. This procedure is documented in the text of this application and optimizes pion beam time for actual patient treatment (by a factor of 1.5 to 2.0); it is essential to the success of this project. The 2.6 FTE's will be split among four persons, each at 65 percent time, so that there will always be one radiological technician and two patient set-up aides to work the PIP system over the 14-16-hour treatment day. The 65 percent time-factor is used because these individuals work only when the patients are being treated, and do not work during down-times.

Salary is requested for a department secretary/receptionist to perform typing and filing of patient-related notes, correspondence, progress reports, and other clinical material, as well as scientific documentation of clinical results and to assist patients in the waiting area, call for transportation, assist with nutrition for patients, and handle phone calls for UNM and LANL staff based at the Pion Biomedical Facility.

Salary increases for UNM staff in Years 02 and 03 are based on 10 percent per year, in accordance with guidelines issued by the UNM Medical Center Comptroller's Office. Fringe benefits are based on 15 percent of salaries and wages.

B. Supplies

The estimated cost of clinical supplies (e.g., dressings, instrument trays, etc.) for pion patients under treatment at Los Alamos is based on current experience. Supplies to maintain patients at LANL apartments include such items as detergent, disposable dishes, cleaning agents, and similar items. The photographic supply costs are based on current experience with clinical photography and graphics requirements for documenting research results. Patient treatment fields are photographed periodically during treatment and at follow-up visits. Immobilization, simulation and radiation treatment supplies for 70 new patients are budgeted based on actual costs.

Cost of supplies for the CT scanner is estimated based on prior experience.

Increases in supply costs for Years 02 and 03 are estimated at 10 percent per year for inflation.

C. Travel

Funds are requested to support travel by radiotherapy, technician, and nursing staff to and from Los Alamos and Albuquerque. All travel costs are escalated 10 percent per year for inflation.

Costs for professional staff travel is greater than for nurses and technicians since their visits tend to be longer and, therefore, involve more per diem payments.

Travel costs are also requested to send CRTC radiotherapists to other cities (estimated four trips per year) to perform follow-up examinations of pion and control patients in regional catchment areas (e.g., Los Angeles, New York, Denver, etc.), in an effort to save patient costs for transporting all patients back to Albuquerque and Los Alamos for regular follow-up. Support is also requested for two scientific meetings per year.

D. Patient Costs (Grant Reimbursement)

Patients accessed to the pion protocols will be billed for costs of physicians' services, clinic fees, treatment fees, and CT fees on the same basis as they would be billed if they were to receive conventional therapy. The amounts collected from third parties are reimbursed to the grant to offset the costs of salaries and wages, supplies, and maintenance expenses associated with these aspects of pion patients' medical care. Amounts not collected are written off to research support. Past experience has shown approximately a 70 percent collection factor for billings to pion protocol patients. The amount anticipated to be collected against billings for Radiation Oncology services is shown in the Radiation Oncology budget as an offset against the total request. The billing component of the pion program is anticipated to start prior to May 1, 1982.

E. Other Expense

Funds are needed for processing color slides of patient treatment fields, and for communications and reproduction costs. Funds are also needed to provide our CT scanner maintenance through a contract with Omnimedical and to support of publication costs. These estimates are escalated by 10 percent per year for inflation.

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Clinical Investigations: Pathology

PRINCIPAL INVESTIGATOR PROGRAM DIRECTOR Robert D. Moseley, Jr., M.D.

BUDGET ESTIMATES FOR ALL YEARS OF SUPPORT REQUESTED
DIRECT COSTS ONLY

BUDGET CATEGORY TOTALS	1st BUDGET PERIOD (from page 4)	ADDITIONAL YEARS SUPPORT REQUESTED			
		2nd	3rd	4th	5th
PERSONNEL (Salary and fringe benefits.) (Applicant organization only)	16,045	17,650	19,415		
CONSULTANT COSTS					
EQUIPMENT					
SUPPLIES					
TRAVEL					
DOMESTIC					
FOREIGN					
PATIENT CARE COSTS					
INPATIENT					
OUTPATIENT					
ALTERATIONS AND RENOVATIONS					
CONTRACTUAL OR THIRD PARTY COSTS					
OTHER EXPENSES					
TOTAL DIRECT COSTS	16,045	17,650	19,415		
TOTAL FOR ENTIRE PROPOSED PROJECT PERIOD (also enter on page 1, item 7)					\$ 53,110

JUSTIFICATION (Use continuation pages if necessary): Briefly describe the specific functions of the personnel and consultants. For all years, justify any costs for which the need may not be obvious, such as equipment, foreign travel, alterations and renovations, and contractual or third party costs. For future years, justify any significant increases in any category in addition to COMPETING CONTINUATION applications. Justify any significant increases over current level of support. If a recurring annual increase in personnel costs is anticipated, give percentage.

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BUDGET JUSTIFICATION
CLINICAL INVESTIGATIONS: PATHOLOGY

Support for the Pathology Section includes reviewing histology specimens, performing autopsies, and preparing reports. Time required by Drs. Black, Kornfeld, and Anderson for this activity is budgeted at 15 percent of an FTE. A morphologic technician at 50% of an FTE is required to prepare the various morphologic materials for evaluation. Fringe benefits are calculated at 15 percent of salaries and wages. Costs are escalated by 10 percent per year for Years 02 and 03, based on guidelines from the UNM Medical Center Comptroller's Office.

BUDGET ESTIMATES FOR ALL YEARS OF SUPPORT REQUESTED
DIRECT COSTS ONLY

BUDGET CATEGORY TOTALS	1st BUDGET PERIOD (from page 4)	ADDITIONAL YEARS SUPPORT REQUESTED			
		2nd	3rd	4th	5th
PERSONNEL (Salary and fringe benefits.) (Applicant organization only)					
CONSULTANT COSTS	18,129	19,942	21,936		
EQUIPMENT					
SUPPLIES					
TRAVEL	DOMESTIC	123,729	136,102	149,712	
	FOREIGN				
PATIENT CARE COSTS	INPATIENT	18,814	20,695	22,765	
	OUTPATIENT	19,828	21,811	23,992	
ALTERATIONS AND RENOVATIONS					
CONTRACTUAL OR THIRD PARTY COSTS					
OTHER EXPENSES	111,472	122,619	134,881		
TOTAL DIRECT COSTS	291,972	321,169	353,286		
TOTAL FOR ENTIRE PROPOSED PROJECT PERIOD (Also enter on page 1, item 7)				→ \$ 966,427	

JUSTIFICATION (Use continuation pages if necessary): Briefly describe the specific functions of the personnel and consultants. For all years, justify any costs for which the need may not be obvious, such as equipment, foreign travel, alterations and renovations, and contractual or third party costs. For future years, justify any significant increases in any category. In addition, for COMPETING CONTINUATION applications justify any significant increases over current level of support. If a recurring annual increase in personnel costs is anticipated, give percentage.

BUDGET JUSTIFICATION
CLINICAL INVESTIGATIONS: PATIENT COSTS

1. Data Used for Projected Patient Costs

A. Patient Categories

1. New Pion Patients: Those patients evaluated, treated and followed during grant year in which accepted in program.

2. Follow-up Pion Patients: Those patients in second year or later after pion treatment.

3. Evaluated and Rejected Patients: Those patients whose tumors were found upon evaluation to be unsuitable for study.

B. Patients Per Locale

Total Patients: 44 percent from New Mexico, 56 percent from out-of-state.

C. Escorts

Some patients require medically authorized escorts for whom expenses will be paid.

D. Food

Costs are based upon actual patient expenditures within the University of New Mexico's meal reimbursement limitation of \$18.50 per day.

E. Inflation Factor

Costs for Years 02 and 03 are based on estimated costs for Year 01 and increased by an inflation factor of 10 percent each year.

F. Patient Travel

A contract (\$7,200) has been negotiated with Yellow Cab Company for van service between Albuquerque and Los Alamos.

2. Projected Number of Patients

Based on the number of new pion patients, follow-up pion patients, and evaluated and rejected patients, the total number of patients for each grant year can be projected. The following chart shows the total number of patients per grant year.

TOTAL PATIENTS/GRANT YEAR

<u>Grant Year</u>	<u>New Pion</u>	<u>Follow-up Pion</u>	<u>Evaluated & Rejected</u>	<u>TOTAL</u>
01	70	96	3	169
02	70	103	3	176
03	70	109	3	182
TOTALS	210	308	9	527

PATIENT COSTS DETAIL: YEAR 01

I. Consulting Physician Fees

A.	New Patients - Pion (70)	=	\$16,855
B.	Follow-up Patients - Pion (96)	=	1,220
C.	Evaluated and Rejected Patients (3)	=	<u>54</u>
	TOTAL CONSULTING PHYSICIAN FEES		\$18,129

The consulting physician fee budget is used to pay physicians for services rendered to our patients.

PATIENT COSTS DETAIL: YEAR 01

IIA. TRAVEL - MILEAGE, AIRFARE, AND CABFARE

A. New Patients - Pion (70)	=	\$ 54,124
B. Follow-up Patients - Pion (96)	=	60,862
C. Evaluated and Rejected Patients (3)	=	<u>1,543</u>
TOTAL		\$116,529

C. 118

PATIENT COSTS DETAIL: YEAR 01

IIB. TRAVEL - ALBUQUERQUE - LOS ALAMOS

A. New Patients - Pion (70)	=	\$2,970
B. Follow-up Patients - Pion (96)	=	4,140
C. Evaluated and Rejected Patients (3)		<u>90</u>
TOTAL		\$7,200

PATIENT COSTS DETAIL: YEAR 01

III. OUTPATIENT COSTS

A.	New Patients - Pion (70)	=	\$34,304
B.	Follow-up Patients - Pion (96)	=	5,123
C.	Evaluated and Rejected (3)	=	<u>229</u>
	Subtotal		39,656
D.	Grant Reimbursement		(19,828)
	TOTAL		\$19,828

C.

PATIENT COSTS DETAIL: YEAR 01

IV. INPATIENT COSTS

A.	New Patients - Pion (70)	=	\$18,041
B.	Follow-up Patients (96)	=	0
C.	Evaluated and Rejected Patients (3)	=	<u>773</u>
	TOTAL		\$18,814

PATIENT COSTS DETAIL: YEAR 01

V. SUBSISTENCE

A. New Patients - Pion (70)	=	\$ 79,089
B. Follow-up Patients (96)	=	32,383
C. Evaluated and Rejected (3)	=	<u>0</u>
TOTAL		\$111,472

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Physics - UNM

PRINCIPAL INVESTIGATOR PROGRAM DIRECTOR Robert D. Moseley, Jr., M.D.

DETAILED BUDGET FOR FIRST 12 MONTH BUDGET PERIOD
DIRECT COSTS ONLY

FROM 12/1/82 THROUGH 11/30/83
DOLLAR AMOUNT REQUESTED (Only costs)

PERSONNEL (Applicant organization only) (See instructions)		TIME EFFORT		SALARY	FRINGE BENEFITS	TOTALS
NAME	TITLE OF POSITION	%	Hours per Year			
Moseley, R.D., Jr., MD	Principal Investigator					
TBA	Co Principal Invest					
Smith, A., PhD	Chief Biomed Phys/LA	100	40			
Hilko, R., PhD	Sr. Res. Scientist	100	40			
Zink, S., PhD	Asst. Prof. Radiology	100	40			
TBA	Biomed Engineer	100	40			
TBA	Treat. Plan. Tech.	100	40			
TBA	Research Technician	100	40			
TBA	Treat. Plan. Physicist	100	40			
SUBTOTALS				206,331	30,950	237,281

CONSULTANT COSTS (See instructions)

EQUIPMENT (Itemize)

See supplemental page 51,200

SUPPLIES (Itemize by category)			
Dosimetry supplies	5,000		
Electronic supplies	2,500		
Mechanical supplies	2,500		
Microdosimetry supplies	1,000		
Tissue substitutes	2,500		
Graphic supplies	1,000		14,500

TRAVEL DOMESTIC See supplemental page 3,474
FOREIGN

PATIENT CARE COSTS INPATIENT
OUTPATIENT Grant reimbursement (34,125)

ALTERATIONS AND RENOVATIONS (Itemize by category)

CONTRACTUAL OR THIRD PARTY COSTS (See instructions)

OTHER EXPENSES (Itemize by category)			
Construction of special equipment - LANL shops	23,100		
Equipment maintenance	4,620		
Publication costs	1,100		28,820

TOTAL DIRECT COSTS (Also enter on page 1, item 8) : 301,150

1091370

BUDGET ESTIMATES FOR ALL YEARS OF SUPPORT REQUESTED
DIRECT COSTS ONLY

BUDGET CATEGORY TOTALS	1st BUDGET PERIOD (from page 4)	ADDITIONAL YEARS SUPPORT REQUESTED			
		2nd	3rd	4th	5th
PERSONNEL (Salary and fringe benefits.) (Applicant organization only)	237,281	261,009	287,110		
CONSULTANT COSTS		2,000			
EQUIPMENT	51,200	29,775	27,145		
SUPPLIES	14,500	15,950	17,545		
TRAVEL	DOMESTIC	3,474	3,821	4,204	
	FOREIGN				
PATIENT CARE COSTS	INPATIENT				
	OUTPATIENT	(34,125)	(37,538)	(41,292)	
ALTERATIONS AND RENOVATIONS					
CONTRACTUAL OR THIRD PARTY COSTS					
OTHER EXPENSES	28,820	31,702	34,872		
TOTAL DIRECT COSTS	301,150	306,719	329,584		

TOTAL FOR ENTIRE PROPOSED PROJECT PERIOD (Also enter on page 1, item 7) → \$ 937,453

JUSTIFICATION (Use continuation pages if necessary): Briefly describe the specific functions of the personnel and consultants. For all years, justify any costs for which the need may not be obvious, such as equipment, foreign travel, alterations and renovations, and contractual or third party costs. For future years, justify any significant increases in any category, in addition, for COMPETING CONTINUATION applications. Justify any significant increases over current level of support. If a recurring annual increase in personnel costs is anticipated, give percentage.

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UNM PHYSICS EQUIPMENT BUDGET

	Year		
	1	2	3
	(02)	(10)	(11)
Calibration			
1. Replacement ion chamber	1,000	1,100	1,200
2. Calibrated pico-amp source		2,275	
3. Standard capacitor		1,200	
Dosimetry			
1. MICA chambers (8)	6,000		
2. Replacement MICA chambers		2,000	2,200
3. New MICA electrometers (7)	3,500		
4. Replacement MICA electrometers		1,000	1,000
Tissue Substitute Lab			
1. Vacuum degasser	3,500		
Treatment Planning			
1. Color printer	15,00		
Laser			
1. Replacement for CT, simulation, set-up & treatment rooms (3/yr)	4,500	5,280	5,800
Treatment Verification			
1. <u>In vivo</u> ion chamber	7,00	770	850
2. Replacement aluminum activation crystal		1,500	
Microdosimetry			
1. Rossi LET chamber	3,300		
2. Replacement NIM modules	2,500	2,750	3,025
3. CAMAC modules		2,000	2,200
4. MCA interface	2,500		
Positron Visualization			
1. Electronics	2,000	2,200	2,400
2. Crystals	7,000	7,700	8,470
Total Physics Budget	51,200	29,775	27,145

BUDGET JUSTIFICATION
UNM PHYSICS

A. Salaries and Wages

The request for staffing is based on the minimal level of personnel required to support the program project. The research and development activities include no individual or basic research. All projects are directly related to the clinical program and are implemented to address specific needs.

The personnel budget for Years 02 and 03 reflects increases of 10 percent each year and, in addition, indicates changes, discussed below, due to termination of other funded projects from which some staff are partially paid. Fringe benefits are calculated at 15 percent of salaries and wages.

1. Alfred R. Smith, Ph.D., Chief Clinical Physicist, CRTC/Los Alamos

Dr. Smith is responsible for the overall clinical physics program and for liaison with and coordination of all LANL physics activities as they relate to the clinical program. He also is responsible for the physics aspects of radiation biology programs related to the program project. To the extent that Dr. Smith is supported from other sources (20% from another grant--AAPM Charged Particle Beam Dosimetry Task Group (terminates Summer 1983)--of which he is principal investigator and a pending grant--NCI-CM-17482-22, Evaluation of Treatment Planning for Particle Beam Radiotherapy) his budget in this application will be reduced accordingly.

2. Treatment Planning

Sandra Zink, Ph.D., is the leader of the treatment planning section.

3. Physics Technical Support

Primary responsibility is direct control of all systems during patient treatment, including verification of beam tune and all interlock systems, patient monitoring, daily calibrations, dose calculations and patient treatment records. Since patients are nominally treated 16 hrs/day, two people each cover one 8-hr shift.

4. Development and Quality Control

a. Robert Hilko, Ph.D. is primarily responsible for in vivo dosimetry systems, microdosimetry, neutron spectra measurements, positron emission visualization and developmental dosimetry. He has extensive training and experience in both nuclear and medical physics and is a valuable addition to the project.

b. Support is requested for a biomedical engineer to be responsible for quality control of the EMI 7070 scanner, calibration of UNM physics lab equipment and maintenance of all patient treatment devices and laser alignment systems. He will also assist with patient and developmental dosimetry.

B. Equipment

1. Calibration

This equipment is necessary to maintain the calibrations and standards for the overall pion dosimetry project. Ionization chambers receive extensive use, and our experience has been that we break or otherwise render useless about one ion chamber per year.

A calibrated pico-amp source and standard capacitor are requested in Year 02. These items are necessary to calibrate our electrometers. The standard capacitor we now have is borrowed from the LAMPF equipment pool. We have an older pico-amp current source, but it often gets used for a utility current source and cannot be relied upon for calibration standards.

2. Dosimetry

The multi-ionization-chamber array (MICA), which we have developed for rapid dosimetry measurements, incorporates any number of chambers in a linear, planar, or volume array. We presently have seven chambers in a linear array. In Year 01 we wish to purchase additional chambers (8) and electrometers (7) to expand our system to a planar array of 14 chambers (this will give us one spare chamber). In subsequent years we request funds to purchase two chambers and two electrometers per year for replacement and expansion.

3. Tissue Substitute Lab

We have initiated a program of studies of various tissue substitutes, liquids and solids, on both the CT scanner and pion therapy beam. We have had some difficulty in making some of the solid materials, and we request a vacuum mixer/degasser in Year 01 to support this activity.

4. Treatment Planning

We will initiate three-dimensional treatment planning calculations and will have the capability to display patient anatomy and isodose distributions in three dimensions. This program is necessary to complement our efforts in beam shaping in three dimensions using dynamic treatment. To support this program, we request funds to purchase a printer in Year 01 to be used with the color terminal purchased from another source. We feel that color display is essential for three-dimensional viewing because of the complex array of data that must be visually integrated. Without the color terminal and the printer, much of the utility of three-dimensional graphics would be lost.

5. Lasers

We have three alignment lasers each in the CT, simulator, and set-up rooms and six lasers in the treatment room. These lasers are essential to ensure that patient alignment is accurately transferred from one site to another. We request funds to replace two of these lasers each year.

6. Treatment Verification

To support our overall in vivo dosimetry effort, we request funds to purchase equipment as follows: (a) A replacement in vivo ionization chamber each year. These chambers are used extensively because we take measurements several times on each patient treatment field. The chamber suffers from chewing (intra-oral measurements) and general trauma. (b) We request funds to replace the NaI crystal in our aluminum activation system in Year 02. This system is used for in vivo measurements of the high-LET dose.

7. Microdosimetry

We have not had our own capability to perform microdosimetric studies, and the need for these studies is increasing. Microdosimetric data are necessary for our understanding of the pion beam and for the biological models that we are developing. We request funds to enable us to implement this capability and to replace some NIM modules that we currently have borrowed. The CAMAC modules are needed for interfacing the microdosimetry system to the multichannel analyzer, which has a programming capability to implement these modules. The Rossi chamber is an essential component of the microdosimetry system.

8. Positron Visualization

We request funds to enable us to continue the studies of pion stopping visualization in patients by positron imaging techniques. We wish to develop a simple system consisting of a rectangular array of four crystals for head scans and a simple 2-crystal system (using larger crystals) for body scans. This will require a total of 6 crystals - we already have three and we request funds to purchase three more.

C. Supplies

Supplies for physics, including dosimetry, electronic, mechanical, microdosimetry, tissue substitute, and graphic supplies are estimated based on actual expenses in the past. Costs for Years 02 and 03 are escalated by 10 percent per year for inflation.

D. Travel

Support is requested for three presentations of pion physics data at scientific meetings. Other travel support is requested for 12 trips between Albuquerque and Los Alamos, based on current experience.

E. Patient Costs (Grant Reimbursement)

Patients accessed to the pion protocols are billed for costs of treatment planning, central axis depth-dose calculations, design and fabrication of treatment devices, and other physics charges normally billed to patients receiving conventional radiation therapy. The amounts collected from third parties are reimbursed to the grant to offset the costs of salaries and wages, supplies, and maintenance expenses associated with these aspects of pion patients' medical care. Amounts not collected are written off to research support. Past experience has shown approximately a 70 percent collection

factor for billings to pion protocol patients. The amount anticipated to be collected against billings for clinical physics activities performed in Los Alamos is shown in the UNM Physics budget as an offset against the total request.

F. Other Expense

Construction of special equipment is estimated on an average basis of \$1,925 per month. This averages less than 1-1/2 weeks of shop construction per month. The anticipated physics activity for the three years of the grant period predicts this rate at which special equipment construction will continue. Equipment maintenance includes the contracts for maintaining the film processor, both the treatment and simulator room couch systems, and the x-ray systems in the simulator room. Publication costs are based on actual experience.

DETAILED BUDGET FOR FIRST 12 MONTH BUDGET PERIOD
DIRECT COSTS ONLY

FROM 12/1/82 THROUGH 11/30/83

DOLLAR AMOUNT REQUESTED (omit cents)

PERSONNEL (Applicant Organization only) (See instructions)		TIME EFFORT		SALARY	FRINGE BENEFITS	TOTALS
NAME	TITLE OF POSITION	%	Hours per year			
Moseley, R.D., Jr., M.D.	Principal Investigator					
TBA	Co Principal Invest					
Bradbury, J.M., Ph.D.	Group Leader		40			
Warner, R.F.	Asst. Division Ldr.		5			
Berardo, P., Ph.D.	Physicist		100			
TBA	Staff Programmer		100			
Paciotti, M., Ph.D.	Physicist		100			
Wing, J.	Engineer		100			
Total includes supplemental page						350,000

CONSULTANT COSTS (See instructions)

EQUIPMENT (itemize)

Computer peripheral/interface equipment		55,000	
Nuclear electronics modules		5,000	
Channel control hardware (spot beam dynamic collimator)		6,000	16,000

SUPPLIES (itemize by category)

Electronics parts	19,500	Dosimetry/electronics	18,700	
Computer expendables (disk packs, tapes, etc)	13,100	Control hardware	23,100	
Photographic materials	4,400	Office materials	5,500	
Chemicals	2,200	Miscellaneous	5,500	92,000

TRAVEL

DOMESTIC 4 Scientific meetings & training sessions @ \$770 3,080
FOREIGN

PATIENT CARE COSTS

INPATIENT
OUTPATIENT

ALTERATIONS AND RENOVATIONS (itemize by category)

CONTRACTUAL OR THIRD PARTY COSTS (See instructions)

OTHER EXPENSES (itemize by category)

ADP equipment maintenance & repair		2,000	
Computer facility charges	10,000	Communications	20,000
Electronic/instrumentation maintenance & repair	9,000	Contractual services	3,000
Machine shop	11,000	Burden (see next page)*	274,750
			329,750

TOTAL DIRECT COSTS (Also enter on page 1, item 8) \$ 790,830

DETAILED BUDGET FOR FIRST 12 MONTH BUDGET PERIOD
DIRECT COSTS ONLY

FROM THROUGH

PERSONNEL (Applicant organization only) (See instructions)		TIME EFFORT		DOLLAR AMOUNT REQUESTED (omit cents)		
NAME	TITLE OF POSITION	%	Hours per Week	SALARY	FRINGE BENEFITS	TOTALS
Moseley, R.D., Jr., MD	Principal Investigator					
TBA	Co Principal Invest					
TBA	Electronic Tech		100			
TBA	Systems Tech		100			
Swenson, B.	Programmer		100			
Rivera, O.	Mechanical Tech.		100			

*Burden %

Indirect	56.0
Program Management	7.5
Supp. R & D	12.0
General indirect & recharge equipment	3.0
	78.5

C O R

BUDGET ESTIMATES FOR ALL YEARS OF SUPPORT REQUESTED
DIRECT COSTS ONLY

BUDGET CATEGORY TOTALS	1st BUDGET PERIOD (from page 4)	ADDITIONAL YEARS SUPPORT REQUESTED		
		2nd	3rd	4th
PERSONNEL (Salary and fringe benefits.) (Applicant organization only)	350,000	385,000	423,500	
CONSULTANT COSTS				
EQUIPMENT	16,000	18,000	20,000	
SUPPLIES	92,000	104,000	118,000	
TRAVEL	DOMESTIC	3,080	3,388	3,328
	FOREIGN			
PATIENT CARE COSTS	INPATIENT			
	OUTPATIENT			
ALTERATIONS AND RENOVATIONS				
CONTRACTUAL OR THIRD PARTY COSTS				
OTHER EXPENSES	329,750	362,725	396,998	
TOTAL DIRECT COSTS	790,830	873,113	964,225	
TOTAL FOR ENTIRE PROPOSED PROJECT PERIOD (Also enter on page 5, item 7)			→ \$ 2,628,168	

JUSTIFICATION (Use continuation pages if necessary): Briefly describe the specific functions of the personnel and consultants. For all years, justify any costs for which the need may not be obvious, such as equipment, foreign travel, alterations and renovations, and contractual or third party costs. For future years, justify any significant increases in any category. In addition, for COMPETING CONTINUATION applications, justify any significant increases over current level of support. If a recurring annual increase in personnel costs is anticipated, give percentage.

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LANL PHYSICS EQUIPMENT BUDGET

	<u>YEAR</u>		
	1	2	3
	<u>(09)</u>	<u>(10)</u>	<u>(11)</u>
Computer Peripheral/Interface Equipment Tape drive, CAMAC, microprocessors	5,000	5,000	5,000
Nuclear Electronics Modules ADC, crate controllers, D/A converters	5,000	5,000	5,000
Channel Control Hardwar Spot beam dynamic collimators Helium bags New entrance slit	6,000	8,000	10,000
<hr/> Total	16,000	18,000	20,000

BUDGET JUSTIFICATION
LANL PHYSICS

A. Salaries and Wages

The organizational structure for the LANL group providing developmental physics and technology development/operations support to the pion biomedical program is shown in Figure 2. The staff requested is the minimum necessary to permit efficient channel operation and development, determination of therapy beam properties, facility operation, and treatment planning code development. Personnel costs are escalated 10 percent per year for Years 02 and 03. Responsibilities of individuals are listed below.

P. Berardo Three-dimensional treatment planning code development, physics computer modeling, code efficiency, multisystem configuration.

TBA, Staff Programmer System programming, ongoing support to application programmers, system software support, new software installation, technical programming.

M. Paciotti Development of therapy beams, documentation of beams for input into treatment planning code, conception and supervision of channel development projects.

J. Wing Facility engineering, liaison to other Medium Energy Physics Division (MP) groups for technical channel support not covered by internal staff, safety officer, technical writer for subsystem procedures, channel system documentation (wiring, cables, etc.), backup system operator, facility interlock system.

TBA, Electronic Technician Electrical, electronic, and electromechanical repair, design and improvement of channel hardware and instrumentation.

TBA, Systems Technician Computer system routine backups and system redressing; hardware, software and computer system support.

O. Rivera Mechanical technician provides mechanical design and fabrication of equipment for dynamic scanning and channel devices.

B. Swenson Programming assistance in treatment planning code project.

B. Equipment

The only major equipment item is development of a spot beam dynamic collimator which is required to provide dose distributions with as sharp edges as possible in dynamic treatment. Other equipment is primarily for replacement of worn-out items and items on loan from other LANL units. Costs are escalated at approximately 10 percent per year.

C. Supplies

A large component of supply costs is allocated to purchase of materials used to fabricate hardware for upgrading the channel and control systems and for fabrication of clinical and experimental apparatus. These costs are escalated 10 percent per year for inflation.

L. Rosen, Ph.D.
LAMPF Director

R. Warner MP-1 Budget Control Computer Support LAMPF Operations MP-2 Practical Applications MP-3 Exp. Area Dev. MP-7 Engtg. Support MP-8 Beam Line Dev. MP-13

J. Bradbury, Ph.D.
Group Leader

Secretary
T. Bradley

Treatment Planning Development Beam Tuning/Channel Development

P. Berardo - Ph.D. Physicist	M. Parlotti - Ph.D. Physicist
B. Swenson - Programmer	TBA - Elec. Tech.
TBA - Programmer	J. Wing - B.S. Engineer
TBA - Systems Tech.	O. Rivera - Mech. Tech.

Figure 2. Organizational structure of the LAMPF physics/technology support group for the pion biomedical program

D. Travel

Funds are requested to support 5 trips per year to scientific meetings for LANL staff assigned to this program, and costs are escalated at 10 percent per year for inflation.

E. Other Expense

Other expenses for LANL are primarily computer facility charges for the patient treatment planning and other calculations performed on LANL's large CDC computers at the Central Computing Facility (small because of the availability of the LAMPF VAX computer), and labor costs associated with fabrication of equipment, electronics modules, and other hardware. Funds are also needed for communications, equipment maintenance and rental, and contractual services. These costs are escalated at the rate of 10 percent per year.

IT IS IMPORTANT TO NOTE THAT THE LANL PHYSICS PORTION OF THE BUDGET INCLUDES AN ITEM CALLED "BURDEN," WHICH IS A DIRECT COST TO THE PROGRAM, SINCE THE LANL PHYSICS EFFORT IS PAID BY SUBCONTRACT. The burden is calculated at an average of 78.5 percent of personnel costs for all three years, and includes the following items: indirect costs, program management costs, support research and development costs, and general indirect and recharge equipment costs, as noted on the budget detail sheet.

DETAILED BUDGET FOR FIRST 12 MONTH BUDGET PERIOD
DIRECT COSTS ONLY

FROM 12/1/82 THROUGH 11/30/83

DOLLAR AMOUNT REQUESTED (omit cents)

PERSONNEL (Applicant organization only) (See instructions)		TIME EFFORT		SALARY	FRINGE BENEFITS	TOTALS
NAME	TITLE OF POSITION	%	MONTHS OF YEAR			
Moseley, R.D., Jr., MD	Principal Investigator					
TBA	Co Principal Invest					
Raju, M.R., D. SC	Fellow	25				
Tokita, N., MD; PhD	Staff Member	25				
Carpenter, S.	Staff Member	25				
Bain, E.	Cell Culture Tech	25				
Administrative costs prorated to all programs for secretarial, clerical, and general support from group and division office staff. VAR						
SUBTOTALS						54,418
CONSULTANT COSTS (See instructions)						
EQUIPMENT (Itemize)						
Isotope detector for kidney and liver studies						4,000
SUPPLIES (Itemize by category)						
Mice (purchase \$3,000 / maintenance \$16,000)				\$19,000		
Rats (purchase \$9,000 / maintenance \$21,000)				30,000		
Cell culture materials				6,000		
Miscellaneous supplies				3,600		58,600
TRAVEL		DOMESTIC 10 LANL/ABQ trips @128. 2 Scientific meetings @770			2,920	
		FOREIGN				
PATIENT CARE COSTS		INPATIENT				
		OUTPATIENT				
ALTERATIONS AND RENOVATIONS (Itemize by category)						
CONTRACTUAL OR THIRD PARTY COSTS (See instructions)						
OTHER EXPENSES (Itemize by category)						
Burden (see next page) *\$42,718						42,718
TOTAL DIRECT COSTS (Also enter on page 1, item B)						162,556

BUDGET ESTIMATES FOR ALL YEARS OF SUPPORT REQUESTED
DIRECT COSTS ONLY

BUDGET CATEGORY TOTALS	1st BUDGET PERIOD (from page 4)	ADDITIONAL YEARS SUPPORT REQUESTED		
		2nd	3rd	4th
PERSONNEL (Salary and fringe benefits.) (Applicant organization only)	54,418	59,860	55,846	
CONSULTANT COSTS				
EQUIPMENT	4,000	-0-	-0-	
SUPPLIES	58,600	64,460	70,906	
TRAVEL	DOMESTIC	2,820	3,102	3,412
	FOREIGN			
PATIENT CARE COSTS	INPATIENT			
	OUTPATIENT			
ALTERATIONS AND RENOVATIONS				
CONTRACTUAL OR THIRD PARTY COSTS				
OTHER EXPENSES	42,718	46,990	51,689	
TOTAL DIRECT COSTS	162,556	174,412	191,853	
TOTAL FOR ENTIRE PROPOSED PROJECT PERIOD (Also enter on page 1, item 7)			\$ 528,821	

JUSTIFICATION (Use continuation pages if necessary): Briefly describe the specific functions of the personnel and consultants. For all years, justify any costs for which the need may not be obvious, such as equipment, foreign travel, alterations and renovations, and contractual or third party costs. For future years, justify any significant increases in any category. In addition, for COMPETING CONTINUATION applications, justify any significant increases over current level of support. If a recurring annual increase in personnel costs is anticipated, give percentage.

BUDGET JUSTIFICATION
LANL BIOLOGY

The biology component is conducted from the Life Sciences Division of the Los Alamos National Laboratory (LANL), with the exception of pathology studies conducted by members of the UNM Pathology Department. Leading the biology team is Mudundi R. Raju, D.Sc., Fellow of the LANL Life Sciences Division and Adjunct Professor of Radiology and Director of the Division of Radiobiology in the Department of Radiology, UNM School of Medicine. For budgetary purposes only, the biology effort is shown in two parts: UNM Biology and LANL Biology because some of the personnel are employees of LANL and some are appointed by UNM. However, resources are pooled as indicated by project need, and for that reason all supplies are listed under LANL Biology.

The hours of 8 a.m. to 10 p.m. or midnight on Tuesdays through Saturdays are allocated to patient treatment. (Mondays are reserved for routine accelerator maintenance.) Therefore, biology experiments are performed on weekends, usually starting at 9 p.m. on Saturdays and continuing until 8 a.m. on Mondays. Fractionation experiments are also conducted during weekdays beginning about 10 p.m. and continuing until about 8 a.m. the following day. Media exchange, animal care and feeding, and scoring of cell cultures and experimental animal radiation symptoms are performed during weekdays and on weekends as needed. For conduct of radiobiology experiments, two persons must be present at the Pion Biomedical Facility for logistical and safety reasons. Post-irradiation care and scoring of cell samples and experimental animals is divided among the UNM and LANL technical staff.

A. Salaries and Wages

Funding is requested for 25 percent of Dr. Raju, who is directing the biology effort and who is personally responsible for the cell culture studies. Funding is requested for 25 percent of N. Tokita, M.D., Ph.D., a radiotherapist and radiobiologist. He will be responsible for studies of pion acute effects (skin and intestinal crypt) and late effects (mouse lens), and for coordinating the laboratory studies with the clinical studies.

Support for 25 percent of S. Carpenter (to assist with mouse skin studies and tissue culture studies and to assist with pion exposures and colony counting), and 25 percent of Elvira Bain (to prepare cells and materials for tissue culture studies and to perform colony counting), is also requested. These staff will also provide backup to the UNM biology technical staff as needed.

Salaries are escalated 10 percent per year for Years 02 and 03 for inflation. Fringe benefits are calculated at 15 percent.

B. Equipment

The equipment requested is needed to carry out the biology experiments as presented in the text of this application.

C. Supplies

Funding is requested for supplies necessary to do the experiments described in the text of this application. The requested amounts for each

year after Year 9 are escalated by 10 percent for inflation. Animal maintenance is estimated to cost 9¢/day per mouse and 18¢/day per rat.

D. Travel

Travel funding is requested for 10 trips between Los Alamos and Albuquerque, in addition to two scientific meetings. Costs for professional staff are greater than for technicians since their visits tend to be longer and therefore involve more per diem payments. Costs are escalated 10 percent per year for inflation.

E. Other Expense

IT IS IMPORTANT TO NOTE THAT THE LANL BIOLOGY PORTION OF THE BUDGET INCLUDES AN ITEM CALLED "BURDEN," WHICH IS A DIRECT COST TO THE PROGRAM, SINCE THE LANL BIOLOGY EFFORT IS PAID BY SUBCONTRACT. The burden is calculated at an average of 78.1 percent of personnel costs for all three years, and includes the following items: indirect costs, program management costs, support research and development costs, and general indirect and recharge equipment costs, as noted on the budget detail sheet.

Biology - UNM

PRINCIPAL INVESTIGATOR PROGRAM DIRECTOR Robert D. Moseley, Jr., M.D.

DETAILED BUDGET FOR FIRST 12 MONTH BUDGET PERIOD
DIRECT COSTS ONLY

FROM 12/1/82 THROUGH 11/30/83

DOLLAR AMOUNT REQUESTED (omit cents)

PERSONNEL (Applicant organization only) (See instructions)		TIME/EFFORT		SALARY	FRINGE BENEFITS	TOTALS
NAME	TITLE OF POSITION	%	Hours per Week			
Moseley, R.D., Jr., MD	Principal Investigator					
TBA	Co Principal Invest.					
van der Kogel, A.J., PhD	Research Scientist	100	40			
Pierotti, D.	Research Tech.	100	40			
Sherman, G.	Research Tech.	100	40			

TOTALS INCLUDE SUPPLEMENTAL PAGE

SUBTOTALS → 65,725 9,859 75,584

CONSULTANT COSTS (See instructions)

See supplemental page 3,410

EQUIPMENT (itemize)

SUPPLIES (itemize by category)

TRAVEL DOMESTIC See supplemental page 2,925
FOREIGN

PATIENT CARE COSTS INPATIENT
OUTPATIENT

ALTERATIONS AND RENOVATIONS (itemize by category)

CONTRACTUAL OR THIRD PARTY COSTS (See instructions)

OTHER EXPENSES (itemize by category)

Pion exposure gadgets	8,000		
Publications costs	1,500		
Histology expenses	7,000		
Shipping of animals	5,000		
			21,500

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TOTAL DIRECT COSTS (Also enter on page 1, item 5) → \$ 102,519

1091390

**BUDGET ESTIMATES FOR ALL YEARS OF SUPPORT REQUESTED
DIRECT COSTS ONLY**

BUDGET CATEGORY TOTALS	1st BUDGET PERIOD <i>(from page 4)</i>	ADDITIONAL YEARS SUPPORT REQUESTED			
		2nd	3rd	4th	5th
PERSONNEL (Salary and fringe benefits.) <i>(Applicant organization only)</i>	75,584	83,142	91,456		
CONSULTANT COSTS	3,410	3,751	4,126		
EQUIPMENT					
SUPPLIES					
TRAVEL	DOMESTIC	2,025	2,228	2,451	
	FOREIGN				
PATIENT CARE COSTS	INPATIENT				
	OUTPATIENT				
ALTERATIONS AND RENOVATIONS					
CONTRACTUAL OR THIRD PARTY COSTS					
OTHER EXPENSES	21,500	23,650	26,015		
TOTAL DIRECT COSTS	102,519	112,771	124,048		

TOTAL FOR ENTIRE PROPOSED PROJECT PERIOD (Also enter on page 1, item 7) \longrightarrow \$ 339,338

JUSTIFICATION (Use continuation pages if necessary): Briefly describe the specific functions of the personnel and consultants. For all years, justify any costs for which the need may not be obvious, such as equipment, foreign travel, alterations and renovations, and contractual or third party costs. For future years, justify any significant increases in any category. In addition, for COMPETING CONTINUATION applications, justify any significant increases over current level of support. If a recurring annual increase in personnel costs is anticipated, give percentage.

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BUDGET JUSTIFICATION
UNM BIOLOGY

The biology component is conducted from the Life Sciences Division of the Los Alamos National Laboratory (LANL). (See the Budget Justification, LANL Biology, for a full justification of the biology program.)

A. Salaries and Wages

Salaries are requested for 1.0 FTE Ph.D. level scientist (Albert J. van der Kogel, Ph.D., Research Scientist) to continue leading the CNS studies and with Dr. Raju, to coordinate other late effects studies proposed in this application. Although assigned to UNM, Dr. van der Kogel is based in Los Alamos with office and laboratory space being provided by the LANL Life Sciences Division.

Technician support by UNM is budgeted at 2.00 FTE (D. Pierotti and G. Sherman) at the Pion Biomedical Facility in Los Alamos under the supervision of Drs. M. Raju, N. Tokita, and van der Kogel. Costs are escalated 10 percent per year for Years 02 and 03. Fringe benefits are calculated at 15 percent of salaries and wages.

B. Consultants

Consultant funds are requested for E. Travis, Ph.D., of the M.D. Anderson Hospital, Houston, to perform late effects studies on lung tissue. These costs include transportation, consulting fees, and per diem at rates allowed by the University of New Mexico. Similar consulting requirements are anticipated for Years 02 and 03.

C. Travel

Travel support is requested for 5 trips between Los Alamos and Albuquerque and for two scientific meetings per year. Costs are escalated 10 percent per year for inflation.

D. Other

Other expenses include pion exposure gadgets, publication costs, histology expenses, and shipping of animals. These expenses are necessary to run the proposed biology program during the life of this grant.

Core: Administration

PRINCIPAL INVESTIGATOR PROGRAM DIRECTOR Robert J. Moseley, Jr., M.D.

BUDGET ESTIMATES FOR ALL YEARS OF SUPPORT REQUESTED
DIRECT COSTS ONLY

BUDGET CATEGORY TOTALS	1st BUDGET PERIOD (from page 4)	ADDITIONAL YEARS SUPPORT REQUESTED			
		2nd	3rd	4th	5th
PERSONNEL (Salary and fringe benefits.) (Applicant organization only)	40,607	44,668	49,136		
CONSULTANT COSTS	17,500	19,250	21,175		
EQUIPMENT					
SUPPLIES	3,200	3,520	3,872		
TRAVEL	DOMESTIC	2,516	2,768	3,045	
	FOREIGN				
PATIENT CARE COSTS	INPATIENT				
	OUTPATIENT				
ALTERATIONS AND RENOVATIONS					
CONTRACTUAL OR THIRD PARTY COSTS					
OTHER EXPENSES	4,174	4,591	5,051		
TOTAL DIRECT COSTS	67,997	74,797	82,278		

TOTAL FOR ENTIRE PROPOSED PROJECT PERIOD (Also enter on page 1, item 7) → \$ 225,072

JUSTIFICATION (Use continuation pages if necessary): Briefly describe the specific functions of the personnel and consultants. For all years, justify any costs for which the need may not be obvious, such as equipment, foreign travel, alterations and renovations, and contractual or third party costs. For future years, justify any significant increases in any category. In addition, for COMPETING CONTINUATION applications, justify any significant increases over current level of support. If a recurring annual increase in personnel costs is anticipated, give percentage.

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BUDGET JUSTIFICATION
CORE: ADMINISTRATION

A. Salaries and Wages

Mr. Davidson and the individual to be appointed will handle the administrative requirements for the CRTC scientific and clinical staff based at or rotating to Los Alamos, as well as housing, travel, and other requirements for visiting scientists. These individuals will also handle purchasing, personnel, budgeting, patient cost reimbursements to health care providers, subsistence reimbursements to patients, and similar duties, as well as liaison with the NCI, LANL, The Los Alamos Medical Center, and other agencies concerned with or participating in the pion clinical trials.

Personnel costs are escalated by 10 percent per year for Years 02 and 03. Fringe benefits are calculated at 15 percent of salaries and wages.

B. Consultants

Consulting funds are requested to pay for travel, per diem, and consulting fees for members of the External Advisory Committee, and general consultations. In addition, physicians from other institutions who are referring patients for pion treatment and/or treating pion protocol control patients at their own institutions are occasionally brought to Los Alamos for technology exchange, to improve comparability of data for pion versus conventional therapy patients. Their travel and per diem expenses are paid from consulting funds. Two consultants will be brought to Los Alamos in Year 10 to perform calorimetry measurements needed for the studies designed to more clearly define absorbed dose for pions. Measurements will be made by a representative of the National Bureau of Standards, using a water and a carbon calorimeter, and by Joseph McDonald, Ph.D., of the University of California/Los Angeles, using a tissue-equivalent calorimeter. This work is necessary to test calculations of the conversion factors for ionization chambers of different materials, gases, and geometry, as described under Section V-B, Physics. Consultant costs are escalated 10 percent year for inflation.

C. Supplies

The cost of clerical supplies is escalated by 10 percent per year for inflation.

D. Travel

Travel costs are requested for one administrative meeting at the national level (e.g., with representatives of the NCI and/or the RTOG), and for 18 trips to and from Los Alamos and Albuquerque. These costs are escalated 10 percent per year for inflation.

E. Other Expenses

These expenses include maintenance for magnetic card typewriters at the Los Alamos administrative office and the Pion Biomedical Facility. Xerox and communications costs include printing and distribution of updated material for the pion protocol and procedure manuals, as well as routine Xerox, phone, and postage expense. These costs are based on current experience and are escalated 10 percent per year for inflation.

Core: Protocol Support

PRINCIPAL INVESTIGATOR PROGRAM DIRECTOR Robert D. Moseley, Jr., M.D.

DETAILED BUDGET FOR FIRST 12 MONTH BUDGET PERIOD
DIRECT COSTS ONLY

FROM 12/1/82 THROUGH 11/30/83

DOLLAR AMOUNT REQUESTED (omit cents)

PERSONNEL (Applicant organization only) (See instructions)		TIME EFFORT		SALARY	FRINGE BENEFITS	TOTALS
NAME	TITLE OF POSITION	%	Hours per week			
Moseley, R.D., Jr., MD	Principal Investigator					
TBA	Co Principal Invest					
Garcia, A.	Program Specialist	100	40			
TBA	Program Specialist	50	20			
SUBTOTALS				23,995	3,599	27,594

CONSULTANT COSTS (See instructions)

EQUIPMENT (Itemize)

SUPPLIES (Itemize by category)

Clerical supplies 1,500

TRAVEL DOMESTIC See supplemental page 1,934
FOREIGN

PATIENT CARE COSTS INPATIENT
OUTPATIENT

ALTERATIONS AND RENOVATIONS (Itemize by category)

CONTRACTUAL OR THIRD PARTY COSTS (See instructions)

OTHER EXPENSES (Itemize by category)

TOTAL DIRECT COSTS (Also enter on page 7, item 8) 31,028

1091398

Core: Protocol Support

PRINCIPAL INVESTIGATOR PROGRAM DIRECTOR Robert D. Moseley, Jr., M.D.

**BUDGET ESTIMATES FOR ALL YEARS OF SUPPORT REQUESTED
DIRECT COSTS ONLY**

BUDGET CATEGORY TOTALS	1st BUDGET PERIOD (from page 4)	ADDITIONAL YEARS SUPPORT REQUESTED			
		2nd	3rd	4th	5th
PERSONNEL (Salary and fringe benefits.) (Applicant organization only)	27,594	30,353	33,388		
CONSULTANT COSTS					
EQUIPMENT					
SUPPLIES	1,500	1,650	1,815		
TRAVEL	DOMESTIC	1,934	2,127	2,340	
	FOREIGN				
PATIENT CARE COSTS	INPATIENT				
	OUTPATIENT				
ALTERATIONS AND RENOVATIONS					
CONTRACTUAL OR THIRD PARTY COSTS					
OTHER EXPENSES					
TOTAL DIRECT COSTS	31,028	34,130	37,543		
TOTAL FOR ENTIRE PROPOSED PROJECT PERIOD (Also enter on page 1, item 7)				→	\$ 102,701

JUSTIFICATION (Use continuation pages if necessary): Briefly describe the specific functions of the personnel and consultants. For all years, justify any costs for which the need may not be obvious, such as equipment, foreign travel, alterations and renovations, and contractual or third party costs. For future years, justify any significant increases in any category, in addition, for COMPETING CONTINUATION applications, justify any significant increases over current level of support. If a recurring annual increase in personnel costs is anticipated, give percentage.

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BUDGET JUSTIFICATION
CCRE: PROTOCOL SUPPORT

A. Salaries and Wages

Support is requested for 1.5 FTE program specialists for this core component to provide the minimum staff support for data management activities; patient scheduling, liaison, and counseling; transportation and housing arrangements; collection and transmission of patient records and films; maintenance of study forms and film files; and related duties.

Salary costs are escalated 10 percent per year for inflation. Fringe benefits are calculated at 15 percent of salaries and wages.

B. Supplies

Supplies are mainly clerical supplies for the significant paper load associated with the activity of this group in support of the pion clinical trials. The estimates are considered minimum amounts, based on current experience, and are escalated 10 percent per year for inflation.

C. Travel

Travel support is requested for one trip to an annual RTOG data managers' meeting for training and coordination on forms and reports. Travel support is also needed for periodic travel to and from Los Alamos (one trip per month).

D. Other Expense

Phone expenses were budgeted based on actual use and projected forward at a 10 percent increase each year

TOTAL SUMMARY

PRINCIPAL INVESTIGATOR PROGRAM DIRECTOR Robert D. Moseley, Jr., M.D.

BUDGET ESTIMATES FOR ALL YEARS OF SUPPORT REQUESTED
DIRECT COSTS ONLY

BUDGET CATEGORY TOTALS	1st BUDGET PERIOD (from page 4)	ADDITIONAL YEARS SUPPORT REQUESTED			
		2nd	3rd	4th	5th
PERSONNEL (Salary and fringe benefits; Applicant organization only)	751,340	864,041	993,647		
CONSULTANT COSTS	39,039	44,943	47,237		
EQUIPMENT	51,200	29,775	27,145		
SUPPLIES	73,679	81,047	89,152		
TRAVEL	DOMESTIC	145,468	160,015	176,017	
	FOREIGN				
PATIENT CARE COSTS	INPATIENT	18,814	20,695	22,765	
	OUTPATIENT	(114,297)	(125,727)	(103,300)	
ALTERATIONS AND RENOVATIONS					
CONTRACTUAL OR THIRD PARTY COSTS	954,156	1,048,372	1,157,010		
OTHER EXPENSES	233,256	256,582	282,240		
TOTAL DIRECT COSTS	2,152,655	2,379,743	2,656,913		
TOTAL FOR ENTIRE PROPOSED PROJECT PERIOD (Also enter on page 7, item 7)				7,189,311	

JUSTIFICATION (Use continuation pages if necessary): Briefly describe the specific functions of the personnel and consultants. For all years, justify any costs for which the need may not be obvious, such as equipment, foreign travel, alterations and renovations, and contractual or third party costs. For future years, justify any significant increases in any category, in addition for COMPETING CONTINUATION specifications. Justify any significant increases over current level of support. If recurring annual increase in personnel costs is anticipated, give percentage.

The contractual or third party costs include both the Biology - LANL and the Physics - LANL budgets.

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OTHER SUPPORT

(USE CONTINUATION PAGES IF NECESSARY)

For each of the professionals named on page 2, list, in three separate groups: (1) active support; (2) applications pending review and/or funding; (3) applications planned or being prepared for submission. Include all Federal, non-Federal, and institutional grant and contract support. If none, state "NONE." For each item give the source of support, identifying number, project title, name of principal investigator/program director, time or percent of effort on the project by professional named, annual direct costs, and entire period of support. If part of a larger project, provide the titles of both the parent grant and the subproject and give the annual direct costs for each. Briefly describe the contents of each item listed. If any of these overlap, duplicate, or are being replaced or supplemented by the present application, justify and delineate the nature and extent of the scientific and budgetary overlaps or boundaries.

PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR: Robert D. Moseley, Jr., M.D.

(1) ACTIVE SUPPORT: None

(2) PENDING SUPPORT:

NIH application "Observer Performance Evaluation of Imaging Technology", Robert D. Moseley, Jr., M.D., Principal Investigator, 20% \$15,000 (Yr. 1).

CO-PRINCIPAL INVESTIGATOR: TBA

(1) ACTIVE SUPPORT:

Los Alamos National Laboratory, Purchase Order 4-L21-2460V: Professional Services: Pion Biomedical Program Direction, TBA, Co-Principal Investigator, 25%, \$25,000, (renewable annually). Support from LANL for pion program direction; does not duplicate funds requested here.

CHIEF, CLINICAL PHYSICS: Smith, A.R., Ph.D.

(1) ACTIVE SUPPORT:

National Cancer Institute 5 R01 CA 22286-04: AAPM Charged Particle Dosimetry Task Group, A.R. Smith, Ph.D., Principal Investigator, 20%, \$53,754 (Yr. 4), 1 August 1980 - 31 July 1983. Support for charged particle intercomparisons and development of charged particle dosimetry protocol; does not duplicate funds requested here.

(2) PENDING SUPPORT:

National Cancer Institute, RFP # NCI-CM-17482-22: Evaluation of Treatment Planning for Particle Beam Radiotherapy, A.R. Smith, Ph.D., Principal Investigator, 15% \$28,720 (Yr. 1), \$250,000 (Total). Evaluation of treatment planning techniques for national particle intercomparison. If approved, release time from this project will be replaced with a technician (.50 FTE total: Smith (15%), Hilko (20%), TBA (15%)).

FELLOW, LOS ALAMOS NATIONAL LABORATORY: Raju, M.R., J.Sc.

(1) ACTIVE SUPPORT:

National Cancer Institute 5 R01 CA 17290-06: Comparative Studies of Heavy Particles in Radiotherapy, M.R. Raju, Ph.D., Principal Investigator, 70%, \$182,160, 1 August 1981 - 31 July 1983. Does not duplicate funds requested here. Release time from this application will be used to obtain additional technical support for comparative studies until completing renewal.

CHAIRMAN, PATHOLOGY UNM SCHOOL OF MEDICINE: Anderson, R.E., M.D.

(1) PENDING SUPPORT:

National Cancer Institute 2 R01 CA 13805-08: Radiation Injury in Subpopulations of Lymphocytes, R.E. Anderson, M.D., Principal Investigator, 25%, \$60,457 (Yr. 1), \$358,892 (Total), 1 January 1982 - 31 December 1986. Does not duplicate funds requested here; effort does not overlap.

RESOURCES AND ENVIRONMENT

FACILITIES: Mark the facilities to be used and briefly indicate their capacities, pertinent capabilities, relative proximity and extent of availability to the project. Use "other" to describe facilities at other performance sites listed in Item 9, page 1, and at sites for field studies. Using continuation pages if necessary, include a description of the nature of any collaboration with other organizations and provide further information in the RESEARCH PLAN.

- Laboratory:** The Pion Biomedical Facility at LAMPF is equipped with a small tissue culture laboratory. Complete tissue culture facilities are available at the CRTC/Albuquerque and the Los Alamos National Laboratory for backup as needed.
- Clinical:** The 8500 square-foot Pion Biomedical Facility is equipped with outpatient examination, CT scanning, simulation, set-up and treatment facilities for patients. Outpatient housing is available by lease from the Los Alamos Medical Center. Inpatient facilities are available at the Los Alamos Medical Center and at the UNM Hospital (an 8-bed cancer research unit). A full range of outpatient clinical facilities is available at the CRTC in Albuquerque.
- Animal:** A small animal holding facility is available at the Pion Biomedical Facility at LAMPF. Larger backup facilities are available at the CRTC in Albuquerque, at the Los Alamos National Laboratory (including a holding area for large animals), and at the UNM Medical Center Animal Resource Facility.
- Computer:** The Pion Biomedical Facility at LAMPF is equipped with PDP-11/45 and 11/70 computers and an array of peripheral devices (terminals, CRT displays, printers, microprocessors, CAMAC modules, etc.). Purchase of a PDP VAX computer for the facility with DOE funds is being explored.
- Office:** Office facilities for research and administrative staff are available at the Pion Biomedical Facility, an adjacent office building, and the Accelerator Technology building approximately one block from the Pion Facility. Office facilities are provided at the CRTC in Albuquerque for staff based there.
- Other (_____):**

MAJOR EQUIPMENT: List the most important equipment items already available for this project, noting the location, and pertinent capabilities of each.

90 McV negative pion channel (fixed vertical beam)	Clinac 6 accelerator (Albuquerque)
2 EMI 7070 whole body scanners	Clinac 18 accelerator (Albuquerque)
Philips Medio 5500 simulator	Picker Simulator (Albuquerque)
GE 300 kVp Maxitron x-ray unit (for biology)	Orthovoltage, superficial and cobalt machines (Albuquerque)
Equipment for physics dosimetry, microdosimetry, <u>in vivo</u> dosimetry, visualization, and treatment planning	Implant sources (Albuquerque)
Computer equipment as described above	Word processing equipment (Los Alamos and Albuquerque)

ADDITIONAL INFORMATION: Provide any other information describing the environment for the project. Identify support services such as consultants, secretarial, machine shop, and electronics shop, and the extent to which they will be available to the project.

The Pion Biomedical Facility includes an electronics shop and medical physics laboratory. Complete shop services and electronics instrumentation services are available through LANL. The LANL Central Computing Facility is available for treatment planning and other applications. The complete clinical and laboratory facilities of the CRTC in Albuquerque are also available for diagnosis, supplemental treatment, and follow-up.

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RESEARCH PLAN

I. INTRODUCTION - STATEMENT OF OBJECTIVES

A. Objective

The primary objective of this program is to conduct the necessary physical, biological and clinical studies to evaluate the efficacy, potential benefit, and role of negative pi mesons (pions) in management of solid tumors not well managed by current methods.

B. Background

Radiation therapy used alone or in combination with surgery or chemotherapy is an effective curative modality for a large number of patients with localized and regional cancers. Considerable progress in the last two decades in the treatment of cancer with radiation therapy has been due to a better understanding of cancer biology and the radiation tolerance of normal tissues, advances in radiation dosimetry, increased use of careful treatment planning, and the use of megavoltage radiation sources (x-rays, gamma rays, and electrons) with improved physical dose distributions. Despite these advances, it has been estimated that approximately 100,000 deaths occur annually due to failure by all means of therapy to control local-regional cancer. Improved local control would aid not only these patients, but also patients with those types of solid tumors in which systemic adjuvant therapy may control distant metastases. Any modality that will enable the radiotherapist to increase the effective radiation dose to the tumor while maintaining or reducing the effective dose to critical normal tissue will enhance control of large lesions. Control of the local lesion will enhance the benefit of systemic therapy on disseminated subclinical disease.

Because of the unique physical and biological properties of particle radiations, it has been proposed that their use will significantly enhance the ability to accomplish uncomplicated local control of cancer. To test this theory, the National Cancer Institute has supported several projects to explore and exploit the theoretical advantages of heavy particles in radiotherapy, including neutrons, protons, heavy ions, and negative pi mesons (pions).

In terms of biological effectiveness, radiation may be classified as low linear energy transfer (low LET), such as x-rays, gamma rays, electrons, protons, and negative pions in their plateau region; or high LET, such as neutrons, heavy ions, and pions in their stopping region. High-LET beams differ from low-LET beams in the greater density of ionization deposited in tissues, which leads to greater destruction of critical molecules, and thus increased cellular lethality.

Beams of heavy charged particles have a characteristic absorption curve with a finite depth of penetration. The depth-dose curve of heavy charged particles has two portions, an initial relatively low-dose plateau, and a high-dose terminal peak (Bragg peak) in the stopping region. The depth at which the Bragg peak is located within the absorbing medium depends on the

initial momentum of the particles. As the particles lose energy, slow down and stop, a proportionately greater amount of energy is absorbed per unit volume of tissue, creating the high-dose peak. The greater the dose at the peak stopping region in comparison with the plateau, the greater the potential improvement in the ratio between dose deposition in tumor and adjacent normal tissue. The depth-dose characteristics of a heavy ion beam, a proton beam (even though it is low-LET), or a pion beam can be modulated to fit a tumor, thus minimizing the amount of energy deposited in adjacent normal tissues. The more the radiation can be limited to the tumor volume itself, the higher the dose that can be delivered, thus increasing the probability of destroying all tumor cells. The physical dose distribution combines with increased RBE to enhance cell killing in the stopping or peak region. Despite sophisticated isocentric equipment and computerized treatment planning, conventional super-voltage radiation and neutron beams (even though they are high LET) cannot be localized to the tumor in the same manner. Particularly in the case of deep-seated tumors in proximity to normal tissues of greater radiosensitivity than the neoplasm, it is necessary to limit the dose of radiation to levels known to be suboptimal in terms of eradication of the disease.

The negative pi meson, or pion, a subnuclear particle with a mass approximately 1/7 that of a proton, behaves as low-LET radiation in the plateau region, but in the stopping region, the effective dose is high for two reasons. One is the increased ionization caused by the charged particle slowing down and stopping, as mentioned earlier, so that increased energy deposition per unit volume of tissue occurs in this peak region. However, as these negatively charged particles lose energy in the peak region, they are captured by the nuclei of atoms, principally carbon, nitrogen, and oxygen. This causes an unstable condition in the nuclei of the atoms, which then undergo fragmentation, with the production of alpha particles, large nuclear fragments, neutrons, protons, and a small percentage of gamma rays. The ionization pattern of this fragmentation, the "star," contains the high-LET portion of the pion beam, and it augments the primary ionization in the peak region. Part of the fragments, including neutrons, are high-LET radiation. The pion peak, therefore, has a mixture of low- and high-LET radiation.

Generally, normal cells have a greater capacity to recover from the damage caused by low-LET radiation than do tumor cells arising in those normal tissues. The increased ability of normal cells to recover from sublethal damage makes cure by radiation possible, since the sensitivity of normal and neoplastic cells to conventional low-LET radiation is about the same. Multiple small daily fractions of x-rays (≤ 200 rad) permit a greater degree of recovery in normal cells than in neoplastic cells in a specific time period. The reduced amount of recovery in normal tissues that occurs with a pure high-LET radiation may overcome the differential recovery favoring the normal tissues and thus may mitigate against the favorable effects of low-LET fractionation. However, the LET differential between plateau and peak for pions should partially overcome this disadvantage by confining the high-LET radiation to the tumor volume, provided the tumor can be adequately localized for dose delivery and that optimal techniques are employed in contouring the dose distribution to the desired treatment volume.

Two radiobiological principles common to high-LET radiation may act to increase cell killing in the peak region: (a) high-LET radiation has been

shown more effective in killing the hypoxic cells which are present in the majority of tumors, and (b) variations of cellular radiosensitivity within cell-cycle phases have been shown to be less marked with high-LET radiation.¹⁻⁴

The fundamental nature of the negative pion and its interaction at rest with nuclei have been known since 1947 when Powell and his group in England first observed these particles. In the early 1960's, Fowler, Richman, and others suggested the use of these particles for cancer therapy. Fowler and Perkins were the first to make calculations of the dose distributions of a pion beam.⁵ Further experimental work ensued with a beam of low intensity at Berkeley,⁶⁻⁸ but a beam of sufficient intensity to perform medical testing was not available until the biomedical pion channel of the 800-MeV proton linear accelerator at the Clinton P. Anderson Meson Physics Facility (LAMPF) was activated in early 1974.

In September 1972, the University of New Mexico (UNM) and the Los Alamos National Laboratory (LANL), then called the Los Alamos Scientific Laboratory, proposed to the National Cancer Institute (NCI) a joint research program of preclinical physics and biology studies for pion radiotherapy, based on the planned availability of a pion beam more than 100 times as intense as that produced at Berkeley. The biomedical pion channel and biomedical facility at LAMPF were then under construction with funding from the Atomic Energy Commission and the NCI. Funding for the preclinical research project was approved for a three-year period, starting July 1, 1973. The following month (August 1973), the 800-MeV proton accelerator at LAMPF produced its first pions, although activation of the biomedical pion channel did not occur until February 6, 1974. Under a grant to support the clinical activity (CA-16127), awarded May 1, 1974, four patients were treated with pions during October-December 1974. The proton accelerator was then shut down for about 15 months for extensive refurbishing to tolerate high intensity beam operations. Clinical treatment resumed in June 1976, although beam intensity was then at only 10 microamperes (1/100 of the planned design intensity of 1 milliampere). Beam current was gradually escalated, as was the number of operating weeks. Current was raised to 500 microamperes in the summer of 1979, and recently escalated to 600 microamperes. An increase to 750 microamperes is planned for the summer of 1982. Each increase in beam current produces a linear increase in pion flux, so that patient treatment time is proportionately reduced. With the increase planned for the summer of 1982, it is estimated that it will be possible to treat 20-25 patients per 16-hour treatment day, compared with 15-18 at present.

The two grants for preclinical studies (CA-14052) and clinical studies (CA-16127) were combined May 1, 1979, into a single grant to support clinical, biological, and physics studies related to pion radiotherapy. This application represents a new application for the period December 1, 1982, through November 30, 1985, to replace a disapproved application (2 PO1 CA 16127-09).

II. INSTITUTIONAL ENVIRONMENT AND RESOURCES

The UNM and LANL have been engaged since 1972 in a joint research effort to test the radiotherapeutic potential of pions produced by the 800-MeV proton linear accelerator at Los Alamos. This accelerator is the only one in the U.S.A. routinely producing pions at sufficient intensity for medical testing, and physicians throughout the nation are sending appropriate patients to this facility for pion radiotherapy.

A. Cancer Research and Treatment Center, Albuquerque

The pion research program provided the impetus for the creation of a regional cancer center in Albuquerque, the population center of New Mexico with approximately one-third of the state's 1.3 million residents. The center was constructed with a \$3.375 million grant from the NCI and \$1.5 million in matching funds from the state, county, and UNM. It was opened for clinical operations in January 1975. The CRTC has developed programmatically into a multidisciplinary center, involving physicians, basic scientists, epidemiologists, and others. The CRTC is the only facility exclusively devoted to cancer research, treatment, education and control activities in a geographic area bounded by Houston to the East, Tucson to the West, Denver to the North, and the United States/Mexico border to the south. The center is operated by UNM as a facility to serve the entire State of New Mexico and contiguous areas of surrounding states. The center has been identified by the New Mexico Health Systems Agency (HSA) and the Navajo Nation HSA as the central cancer facility for the State of New Mexico and the Navajo Nation. The patient catchment area for the center is depicted in Figure 3.

The CRTC is an outpatient hospital, with 56,975 net square feet of space for diagnostic, clinical, laboratory, epidemiology, and administrative activities. Inpatient facilities are provided by the UNM Hospital/Bernalillo County Medical Center adjacent to the CRTC, and by the UNM-affiliated hospitals (Lovelace-Bataan Medical Center and the Albuquerque Veterans Administration Medical Center). These hospitals have a combined total of 900 beds. An eight-bed research unit is available at the UNM Hospital for research protocol patients of the CRTC. The UNM Hospital is connected with the CRTC by a common corridor at the clinic floor level. The CRTC also has service tunnels connecting with the UNM School of Medicine Basic Sciences Building and the Colleges of Nursing and Pharmacy. The UNM north campus health complex also includes the Bernalillo County Mental Health Center, the New Mexico State Laboratory Building (for Health, Environmental and Medical Investigation laboratories), New Mexico Children's Psychiatric Center, a building housing the departments of Family, Community, and Emergency Medicine and Psychiatry, a new medical library, and a dental hygiene building. A \$9 million basic research building is under construction adjacent to the CRTC and Basic Sciences Building, and will be connected by the same service tunnel system with the CRTC.

Approximately 31 percent of CRTC cancer patients are Bernalillo County residents, while 57 percent are New Mexico residents of counties other than Bernalillo and 12 percent are residents of other states. A total of 4,548 new and follow-up patients were seen at the CRTC in calendar year 1980, of whom 559 were cancer patients seen in the Radiation Oncology Section. Collaborative arrangements with participating institutions throughout the country are discussed in detail in Section V-A (Clinical Investigations).

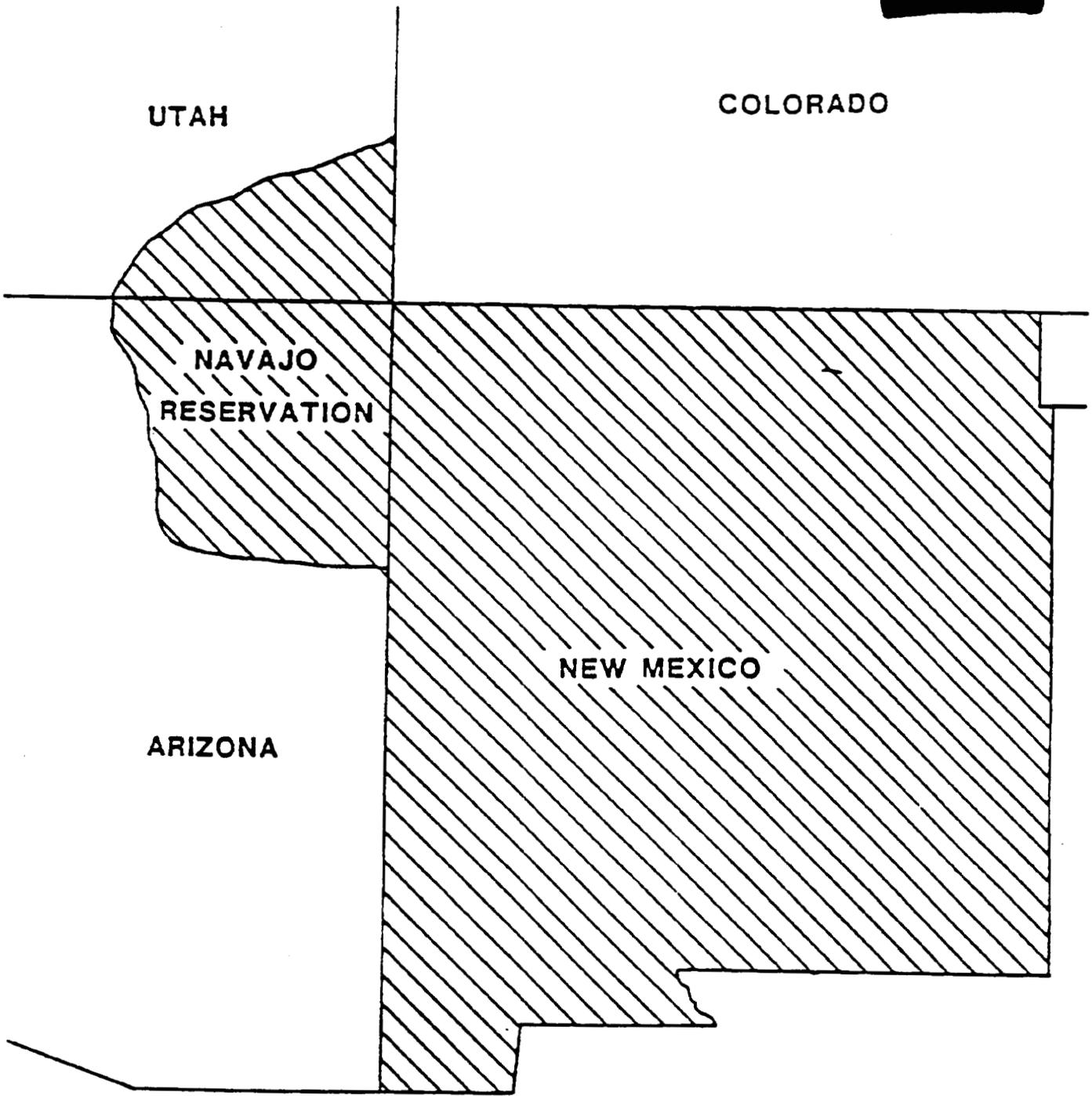


Figure 3. CRTC patient catchment area

In addition to the pion research program, the CRTC's clinical investigations include participation (with full membership) in the Southwest Oncology Group and Radiation Therapy Oncology Group.

The clinical floor of the CRTC has been planned for ease of rapid work-up and decision-making for patient treatment. A full range of diagnostic, therapeutic and follow-up services is provided. The primary goal is to provide rapid pretreatment evaluation for most patients. To improve efficiency, a computerized system for scheduling patients with various specialists and specialized diagnostic equipment has been implemented.

The center's clinical operations are organized under a multidisciplinary joint clinics concept, with patients seen in one area by physicians of various specialties. In addition, a number of specialty clinics are operating at the center, including gynecologic oncology, colposcopy, gastroenterology, dental oncology, psychiatry, and a pain control clinic. The center is designed as an outpatient hospital, since most radiation therapy and many chemotherapy and minor surgical procedures can be performed on an outpatient basis. A patient holding area is available for patients who are recovering from minor surgery or who are undergoing chemotherapy which requires a short stay at the center. Patients may stay in the holding area for periods less than 24 hours, but if they need inpatient care are admitted to one of the local hospitals.

Specialized equipment available at the CRTC includes a full range of diagnostic equipment (with an EMI 7070 whole-body scanner installed in February 1982), a Picker simulator, a Varian Clinac 18 linear accelerator, a Varian 6 MeV accelerator, a cobalt-60 teletherapy machine, an orthovoltage machine, and a superficial therapy machine. Research laboratory and animal holding facilities are also available at the CRTC, with additional animal holding facilities available through the UNM Medical Center Animal Resource Facility.

The CRTC provides education through training rotations for medical students, residents, and interns; conferences, seminars and lectures for medical professionals; a residency program in radiation therapy and fellowships or residency rotations in medical oncology, and gynecologic oncology; and continuing education programs for paraprofessionals.

Outreach programs began in 1973 and are conducted in cooperation with the New Mexico Cancer Control Program. Under the program, teams of oncology specialists from the CRTC, other units of the School of Medicine, and the community, regularly visit New Mexico communities for working tumor boards with local physicians. These conferences are classified for Category IV credit toward recertification of physicians for licensure in the State of New Mexico. Telephone consultation is also available for the state's physicians on a daily basis. In addition to the outreach program and the CRTC's own multidisciplinary tumor boards (held weekly in conjunction with the UNM Hospital), the CRTC is represented at weekly or bi-weekly tumor boards at Lovelace-Bataan Medical Center, the Veterans Administration Medical Center, and St. Joseph Hospital in Albuquerque. It is estimated that through the CRTC's own activity, and through the outreach program and local tumor board participation, the CRTC impacts on approximately 50 percent of the state's cancer patients, who thereby receive the benefit of multidisciplinary consultation.

The New Mexico Tumor Registry, a unit of the CRTC, has been in operation since 1969 and is a participant in the NCI's Surveillance Epidemiology and End Results (SEER) program. The NMTR collects and analyzes the incidence of cancer in the State of New Mexico and the Navajo Nation through the cooperation of hospitals, clinics, physicians, laboratory and radiation therapy centers throughout the region. The New Mexico Health Services Board has designated the NMTR as the official repository for cancer data in New Mexico.

B. Los Alamos National Laboratory, Los Alamos

LANL is a multiprogram national research and development laboratory. It is located on a 7,300-foot-high mesa in northern New Mexico, 35 miles northwest of Santa Fe and two hours by car or 30 minutes by air from Albuquerque (Ross Aviation provides nine round-trip flights per weekday and two on Sundays between Los Alamos and Albuquerque). Los Alamos County, which includes nearby White Rock, has a population of approximately 20,000.

LANL was founded in 1943 to design and build the first atomic bombs. Following the completion of this work and the end of World War II, the United States found it necessary to maintain continued nuclear weapon development. Consequently, Los Alamos continued to function not only as a nuclear weapons laboratory, but also as a basic nuclear science research institution to support its primary role. The laboratory is operated by the University of California, under contract from the U.S. Department of Energy. The principal fields of research today include nuclear, medium energy, plasma, and cryogenic physics; inorganic, physical, and nuclear chemistry; mathematics; metallurgy; earth and life sciences. These scientific disciplines support programs in nuclear weapons design and development, in the use of nuclear energy for the production of electric power, in nuclear safeguards, in controlled release of thermonuclear energy both through magnetic energy confinement and through laser-induced implosions, in development of geothermal and solar energy utilization, in biomedical applications of stable isotopes and meson therapy, in cryogenic applications for electrical energy transmission and storage, in advanced accelerator design and in other advanced instrumentation development and basic research in life sciences including molecular and mammalian biology and flow cytometry.

Laboratory facilities encompass approximately 32 square miles of Los Alamos County, with an investment in plant and equipment of approximately \$600 million. Laboratory floor space totals approximately 5 million square feet, of which approximately 70 percent is dedicated to direct research and development activities.

The Clinton P. Anderson Meson Physics Facility (LAMPF), which is a unit of LANL, is one of the world's largest and most powerful nuclear science facilities. The heart of the installation is a linear accelerator (linac) designed to provide a beam of protons of variable energy up to 800 MeV and an average beam current of 1 milliamperes. It is a scientific community, and provides a new and powerful means for carrying out an extensive program of research over a broad spectrum of scientific interests. It is a tool for the atomic, nuclear and elementary particle physicist, nuclear chemist, radiobiologist, radiotherapist and solid-state physicist, and has important applications in medicine, isotope production, defense science, and the study of the structure of materials.

Groundbreaking for the \$100 million facility was held in February 1968, and the first proton beam with an energy of 5 MeV was achieved on June 10, 1970. The full design energy of 800 MeV was reached on June 9, 1972. In 1974, the first full year of operation, beam was supplied to 65 experiments involving 400 scientists from 56 institutions.

LAMPF consists of a three-stage, high-intensity linear proton accelerator with experimental research areas, installations for radiation therapy and isotope production, and support facilities. The first stage is the proton injector (a Cockroft-Walton generator), the second an Alvarez drift tube accelerator which takes the particles to an energy of 100 MeV, and the third (and longest) is a side-coupled accelerator which carries the particles to 800 MeV. The side-coupled design developed for LAMPF: H^+ ions (hydrogen nuclei or protons), H^- ions (hydrogen atoms with an extra electron), and polarized H^- ions (with the protons spinning in the same direction). Both H^+ and either H^- or polarized H^- beams can be accelerated at the same time. When the particles leave the accelerator, they enter the switchyard, where the particles are directed to various targets to produce new particles: pions, muons, neutrons, and neutrinos--research tools for varied experimental projects. More than 10 experiments can be conducted concurrently at LAMPF in the various experimental areas. Thus, when the accelerator is in its production cycle, the pion biomedical channel is used exclusively (24 hours a day) for biomedical research. Time-sharing with unrelated physics projects, as is required at many major accelerator installations throughout the country, is not necessary for the biomedical users at LAMPF. To date, approximately 90 percent of available biomedical pion beam time has been devoted to this program, although other researchers perform biological and physics experiments when beam time is available and their projects meet the required criteria of scientific merit.

The biomedical pion channel is 33 feet long from target to treatment room. The Pion Biomedical Facility, which houses the treatment room and ancillary laboratory and clinical space and equipment, contains 8500 square feet. Specialized equipment available, most of it purchased under this grant, includes an EMI 7070 whole-body scanner, a Philips Medio 5500 simulator, PDP 11/70 and 11/45 computers (the latter dedicated to treatment planning applications), a small animal holding facility, and an array of physics, biology, and clinical equipment for support of the pion program.

III. ORGANIZATIONAL AND ADMINISTRATIVE STRUCTURE

TBA co-principal investigator will be responsible for supervision of all components and directly responsible for the clinical investigations component. He/she will also direct the work of LANL staff assigned to the program (LANL participates in salary support through a \$25,000/annum purchase order to UNM).

The organizational structure of the pion biomedical program is shown in Figure 4. Christopher Gilman, M.D., Radiation Oncologist, will be based full-time in Los Alamos and serve as deputy for pion clinical investigations. William C. Black, M.D., Chief of Oncologic Pathology at the CRTC, is pathologist of record for the pion clinical trials, and Fred Mettler, M.D., Chief of Diagnostic Imaging at the CRTC, is diagnostic radiologist of record.

Alfred R. Smith, Ph.D., is Chief of Clinical Physics for the program, and James N. Bradbury, Ph.D., is Chief of Developmental Physics. Dr. Smith also holds an appointment as Associate Professor in the UNM Department of Radiology; Dr. Bradbury is Group Leader of the Practical Applications Group (MP-3) of LAMPF. The UNM physics group is charged with clinical physics aspects, and the LANL group with beam development, channel operating systems, and computerized treatment code development. The two units work together as a team on almost all projects. An example is the development of dynamic scanning technology, which involves close interaction among all member of the physics team. Since the pion beam is operated 24 hours a day during treatment cycles, the physics group normally work approximately 50 hour weeks (and sometimes much more) during patient treatment cycles. After the treatment day ends (between 8 p.m. and midnight), physics dosimetry, beam characterization, and other experimental measurements are performed with the beam. The balance of beam time after patient treatment hours is devoted to biology research.

The LANL Medium Energy Physics Division provides additional support (for which no funds are requested from the NCI) to the pion therapy project including:

1. Computer/peripheral purchase, maintenance and repair
2. Magnet and magnet power system maintenance and repair
3. High-intensity target development
4. Fabrication of entrance target triplet spare
5. New slit 1
6. Management/administrative support (0.5 FTE)
7. Secretarial support (0.5 FTE)
8. Senior designer support (0.5 FTE)
9. General engineering support

Biology is under the direction of Mudundi R. Raju, D.Sc., Fellow of LANL's Life Sciences Division and Adjunct Professor of Radiology and Chief of the Division of Radiobiology in the Department of Radiology, UNM School of Medicine. Dr. Raju was instrumental in early radiobiologic and dosimetry experimentation with pions at the University of California, Berkeley, and has been associated with the pion radiobiology program since its inception, with emphasis on studies comparing radiobiologic properties of a variety of particle beams, including pions. A.J. van der Kogel, Ph.D., Research Scientist, will lead the late effects studies with assistance from Robert E. Anderson, M.D.,

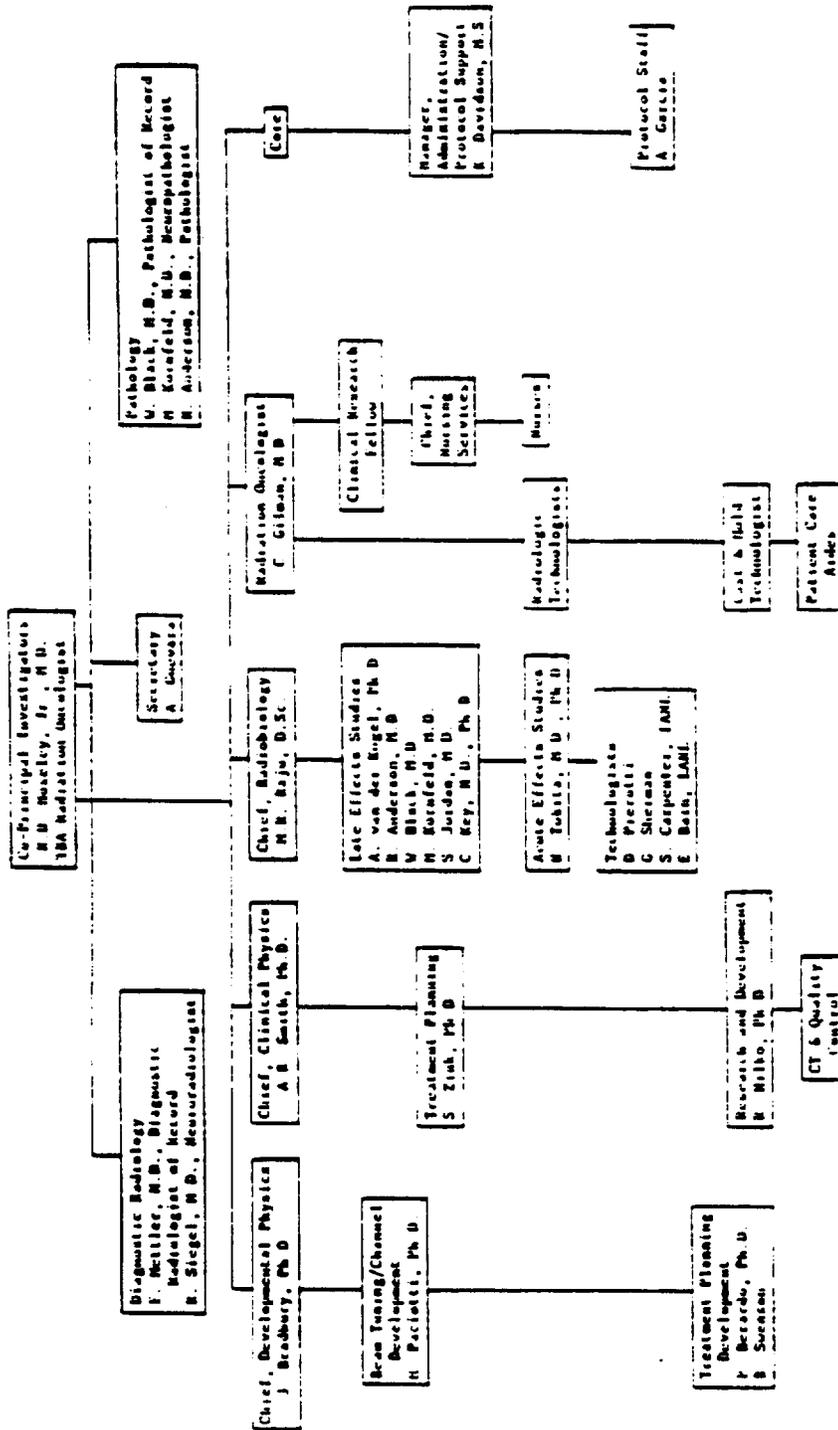


Figure 4. Organizational structure, pion biomedical program

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Chairman, UNM Department of Pathology, along with William C. Black, Mario Kornfeld, M.D., Scott Jordan, M.D., and Charles R. Key, M.D., UNM Department of Pathology. Dr. Black is also Chief of Oncologic at the CRTC, and Dr. Key is Medical Director of the new Mexico Tumor Dr. N. Tokita, M.D., Ph.D., of the LANL Life Sciences Division, is acute effects studies and performing late effects studies on mouse

Administrative officer for the program is Kincaid Davidson, Program Manager. He also supervises the Protocol Support staff, which provides clerical support, data management, patient liaison and counseling, RTOG liaison scheduling, and other services. Technical/fiscal monitoring; accounting; purchasing; personnel management; budgeting; logistic support for staff; patients and visitors; and liaison with LANL, the Los Alamos Medical Center and other organizations contributing to the pion radiotherapy studies are performed by the Los Alamos administrative staff, with documentation channeled through appropriate units of UNM.

The CRTC is a discrete entity within the UNM Medical Center, with independent lines of authority for allocation of funds, space, and personnel for center activities. Physicians and some senior scientist personnel of the center hold joint appointments in the CRTC and the UNM school of Medicine or other UNM academic units as appropriate.

An External Advisory Committee has been appointed by Dr. Napolitano, Dean of the UNM School of Medicine, to provide consultation to the co-principal investigator, and to the leaders of other scientific components of the program. The committee, established in August 1980, is composed of the following persons:

Malcolm Bagshaw, M.D. (Chairman)
Chairman, Department of Radiation Therapy
Stanford University

Luther Brady, M.D.
Chairman, Department of Radiation Therapy
Hahnemann Medical College
(and Executive Director, Radiation Therapy Oncology Group)

Joseph Castro, M.D.
Department of Radiation Therapy
University of California/San Francisco
(and principal investigator of the Lawrence Berkeley Laboratory
Heavy Ion Radiotherapy Program)

George Goodman, M.D.
Medical Director
Cancer Control Agency of British Columbia
(and principal investigator of the TRIUMPF Pion Radiotherapy Program)

David Hussey, M.D.
Department of Radiation Therapy
M.D. Anderson Hospital and Tumor Institute
(and principal investigator of the M.D. Anderson Neutron Radiotherapy
Program)

Moseley, Robert D., Jr., M.D.

Carl von Essen, M.D.
Swiss Institute of Nuclear Research (SIN)
(and principal investigator of the SIN Pion Radiotherapy Program)

Peter Fessenden, Ph.D.
Radiologic Physicist
Stanford University

Meetings are scheduled as needed, but are anticipated to occur 3 to 4 times per year.

IV. PREVIOUS INVESTIGATIONS

A. Summary of Major Accomplishments

1. Clinical Investigations

Clinical aspects of the pion radiotherapy program have focused on performance of clinical trials defining tumor response, normal tissue reactions, and optimal time-dose-fraction relationships for pion irradiation, as well as definition of those disease sites and categories most likely to benefit from pion irradiation and comparison of x-irradiation and pion irradiation for such locally advanced neoplasms.

Phase II studies have been continued, with particular emphasis on treatment of patients with astrocytoma, Grade III or IV, unresectable carcinoma of the pancreas, and squamous carcinoma of the uterine cervix, Stage III and IVA. Limited Phase III trials have been accomplished for squamous carcinoma of the oral cavity, nasopharynx, oropharynx, and hypopharynx; inoperable or locally recurrent adenocarcinoma of the rectum; and T₃/T₄ transitional carcinoma of the urinary bladder. Accessions to these studies to date totaled 154 (147 treated with pions, and 7 randomized to conventional radiation arms of the oral cavity/pharynx, rectum, and bladder studies).

The concept of a Phase III trial is to compare the best experimental therapy with the best conventional therapy. Pion therapy is not yet optimized, since dynamic treatment has not been routinely implemented and since alternative schedules of time-dose fractionation have not yet been adequately explored. Comparison between pion therapy and conventional therapy is prejudicial to the experimental technique until further development of pion therapy has occurred in Phase II investigations.

Referrals for nonrandomized trials have been received in unprecedented numbers. This increase reflects not only an increasing interest on the part of the referring physicians but also a wider base of referral (particularly from Southern California and New York City). An additional aspect of increased patient through-put is the increasing use of pions in treatment of malignant gliomas. Conventional radiation doses of 4000-5000 rad in 4-5 weeks are preceded or followed by treatment of cone-down volumes by 1200-1500 π rad, maximum dose. The possibility of brief (1½-2½ week) boost treatments allows accession of patients throughout the treatment cycle and maintenance of the maximum patient census.

A pilot study of 21 patients with T₃/T₄ adenocarcinoma of the prostate has been completed.

To facilitate interpretation of pion clinical data, a data base system has been implemented that permits sequential compilation and analysis of clinical data being accumulated by the pion project. The data base utilizes eight different forms for initial observation, follow-up reports, and other data. Detailed analyses have been performed with this new system of all previously treated cases with regard to demographic data, staging, previous therapy, treatment parameters, supplementary treatment, survival, local control, and type, timing, and severity of acute and chronic reactions.

A total of 230 patients have received pion therapy, alone or in combination with surgery or conventional radiation through November 1981. Nine patients treated in 1974 and 1976 received randomly assigned x-irradiation or pion irradiation for multiple subcutaneous metastases, a study which established an RBE of 1.4 for pions, compared to 100 kVp x-rays, in acute injury to human skin. Trials with deep-seated tumors began in August 1976, and proceeded with gradual increments in total pion dose and adjustments in daily dose for each new type of tumor and normal tissue irradiated.

Installation of an EMI 7070 CT scanner at the Pion Biomedical Facility in Los Alamos in February 1980 has resulted in major improvements in many aspects of patient care, assuring vastly improved quality control in regard to patient positioning and allowing implementation of a more efficient and accurate treatment planning system. The radiotherapist may now superimpose treatment volumes, skin surfaces, and critical organs directly on CT data by use of region-of-interest software and the diagnostic console, which can be translated into life-sized hard copy for treatment planning. The ability to vary window settings and to superimpose treatment volumes on adjacent slices allows improved delineation of the anatomy of interest. On-site CT scanning also permits confirmation of positioning of bolus, frequent checks of changes in tumor volumes and internal anatomy during the course of therapy, and a method of routine monitoring of inaccessible lesions such as tumors of the brain and pancreas during the follow-up period.

The ability to reproduce patient position at each step of treatment planning from CT scanning, through simulation, to treatment has been thoroughly facilitated by installation of three-point laser set-up systems in the CT scanning, set-up, and treatment rooms, obviating the need for immobilization casts other than for head and neck and brain tumor patients. When needed, immobilization casts are constructed from a fiberglass material (Lightcast II) that hardens under ultraviolet light. The casts are made on the patient, then bisected in the sagittal plane for lateral head and neck treatments to accommodate the vertical pion beam. Special oblique casts are made for specific treatment situations. With on-site CT scanning, appropriate approximations of field centers may be obtained from "scanogram" images, and use of a line-laser system in the CT scanner permits marking and tattooing of the patient's skin indicating the direction of movement through the CT scanner and the plane of the individual scans. These marks permit accuracy in subsequent repositioning of the patient and alignment of beam-shaping devices.

After CT scanning and preparation of bolus and collimator designs, patient and field positions are checked by orthodiagraphic films obtained at final simulation.

Lengthy treatment times and set-ups necessitate patient positioning and alignment of beam-shaping devices in a staging area, thus reducing beam-off time while patients are exchanged within the treatment room. This exchange time is routinely on the order of five minutes. The impact of attention to the technique of patient immobilization, simulation and transport is apparent in the excellent correlation of simulation films with post-treatment port films obtained by orthodiagraphic scanning through the treatment collimator, and in the predictability of in vivo dosimetric measurements, which are obtained in every patient.

All aspects of treatment planning, dosimetric confirmation, channel tuning, and hardware and software interfacing have been implemented successfully in the treatment of several patients with dynamic scanning.

Under current treatment policies, maximum daily doses of 125 π rad are given for most sites, including brain, head and neck, and pelvis. Minimum doses at the periphery of treatment volumes are routinely 80 percent of the maximum dose. A brief experience with treatment planning to a minimum of 90 percent resulted in greater acute and chronic normal tissue reactions, presumably related to the increased volume of normal tissue receiving relatively high dose irradiation, and has been abandoned. A notable exception to the routine daily dose of 125 π rad is in the treatment of pancreatic carcinoma. For these patients, 160 π rad is given daily in two treatments divided by a minimum of six hours. One hundred π rad maximum is given to a volume encompassing the entire pancreas, tumor, and regional nodes through AP:PA opposed ports, followed at six hours by an additional 60 π rad maximum through an anterior portal to the site of radiographically demonstrable disease. A total of 3840 π rad is delivered to the site of gross disease in 4 weeks, followed by an additional 2400 rad/3 weeks photon irradiation to the entire liver, pancreas and tumor. The other example of routine combination of conventional and pion irradiation is in the treatment of malignant astrocytomas, in which conventional megavoltage irradiation of the whole brain to doses of 4200-4500 rad/4-5 weeks is combined with pion irradiation of cone-down volumes to doses of 1200-1500 π rad maximum in 2-3 weeks.

This application details clinical observations of 196 patients who have received pion irradiation, with particular emphasis on a group of 129 patients treated with curative intent and followed for a minimum of one year. A group of 33 patients treated between June 1980 and November 1980 is included in the analyses of survival, local control, and acute reactions, but excluded from the analysis of late effects due to inadequate follow-up time. Excluded from the total analysis are 23 patients treated since January 1981 (due to inadequate follow-up time), 9 patients treated in Phase I trials for cutaneous metastases, 15 patients with known distant metastases at time of treatment, and 20 patients receiving fewer than 2700 π rad maximum, that dose at which complete tumor regression was first noted, for reasons including deliberately planned low doses in conjunction with Phase I studies, machine malfunction, and interruption of treatment for medical reasons.

The distribution of 130 tumors treated with curative intent before November 1980 according to treatment modality includes 90 tumors (89 patients, one with simultaneous but histologically distinct prostate and bladder primaries) treated with pions alone, 29 tumors treated with pions plus external radiation therapy and/or implant, and 11 patients treated with pions plus surgery. Except for six patients receiving cone-down pion irradiation to the brain, all patients received a minimum of 2700 π rad. Only 49 were treated to dose levels currently thought to approximate tolerance doses of relevant normal tissues (approximately 4500 π rad in 35 fractions/7 weeks).

Crude survival statistics for the group of 129 patients treated with curative intent are: head and neck, 42 percent (16 of 38 patients); brain, 39 percent (14 of 36 patients); prostate, 90 percent (19 of 21 patients); pancreas, 31 percent (5 of 16 patients); and other miscellaneous sites, 53 percent (10 of 19 patients).

Local control in pion patients treated with curative intent is as follows: head and neck, 50 percent (19 of 38 patients); brain, 17 percent (6 of 36 patients); prostate, 90 percent (19 of 21 patients); pancreas, 0 percent (0 of 16 patients); and other miscellaneous sites, 53 percent (10 of 19 patients). Local control is scored in the case of glioma only if the patient has stable neurologic symptoms, no steroid dependence, and no evidence of contrast enhancement or mass effect on CT scan. Local control is scored in the case of pancreatic carcinoma only if there is resolution of tumor mass as documented by CT scanning or autopsy confirmation.

Acute reactions recorded for the group of patients treated with curative intent are scored on a scale of 0-4 as follows: 0 - nil; 1 - skin erythema, mucosal injection, mild dysuria or diarrhea \leq 4 stools per day, etc.; 2 - dry desquamation, patchy mucositis, moderate dysuria, diarrhea with mucus ($>$ 5 stools per day), etc.; 3 - moist desquamation, confluent mucositis, severe dysuria with bladder spasms, diarrhea with blood, etc.; and 4 - acute necrosis. Average acute reaction scores were obtained by summing severities of all reactions for individual anatomic sites as follows: head and neck - mucosa, skin, salivary glands; pelvis - skin, rectum, bladder; thorax - skin, dysphagia; abdomen - nausea, diarrhea; brain - skin, and dividing by the number of scoring criteria for each category. For dose ranges $<$ 4000 π rad/(versus) $>$ 4000 π rad the average acute reaction scores were; head and neck, 1.7/1.9; pelvis, 1.4/1.6; thorax 1.2/1.5; abdomen, 0.9/1.1; brain, 1.1/1.5. The analysis shows a trend to more severe reactions at all sites in the higher dose range, although these data ignore such potentially contributory factors as dose per fraction, hyperfractionation, and volume. The average acute reaction score in 11 patients (10 with carcinoma of the head and neck and one with stomach cancer) receiving more than 5000 π rad maximum was 2.2.

Seventeen patients treated with pions were subsequently scored as having severe chronic reactions (Grade III or greater, according to the late effects scoring system of EORTC/RTOG). Only four of these patients had such chronic effects related to pion irradiation alone. Case [redacted], a [redacted]-year-old female had chronic, severe laryngeal edema after 5000 π rad for a T₄ squamous carcinoma of the larynx. Patient [redacted], Case [redacted], had severely symptomatic pulmonary fibrosis after 4000 π rad for a large adenocarcinoma of the lung. Patient [redacted] (Case [redacted]) developed necrosis of a portion of the pharyngeal wall four months after 4600 π rad for a T₃N₂M₀ squamous carcinoma of the base of the tongue. Patient [redacted] (Case [redacted]) received 4950 π rad in 140 π rad increments for a large pelvic recurrence of cloacogenic carcinoma of the anus. Ten months later he developed small bowel obstruction and bleeding necessitating ileostomy.

Average chronic reaction scores have been determined for various treatment sites in a population of patients receiving pion irradiation alone and followed for a minimum of one year. The analysis for doses $<$ 4000 π rad/(versus) $>$ 4000 π rad showed: head and neck, 0.7/0.9; pelvis, 0.5/0.9; and other sites, 1.4/0.7.

The group of patients receiving therapy for pelvic primaries has been analyzed for chronic effects as related to treatment planning policy, i.e., whether the minimum tumor dose was determined as 80 percent or 90 percent of maximum. The average chronic reaction score for patients treated at 80 percent is 0.6 (n = 6), while it is 1.2 (n = 3) for those treated to 90 percent. All patients received 4000-4500 π rad at 115-125 π rad per fraction. Four

patients treated with pions alone for prostate cancer had rectal bleeding at 9-12 months after therapy, and two, both treated at 90 percent, developed mild to moderate rectal strictures after 4500 π^- rad in 125 π^- rad fractions. These data suggest that in the dose range above 4000 π^- rad, chronic injury increases disproportionately in comparison to acute injury and may manifest itself only after periods of 9-12 months.

2. Physics

a. Beam tuning and channel development. The catalog of broad beams for static treatments has been expanded to provide fields with transverse dimensions up to 20 cm at each of three momenta corresponding to nominal depth penetration of 12 cm, 16 cm, and 23 cm. Fan beams for dynamic treatments have been prepared at several channel momenta, and extensive beam tuning and dosimetry have been performed. Measured beam data have been provided for PIPLAN, with particles identified by position, angle, momentum, and type, i.e., pion, muon, or electron. An experimental method has been developed for detecting muons resulting from pion decay, using multiwire proportional counters located before and after the beam-shaping section of the channel. Analysis of these data has been facilitated by the use of a ray-tracing code. A new pyrocarbon target has been installed in the biomedical channel, and is considered nearly optimum for high-intensity operations. The target can be set by the operator to maintain constant electron contamination. A multiwire chamber has been constructed and tested for use as a beam profile monitor.

Considerable dosimetry has been directed toward providing characterization for a large variety of patient beams: broad, essentially parallel beams for static treatment; beams focused in one dimension and broad in the perpendicular dimension for one-dimensional dynamic treatment; and beams focused in two dimensions for two-dimensional dynamic treatment. For the static beams, three beam sizes (small, medium, and large) have been developed and characterized for each of three penetrations. Target volumes requiring larger field sizes are treated with combinations of abbutted fields.

Dose rates for the pion therapy beams are a function of beam momentum, the beam tune (size) for a given momentum, and the size of the spread peak region. Typical dose rates for the beams in use range from .02 to .03 rad/min/liter for each microampere of proton beam current on the biomedical pion target. In the summer of 1982, the proton beam current will be raised to 750 microamperes, resulting in about 600 microamperes of proton current on the biomedical pion target, yielding dose rates from 12 to 18 rad/min/liter. The design current for the LAMPF accelerator is 1000 microamperes. The average treatment volume is about two liters for single parallel-opposed fields (abutting) during each treatment cycle, so that the overall average treatment volume is probably closer to 2.5 liters.

b. Development of range-modulation functions. The narrow Bragg peaks of the pion beams are spread in depth by the use of a dynamic range-shifter. The range-shifter is computer controlled and can be programmed to produce spread peaks of varying dimension and shape, ranging in depth from 3 to 14 cm in 1-cm intervals. A series of such range-modulation functions has been developed for each momentum (148, 167, and 190 MeV/c). This is necessary because the peak-to-plateau ratio, beam contamination (electrons and muons), and momentum spread (resulting in differences in the full-width-half-maximum of the spread peak) are different for each momentum. For each spread peak it

is possible to tailor the slope of the physical dose, and consequently the distribution of stopping pions. It is possible to produce spread peaks with uniform total dose, uniform high-LET dose, or uniform biologically effective dose.

The range-modulation function describes the thickness of a bellows-controlled column of oil in the beam path versus time. The range-modulation development code takes measured, central-axis, unmodulated total and high-LET distributions, and applying time-weights, offsets each curve by prescribed shifts in depth; sums all the offset curves together; and renormalizes to obtain the resultant modulated total and high-LET depth-dose curves. The program then uses an RBE model to calculate the effective dose. The range-modulation functions have been completely redesigned, based on data obtained from gel-tube cellular experiments designed to measure cell-killing uniformity, so as to accomplish greater uniformity in biological effect for single-field treatments and to confirm biological uniformity of treatments performed with opposed, overlapping portals.

c. Dosimetry. An automated data-acquisition and analysis system has been developed for dosimetry measurements on the pion therapy beam using a PDP-11/70 computer and CAMAC interface. A multiple ionization chamber array (MICA) system, with associated software control, has been developed for dosimetry measurements. This system increases dosimetry data-acquisition rates by a factor equal to the number of data channels in use. The system has been tested and used with a linear array of 10 ionization chambers.

The object of patient dosimetry is to determine the central-axis depth dose and the output calibration (rad/monitor unit) at the maximum of the peak dose, using the beam tune, range-modulation function, and collimator assigned to a particular patient field with the geometry (air gaps) between appliances and between the collimator and water phantom the same as that expected for the actual patient treatment. The channel is calibrated each morning, and daily treatments are adjusted to this calibration. The depth-dose curves are used as input to a code which uses the collimator geometry, multiple scattering, beam emittance, and uncollimated beam dosimetry to calculate isodose distributions, in water, for a plane corresponding to a CT slice in the patient. These isodose distributions are then folded into the bolus design and CT data to calculate an isodose distribution on the patient. In addition to specific patient treatment measurements, routine measurements are also made to determine the integrity (constancy) of the individual beam tunes used for patient treatment.

To eliminate a large fraction of the manpower and beam time used in the measurement of dosimetry for each patient field, a project of extensive measurements has been undertaken from which models will be extracted that will predict the depth dose for any given beam tune, collimator, and range-modulation function. Depth-dose curves can be calculated for any collimator size, taking into account the neutron spectra produced by pions stopping within the collimator. This process then results in a calculated depth-dose distribution for any spread peak using any collimator opening.

Accurate microdosimetry data are required as input to the algorithms used in the calculations of RBE, pion effective dose, and range-shifter functions. Such data are obtained from a variety of experimental techniques, including Rossi chamber proportional counters, solid state detectors (totally

depleted lithium-drifted silicon), and aluminum activation measurements. Rossi chamber measurements are used as the primary source of microdosimetric data, but are time-consuming. Therefore, one or two Rossi chamber spectra are obtained for each beam tune, and additional data are obtained from either solid state detectors or aluminum activation, both of which permit rapid data collection. These are normalized by comparison with the Rossi chamber data to obtain complete information on the spatial variations of high-LET dose for all therapy beams.

To tailor beams for individual treatment situations, studies have been performed of the effects of inhomogeneities, compensating bolus, collimation and air gaps between patient treatment devices. To realize the beam-shaping advantages of pions, the influence of tissue inhomogeneities upon the dose distribution must be understood so that adequate compensation can be made to shape the stopping pions in the direction of the beam. Beam shaping in the transverse dimensions for patient treatments is achieved by use of collimators individually designed for each patient. The penetration of the beam to the distal surface of the treatment volume can be controlled by using bolus, designed to compensate for all geometrical and tissue inhomogeneities in the beam path. The proximal edge of the peak dose is controlled by properly modulating the pion peak width using a range-shifter.

Measurements have been made for inhomogeneity and bolus compensation for pion beams of different energy; variation of the inhomogeneity depth beneath the surface; air and Teflon inhomogeneities to simulate lung and bone; bolus compensation using a parallel beam model; and bolus-inhomogeneity misalignment. Such measurements have shown it is possible to predict the effect of inhomogeneities and to compensate for these effects in treatment planning. In designing patient bolus, one must compensate for skin contour, tumor shape, tissue inhomogeneities, movement of anatomy due to breathing, and changes in anatomy due to fluctuations in bowel gas, and bladder or rectal filling. At present, anatomy changes are handled by prescribing target volumes that will encompass expected deviations. Considerable effort has been expended to develop casting and immobilization techniques that minimize patient movement during treatment and that reproduce the treatment positions from day to day.

Stopping pions give rise to a variety of secondary charged particles by virtue of their interaction with, and subsequent fragmentation of, the nuclei of the stopping material. Ionization chambers have become the principal instruments employed for determining the absorbed dose in tissue, but require conversion factors that rest on physical interpretation of the energy absorption processes and involve such considerations as secondary charged particle spectra, relative stopping power ratios, the energy required of secondary charged particles to produce ion pairs in various gases, and corrections for non-tissue equivalence of chamber walls. Precise information required for these interpretations and considerations is not well known for charged particle beams, giving rise to uncertainties (~10 percent) in the specification of the absorbed dose in tissue from pion beams when ionimetry is used. Calculations of the conversion factor for the cylindrical chambers currently in use have been checked by direct comparison of the ionization chambers with a calorimeter. Measurements were obtained in various positions of modulated and unmodulated negative pion beams. The differences between two experiments conducted a year apart, using a different calorimeter and using a different electrometer for the ionization chamber measurements, are within experimental uncertainty, and no systematic differences have been detected in

the data. Based on comparison of these experimental results and recommended values resulting from them, with the values that have been used for patients since June 1976, changes in our current statement of absorbed dose in TE plastic cannot be justified.

For biological experiments requiring special small-volume beams, custom collimators and/or bolus have been fabricated for each experiment, and dosimetry has been performed using a combination of ion chambers and thermoluminescent detectors. Microdosimetric measurements have also been made to aid in the interpretation of results.

d. Treatment planning

i. Previous methods of treatment planning. Treatment planning for patients with and without the aid of CT scans has made it apparent that adequate treatment plans cannot be developed without the use of CT scan data. CT scans allow a three-dimensional tumor treatment volume to be uniquely prescribed by the radiotherapist, nearby critical structures to be placed in their proper perspective, and dose delivered to normal tissue to be minimized. Information concerning the longitudinal dimension (parallel to direction of incident beam) of the treatment volume can be obtained only from CT scans, by relating CT numbers to pion stopping powers. Probably the most useful information obtained from CT scans is the quantitative description of inhomogeneities.

When a patient is accepted for pion therapy, the first procedure is to prepare an immobilization cast of the patient to be used during CT scanning and treatment. CT scans are taken at 0.9-cm intervals throughout the volume of interest. All scans are numbered in reference to a tattoo for each series of scans. After CT scanning the CT slices are displayed on a CT diagnostic console. The physician delineates, by means of a tracking ball, the skin contour, target volume, and critical normal structures. These regions of interest (ROI's) are overlaid and stored on the CT data. The magnetic tape containing CT scan data is read into the bolus design computer file. Additional input data are the appropriate beam penetration and range-shifter function. The bolus (Lucite) required to stop the pions at the prescribed target volume boundary is then calculated automatically by the computer programs from examination of the CT data, and is printed life-size on a plotter. These series of bolus templates are traced on a 0.9-cm-thick Lucite sheets, cut out on a band saw, and glued together using as reference a common axis drawn on each bolus design to form the three-dimensional bolus. Collimators are designed directly from treatment volumes prescribed on each CT slice. The collimator thickness is governed by the beam momentum and may vary from 2.5 cm to 5.0 cm of low-melting-point alloy.

Presently, patient isodose contours are calculated from dosimetry measurements that simulate the patient set-up. Dosimetry includes a central-axis depth-dose scan, a transverse scan at mid-peak, and a peak dose calibration for each static beam pion port. Isodose distributions are calculated in the plane perpendicular to the central axis. The calculated isodose distributions are then folded into the bolus design and patient CT data files to produce patient isodose distributions for any CT scan that the therapist wishes to evaluate. Calculations for several slices in the treatment volume are done to evaluate the dose to adjacent critical structures.

ii. PIPLAN--Three dimensional treatment planning code.

Dynamic treatments require the use of the three-dimensional treatment planning code, PIPLAN. This code utilizes a ray-tracing model where actual pion trajectories in the three-dimensional volume represent pencil beams. PIPLAN calculates a dose distribution by summing the contributions of individual pencil beams as they pass through various parts of the anatomy (determined by CT scans) and clinical appliances. The dose distribution for a pencil beam is predetermined analytically in water as the sum of its separate components, including the effects of in-flight interactions and straggling. This dose is distributed in depth as a function of water-equivalent range along the trajectory, and radially as a function of multiple Coulomb scattering (which is both geometry and energy dependent). Distributing this dose entails accumulating at each point of interest the relative amount of dose at that point from each pencil beam. Because the treatment beams contain spatially nonuniform ratios of pions, muons, and electrons, and because each particle type has a distinctly different dose distribution, separate calculations are required for each particle type. To model an actual beam, then, requires an accurate phase-space representation of pencil beams. PIPLAN uses individually measured trajectories for each beam tune, with the spatial coordinates, angles, momentum, and particle type identified.

To improve the accuracy of PIPLAN, considerable effort has been devoted to development and incorporation of sophisticated models for beam smoothing, neutron dose due to in-flight interactions in the plateau as well as in the peak region, multiple scattering through tissue inhomogeneities and air gaps between treatment appliances, range-modulation effects, external appliances effects (notably neutrons produced from pions stopping within the collimator), improved spatial resolution, and contour processing. A new computer code was written to reconstruct the same kind of image as digital x-ray radiography from integrated CT images, and automatic methods and algorithms have been developed and implemented to transcribe CT-scanner ROI's to vector contours in treatment planning programs. A new display capability was developed to superimpose pion dose distributions on patient CT data on the CRT of the EMI 7070 scanner. Two supporting libraries were completed: a beam-tune library and a range-shifter-function library. New models were also installed to account for the dose deposited by electrons from muon decay in the patient and by muons from pion decay both in the beam channel and the patient. Improvements to the casefile system, where all treatment-planning data for a given patient are collected; in resolution and reduction of CT data; and in folding CT data into pion dose calculations were also implemented. By the summer of 1982 it is expected that PIPLAN will be capable of performing, in one 3-D calculation, all the capabilities of the 2-D programs and the associated manual treatment-planning operations. This projection applies for both static and dynamic treatments and includes automatic appliance design, range-shifter function selection, patient orientation, positive pion beams, and effective dose. Extensive experimental comparisons will be made for verification, especially for dynamic treatment.

iii. CT scanner. An EMI 7070 whole-body CT scanner was installed in February 1980 in the LAMPF biomedical area, and patient scanning began in March. During the period March 1980 to March 1981, the scanner software and hardware were updated several times. In March 1981, the machine was accepted after having passed all acceptance tests. In February 1982, a second EMI 7070 was installed by UNM in the CRTC in Albuquerque.

e. Treatment delivery and verification

i. Patient immobilization, alignment and transfer systems.

These systems have undergone several changes during the past three years, but the basic approach has remained the same: (a) the patient must maintain the same position, and this position must be easily reproducible during CT scanning, simulation, set-up, and treatment, and (b) patients must be set up outside the treatment room so that beam time will not be wasted.

The basic components of the immobilization system are orthopedic casting materials and vacuum bags. Casts are used for patients receiving treatment to the head and neck or the brain, while all other patients are immobilized with vacuum bags alone. New laser alignment systems have been installed in the CT scanner room, simulator room, set-up area, and treatment room, and provide for precise reproduction of patient positioning in every area. During the past year, the mechanism for supporting and aligning the patient bolus was completely redesigned. New treatment tables have been installed on the two treatment modules, and an identical table has been installed in the simulator room.

ii. Dynamic treatment. A method for delivering pion doses to deep-seated tumors that provides greater normal tissue sparing than does the static treatment method has been developed and is designated the "dynamic treatment mode." Implementation of this method of treatment has required the development of special beam tunes in the pion transport channel, new treatment hardware, and a special computer-microprocessor-based control system. In addition, methods of treatment planning and dosimetry have been modified to accommodate this new treatment mode.

Two modes of dynamic treatment have been proposed, one using a "fan" beam and another using a "spot" beam. The dynamic "fan" mode one-dimensionally scans the patient across a highly focused beam, which is narrow in the y-dimension and broad in the x-dimension. The ability to vary the range modulation as the patient is scanned along y allows beam shaping of the peak dose in the y-z plane, but not in the x-z plane. In addition, the ability to control the weighting of each scanning position permits the dose profile in the y-scanning dimension to have improved uniformity. The dynamic "spot" mode two-dimensionally scans the patient across a beam moderately focused and narrow in both x- and y-dimensions. The ability to vary the range modulation as the patient is scanned results in complete removal of constraints on the width of the dose peak in the z-dimension at each x-y position. Also, the dose profiles in both x and y will have improved uniformity with proper weighting of the scan positions. The dynamic "fan" treatment mode has been implemented, and three patients have received part of their total treatment with this technique. The weight of each step in the treatment is adjusted for changes in RBE for peaks spread to different dimensions, taking into account the difference in both the neutron and charged particle components of the high-LET dose. Measurements thus far have confirmed the treatment plan to be accurate within 5 percent.

The next step in the development process is to implement dynamic "spot" scanning in which the patient is scanned in two dimensions, thus allowing for beam shaping in three dimensions. It is planned ultimately to have all three types of treatment available. Patients will be treated by whatever mode best suits the needs of that particular treatment.

iii. In vivo dosimetry. In vivo measurements are routinely taken on pion therapy patients, with a small-volume ionization chamber. These include skin dose at the center of the treatment field and at the edges of the target volume projected to the skin surface. For whole brain irradiations, measurements are taken on both eyes during treatment with right and left lateral fields. Whenever possible, measurements are also taken at various places in the nasal and oral cavities of head and neck patients and in the rectum of patients receiving pelvic irradiations. On occasion, thermoluminescent dosimeters are also used to measure the total dose, and aluminum pellets are used to measure the high-LET dose.

Thermoluminescent dosimetry (TLD) is also used extensively to verify treatment plans, especially for dynamic treatment, in a water phantom under conditions that simulate actual patient treatment. Because a large number of dosimeters are exposed at one time, the required read-out time is considerable. For greater efficiency, the read-out system has been automated.

iv. Positron visualization of stopping pion distribution. The method of positron emission tomography for visualizing the stopping distribution in patients irradiated by negative pi mesons is under investigation. Five problems have been studied: (a) the correlation of positron activity with stopping pions, (b) the effects of biological diffusion of positron emitting isotopes from the production site, (c) the development of an experimental positron imaging system, (d) the evaluation of the system using animals, and (e) the clinical evaluation of the system on patients. Preliminary measurements with a positron detection system on patients with lesions of the pancreas, rectum, head and neck, and lung indicate that diffusion rates of activity from these sites should not be a limiting factor in measurements. Three NaI crystals have been purchased and will be used to test the feasibility of a low-cost one-dimensional Anger camera for positron detection. Hardware tests for determination of detector configuration to provide for optimal resolution are in progress, as is software development for the data acquisition system.

f. Systems operation, development, and maintenance. A pion production target capable of withstanding very high power density has been designed and installed. A computerized control system is used for control, monitoring, and data acquisition (where appropriate) of all channel hardware, and for treatment couch motion in dynamic scan treatments. A new air-operated channel beam plug has been designed, fabricated, and installed in the channel.

The channel control computer was upgraded from a PDP-11/45 to a PDP-11/70 with associated improvement in mass storage devices. The PDP-11/45 has been dedicated to treatment planning (with backup for peak periods possible on the 11-70). Both systems are interconnected with a DECNET communications link and operate under an RSX-11D operating system. The CAMAC parallel highway system has been upgraded, and a DEC graphics subsystem with a PDP-11/04 microprocessor has been attached to the PDP-11/70 computer. The RSX-11D operating system was modified to improve central processing unit (CPU) utilization by the addition of background priorities for calculational programs which would otherwise place too heavy a load on the machine to co-exist with patient treatment procedures.

An improved range-shifter (for either backup or routine use) was fabricated and is currently under test. Mechanical redesign of the Philips treatment couch feedback encoders has vastly improved couch reliability during dynamic treatments. Gray scale encoder linkages for the Philips treatment table have been redesigned for increased mechanical resolution and reliability during dynamic patient treatments.

A data base system to aid in analysis of clinical data being accumulated by the pion project has been acquired, modified, and installed on a VAX computer at LAMPF. It is an interactive system, accessed by a dial-up terminal from the Pion Biomedical Facility. The system, DATARIEVE, uses an English-like command language combined with interactive data input to make an easily used data base system for those whose expertise does not normally include computers, i.e., physicians and other health care workers.

3. Biology

Radiobiological studies of pion irradiation in both in vivo and in vitro experimental systems have been undertaken under the direction of Dr. Mudundi R. Raju of the LANL Life Sciences Division. His group is involved in the performance of detailed studies of the biological characteristics of the beams used in clinical applications. Cell culture studies have focused since that time on the gel-tube system, which is believed to be a more sensitive indicator of biological change than are multicellular tumor spheroids used previously. Results with all these systems have been reported (Yuhas et al.⁶⁰).

Using a sensitive gel-tube suspension system (Raju et al.), cell-killing across the range-modulated peak for various beam tunes was examined, along with differences in RBE among beams of different peak widths of a given beam size and differences in RBE among pion beams of different sizes but of a given peak width.

The data showed uniform cell-killing across the peak of a pion beam of 14-cm peak width, of a tune (16B) designed for uniform biological effectiveness from previously developed biological models, and identified variations in cell-killing across the peak of other beams with varying slope in physical and high-LET dose designed for use with opposed, overlapping portals. Effects of collimation on cell-killing with these beams were also identified. For Tune 16B, studies indicated that biological effectiveness decreases with increasing peak width (ranging from 6 to 14 cm).

Studies with a constant peak width, but varying beam size, did not indicate significant differences in cell-killing when beam size was altered by collimation or channel tuning. Preliminary experiments have been done using fractionated doses of pions on the mouse intestinal crypt cell system to see if the biological effects of fractionated pion exposures depend upon beam size when peak width is kept the same. The results indicated that the large size beam was slightly more effective than the small size beam.

In in vivo studies, mice bearing the MCa-11 mammary tumor were exposed to graded total doses of high-intensity peak pions or x-rays either as single fractions or as three daily fractions. Delay in growth analysis showed that pions were 1.2 to 1.4 times more effective than x-rays in single-dose studies, and that delay induced by three daily doses of pions was almost as

large as that induced by single pion doses, while that for x-rays showed far greater tumor recovery from fractionation.

Late effects studies on kidney have been conducted with 1, 2, and 5 fractions, and resulted in RBE's of 1.18, 1.33, and 1.44, respectively. Studies with 15 fractions are in progress. Spinal cord injury studies with 1, 5, and 15 fractions were initiated, and animals were observed weekly for signs of paralysis, for up to one year post-irradiation. The RBE for pions was shown to increase from 1.3 for single-fraction exposure to 2.1 and 3.2 for 5 and 15 fractions, respectively. Fractionated studies with as many as 10 fractions have been completed on the colon and rectum in rats. The high total doses required for the 10-fraction experiment (2500-7000 rad) proved to be problematic, as most animals in the high-dose groups died due to overexposure of the gut before long-term colon effects could be assayed. Consequently, the experiment was repeated using an improved collimator design, and results are being analyzed. These late effects studies have all been performed with small pion fields with high dose rates but limited clinical applicability.

Mechanism studies have explored effects of positive pions versus negative pions, with results indicating that the "star" formation by pions is largely responsible for the reduction in threshold seen with negative pions versus x-rays or positive pions (which have no high-LET component); and radioprotection of cysteine against effects of negative pions, demonstrating that cysteine is nearly as effective in protecting against pions as against x-rays.

4. Core

Mechanisms for billing appropriate medical costs for pion patients to third party providers have been streamlined to maximize recovery of costs at rates comparable to those for routine radiotherapy, improving the rate of reimbursement to the grant for appropriate expenses.

Facility improvements have been provided by LANL with funds from the U.S. Department of Energy, including modifications to the Pion Biomedical Facility to house the EMI 7070 whole-body CT scanner and peripherals and an expanded treatment planning area, the installation of a prefabricated building for additional office space and conference space, and new air-conditioning, fire alarm and smoke detector systems.

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C. Projects Discontinued, Modified, or Completed

1. Clinical Investigations

a. This application encompasses no plans to initiate new randomized trials, and protocol planning emphasizes development of additional well-designed Phase II pilot studies to determine those sites for which Phase III studies are best warranted. New sites added to those already under study are inoperable epidermoid carcinoma of the lung and advanced, inoperable carcinoma of the esophagus.

b. Recent radiobiological evidence (Fowler, personal communication) suggests that if tumors can be identified which have not re-oxygenated very well, they should be selected for clinical trials of high-LET radiation and not all the tumors from a particular site. A simple technique to accomplish this would be to look at the size of a tumor, preferably by CT scanning half-way through treatment. If it has regressed well, assume it's reoxygenating well and continue treatment with standard photons. If it has not regressed, continue the pilot study with pion radiotherapy. Such a protocol would assist in optimizing patient accession and complete utilization of pion beam time.

c. Shorter overall fractionation times should be investigated with pion and other high-LET beams (Fowler, personal communication) since reoxygenation has less effect and since differences between early and late injury are less marked than with photons. The possibility of using 10 or 12 fractions of pion radiation would also improve beam utilization and will be explored. Such small numbers of fractions are currently being used with neutron radiation (Hammersmith and Fermilab) with satisfactory results. Short schedules with doses per fraction, not exceeding about 400 rad photon equivalent, is going to be tried with neutrons and could, even more safely, be tried with pions.

d. An amendment to RTOG 79-23 (nonrandomized pion therapy of advanced/recurrent neoplasms), approved in July 1979, allows the planned combination of pion irradiation as boost therapy with conventional irradiation of more generous volumes. Conventional radiation doses of 4000-5000 rad in 4-5 weeks are preceded or followed by treatment of cone-down volumes by 1200-1500 rad of peak pions, maximum dose. An advantage of this treatment plan is that the benefits of dose localization and normal tissue sparing can best be used for localized volumes. The number of lengthy, multi-port treatments of the whole brain using pions can be reduced, and the beam time can be used in treatment of more patients with localized, critical volumes. The possibility of brief (1½-2½ week) boost treatments also allows accession of patients throughout the treatment cycle and maintenance of the maximum patient census.

e. Treatment of pancreatic carcinoma has been radically revised, in light of early experience with 18 cases, most of whom succumbed to distant metastases and received relatively low doses as we were working toward a tolerance dose. Pancreatic tumors are now being treated with higher doses of pion radiation to the primary and nodal drainage area, preceded or followed by prophylactic large field conventional irradiation to the liver and pancreatic bed (including peripancreatic nodes). Patients are accepted only after meticulous evaluation for metastatic disease, including surgical staging with wedge biopsy of the liver and a sampling of the primary tumor mass and peripancreatic, periaortic, and mesenteric nodes. In addition, to avoid delays and undesirable breaks in therapy, most patients require biliary and GI bypass procedures at the time of original exploration.

f. An External Advisory Committee has been established to advise the principal investigator (see Section III). This committee supersedes the Committee on Human Trials of Pion Radiation Therapy, UNM/LASL, which formerly was both an advisory group and a referral group for the pion studies. Previous experience has demonstrated that strong referral relationships were not established as a result of membership on the Human Trials Committee but have developed over the years as physicians have referred cases and expressed a continuing interest in the program. Further, the most fruitful scientific guidance has been obtained from radiotherapists, physicists, and biologists knowledgeable about particle radiation. Thus, the External Advisory Committee is primarily a scientific advisory body, while other mechanisms have been established to maintain ties with referring physicians, who are often surgeons or other specialists rather than radiotherapists

2. Physics

- a. The pion patient data base system has been installed and is fully operational.
- b. A complete catalog of static pion beams has been designed and fully characterized.
- c. Single-chamber dosimetry system software and hardware are completed and in routine operation.
- d. Patient alignment and transfer systems have been designed, fabricated, tested, and modified, and are now in routine use.
- e. EMI 7070 whole-body CT scanners are available at the CRTC/Los Alamos and the CRTC/Albuquerque.
- f. Hardware and software systems for implementation of dynamic treatments have been designed, tested and implemented. Further development and modifications are planned as described in Section V-B.
- g. A new PDP-11/70 computer has been installed at the Pion Biomedical Facility and linked to the PDP-11/45 via a DECNET data transfer system.
- h. A new biomedical target assembly has been designed and installed.
- i. In vivo dosimetry systems for read-out of TLD and aluminum activation pellets have been installed.
- j. Two-dimensional treatment planning systems are completed and are in routine operation.

3. Biology

- a. The in vitro system for studying biological effectiveness across the modulated peak of various pion beams used for patient treatment has been changed from single cell suspensions and multicellular tumor spheroids to the gel-tube system, as it appears to be a much more efficient and sensitive indicator of cell-killing.
- b. Biological characterization of the radiobiological effectiveness of some of the pion tunes and peak widths in routine use with static treatments has been completed, and data have been incorporated into beam range-modulation functions.
- c. New biological assays for CNS, kidney, and lung are being explored as part of the late effects studies (see Section V-C).

4. Core

- a. The operation of the Los Alamos administrative office has been reorganized so that it is under a program manager with sole responsibility

for pion activities, rather than an administrative officer for all CRTG research programs.

b. Development of a pion protocol manual, pion procedure manual, slide show, slide cataloging system, information packets for referring physicians and potential referring physicians, financial guidelines for patients, and other similar materials have been completed, and will be modified as the need dictates in the future.

V. RESEARCH PROJECTS AND CORE COMPONENT

A. Clinical Investigations

1. Investigators

<u>Name</u>	<u>Title</u>
Robert D. Moseley, JR., M.D. TBA	Co-Principal Investigator, UNM Radiation Oncologist, UNM
William C. Black, M.D.	Chief, Oncologic Pathology, UNM
Mario Kornfeld, M.D.	Neuropathologist, UNM
Robert E. Anderson, M.D.	Chairman, Pathology, UNM
Fred Mettler, M.D.	Chief, Diagnostic Imaging, CRTIC/UNM
Robert Seigel, M.D.	Neuroradiologist, UNM

2. Introduction

a. Objective. Clinically, this project is designed to study systematically the applicability of negative pi meson radiotherapy in the eradication of locally advanced human neoplasms that are not satisfactorily managed by conventional therapeutic modalities. This objective requires development of optimal techniques of treatment, definition of appropriate time-dose-volume relationships as related to response of a variety of normal and neoplastic tissues, and collection and analysis of clinical data as the basis of a rational decision-making process regarding wider development of such therapeutic technology in the interest of the public health.

b. Background. Failure to control locally advanced neoplasia is a major source of morbidity and mortality in most industrialized societies. All too frequently, surgery or conventional irradiation is unsuccessful in eradicating locally advanced tumors of a variety of sites and histologies. Among these diseases are squamous cell carcinoma of the oral cavity and pharynx, adenocarcinoma of the rectum, squamous cell carcinoma of the uterine cervix, adenocarcinoma of the pancreas, squamous cell carcinoma of the esophagus, high-grade gliomas, and epidermoid carcinoma of the lung. Five-year survival for advanced stages of these diseases ranges from approximately 0 to 40 percent, with corresponding local failure rates of 33 to 100 percent. Results for the latter four sites show survival of 10 percent or less, with local failure rates of 50-100 percent. Approximately 132,000 cases of these four diseases were predicted for 1979, with anticipated mortality predicted for 114,700 of those cases.¹³ Seventy-five to 100 percent of all patients with carcinomas of the pancreas, esophagus, and lung, as well as high-grade glioma, are unsuitable for surgical therapy alone, as are virtually all patients with advanced tumors of the head and neck. By definition, advanced (inoperable or unresectable) adenocarcinoma of the rectum is not amenable to surgical management. Conventional radiotherapy is also ineffective in controlling these lesions in the vast majority of cases. Detailed, pertinent background information is provided for individual disease sites proposed for pion radiotherapy under Methods of Procedure below.

[REDACTED]

Given these considerations, clinical trials commenced in 1976 for treatment of locally advanced, deep-seated human neoplasms of these and other sites using pion radiotherapy in an attempt to improve local control and survival. A total of 196 patients were treated as of April 1981. The detailed progress report below enumerates the clinical results, including survival, local control, acute and chronic normal tissue reactions, and relationships of tumor control to treatment parameters including fraction size, total dose, and treatment volume.

c. Rationale. The hypothesis to be tested is that pion radiotherapy will prove more effective in Phase II trials than conventional radiotherapy in the curative treatment of one or more of the following neoplasms:

- i. High-grade glioma (astrocytoma Grade III and IV),
- ii. Inoperable/unresectable carcinoma of the pancreas,
- iii. Advanced carcinoma of the uterine cervix (Stage III and IVA),
- iv. Inoperable/unresectable carcinoma of the esophagus, and
- v. Inoperable/unresectable carcinoma of the lung (epidermoid carcinoma).

It is postulated that inability to obtain local control with conventional radiotherapy in many advanced neoplasms is due to a suboptimal ratio between effective radiation dose to the tumor and to intervening or surrounding normal tissues, i.e., a suboptimal therapeutic ratio. This is most apparent in the situation of a deep-seated tumor surrounded by normal tissues of greater radiosensitivity than the neoplasm itself, in which attempted delivery of potentially curative doses of radiation results in unacceptable treatment-related morbidity and mortality. It is also postulated that failure of local control in such neoplasms may be related to the presence of a large number of hypoxic cells that are relatively resistant to radiation injury by conventional low-LET radiations, such as x-rays or γ rays. Such cells may then be a source of persistent or recurrent disease after maximally tolerated doses of conventional radiations.

Negative pi meson irradiation offers potential solutions to both of these problems in that it:

- i. Offers more favorable depth dose distribution characteristics than conventional radiations, with deposition of the majority of dose in a confined region at depth (Bragg peak) and minimization of exit dose, allowing sparing of adjacent normal tissues; and
- ii. Contributes a significant dose of high-LET radiation, to which hypoxic cells are relatively more sensitive than to low-LET radiation, in the region where the pion dose is maximal.

By application of techniques already developed in the course of the project, it is possible to tailor the distribution of pion irradiation to include appropriate treatment volumes with relative sparing of neighboring normal tissues and to deliver localized high-LET radiation to advanced neoplasms in those sites listed above. Routine implementation of the treatment techniques of dynamic scanning may be expected to improve the therapeutic ratio even further.

Thus, the physical characteristics of pion irradiation allow the delivery of higher doses of radiation with potentially more lethal effect on hypoxic cells to the region of tumor involvement than is possible with conventional radiations. For the same normal tissue toxicity, an increment in effective dose to the tumor may be obtained, with resultant improvement in local control and, therefore, survival.

Clinical aspects of the pion radiotherapy program have focused on performance of clinical trials defining tumor response, normal tissue reactions, and optimal time-dose-fraction relationships for pion irradiation, as well as definition of those disease sites and categories most likely to benefit from pion irradiation and comparison of x-irradiation and pion irradiation for such locally advanced neoplasms.

Phase II studies will be continued, with particular emphasis on treatment of patients with astrocytoma, Grade III or IV, unresectable carcinoma of the pancreas, and squamous carcinoma of the uterine cervix, Stage III and IVA. Limited Phase III trials were conducted prior to 1982 for squamous carcinoma of the oral cavity, nasopharynx, oropharynx, and hypopharynx; inoperable or locally recurrent adenocarcinoma of the rectum; and T₃/T₄ transitional carcinoma of the bladder. Phase III trials are not contemplated by this application. Previous accessions to these studies are shown in Table 3.

(1) Planning and protocol development. Phase I-II clinical trials will be conducted under RTOG protocols 79-23 and 79-24 for locally/regionally advanced and metastatic neoplasms, respectively.

Accession to the randomized protocols was slow with only 10, 3, and 1 patients randomized to RTOG protocols 78-28, 78-25, and 78-26, respectively. This problem was related to beam time availability of the LAMPF accelerator and the necessity for a very large catchment area to assure adequate numbers of patients fulfilling all protocol criteria at appropriate times. In addition, referring physicians outside New Mexico expressed concern over the policy of bringing all patients to the CRTC in Albuquerque for randomization and planning. To obviate this problem, the randomization policy was modified to allow both randomization and treatment at the referring institution, provided that all diagnostic evaluation, pathology, conventional treatment plans, simulation films, and port films were submitted for review by the Radiation Oncology Section of the CRTC and the pathologist of record for the pion project. Only after an exhaustive diagnostic evaluation, including CT scanning and localization steps similar to those employed for pion-treated patients, were the patients accepted to the study and randomized. Phase III randomized trials are not contemplated in this application because of these almost insurmountable difficulties.

Accession of patients to nonrandomized trials is to be continued with particular emphasis on patients with high-grade (Grade III or IV) astrocytoma, unresectable adenocarcinoma of the pancreas, and advanced (Stage III and IVA) squamous carcinoma of the uterine cervix. Referrals for nonrandomized trials were received in unprecedented numbers, particularly after July 1980. This increase reflects not only an increasing interest on the part of referring physicians but also a wider base of referral. Formal ties were established with the Albuquerque Veterans' Administration Medical Center with anticipation of a possible nationwide VA referral network. In

TABLE 3

ACCESSION TO PION PROTOCOLS
1 May 1978 - 30 April 1981

<u>Protocol</u>	<u>1979</u>	<u>1980</u>	<u>1981</u>	<u>Total</u>
RTOG 79-23: Phase II, Miscellaneous Advanced/Recurrent Primarys (Pion Only)*	46	41	52	139
RTOG 79-24: Phase II, Miscellaneous Metastatic Lesions*	1	0	0	1
RTOG 78-25: Phase III, Rectum/Rectosigmoid (Pion/Conventional) (Total)	0	1 (0/1)	2 (2/0)	3 (2/1)
RTOG 78-26: Phase III, Urinary Bladder (Pion/Conventional) (Total)	0	0	1 (0/1)	1 (0/1)
RTOG 78-28: Phase III, Pharynx, Oral Cavity (Pion/Conventional) (Total)	0	5 (3/2)	5 (2/3)	10 (5/5)
TOTAL (Pion/Conventional)	47	47 (44/3)	60 (56/4)	154 (147/7)

*Accession started in 1976, although assigned official RTOG status in 1979.

addition, efforts to establish referral patterns with Loma Linda University and the University of Southern California through their affiliated Community Radiation Oncology Program (CROP), resulted in several referrals for the most recent treatment cycle.

An additional aspect of increased patient throughput is the increasing use of pions in treatment of malignant gliomas. An amendment to the Phase I-II protocols, approved in July 1979, allows the planned combination of pion irradiation as boost therapy with conventional irradiation of more generous volumes. Conventional radiation doses of 4000-5000 rad in 4-5 weeks are preceded or followed by treatment of cone-down volumes by 1200-1500 rad of peak pions, maximum dose. This treatment plan has two major advantages, the first of which is that the benefits of dose localization and normal tissue sparing can best be used for localized volumes. The number of lengthy, multi-port treatments of the whole brain using pions can be reduced, and the beam time can be used in treatment of more patients with localized, critical tumor volumes. The possibility of brief (1 1/2-2 1/2 week) boost treatments also allows accession of patients throughout the treatment cycle and maintenance of the maximum patient census.

An extremely important aspect of protocol planning, particularly during Phase II studies, is the ability to efficiently review previous clinical experience with regard to disease characteristics, treatment parameters, tumor response, and normal tissue reactions. A data base system has been obtained that would permit sequential compilation and analysis of clinical data being accumulated by the pion project.

The data base has been established on a Digital Equipment VAX computer, using eight different forms for initial observation, follow-up reports, and other data. The data base currently includes information on 173 patients. Experience in setting up and using the data base has been excellent, with no major problems encountered. Installation of an advanced biostatistical package for interactive statistical analysis has been accomplished.

A total of 196 patients received pion therapy, alone or in combination with surgery or conventional radiation, through April 1981. Nine patients treated in 1974 and 1976 received randomly assigned x-irradiation or pion irradiation for multiple subcutaneous metastases. These studies established an RBE of 1.4 for pions, compared to 100 kVp x-rays, in acute injury to human skin, and provided the basis for present Phase II pilot protocols, as well as for Phase III trials in certain anatomic sites. Trials with deep-lying tumors began in November 1976, and proceeded with gradual increments in total pion dose and adjustments in daily dose for each new type of tumor and normal tissue irradiated.

Installation of an EMI 7070 CT scanner at the Pion Biomedical Facility in Los Alamos in February 1980 resulted in major improvements in many aspects of patient care. The presence of an on-site CT scanner assures vastly improved quality control in regard to patient positioning and has allowed implementation of a more efficient and accurate treatment planning system. The radiotherapist may now superimpose treatment volumes, skin surfaces, and critical organs directly on CT data by use of region-of-interest software and the diagnostic console. This information can be translated into life-sized hard copy for treatment planning. The ability to vary

window settings and to superimpose treatment volumes on adjacent slices allows improved delineation of the anatomy of interest. On-site CT scanning also permits confirmation of positioning of bolus, frequent checks of changes in tumor volumes and internal anatomy during the course of therapy, and a method of routine monitoring of inaccessible lesions such as tumors of the brain and pancreas during the follow-up period.

The ability to reproduce patient position at each step of treatment planning from CT scanning, through simulation, to treatment has been thoroughly facilitated by installation of three-point laser set-up systems in the CT scanning, set-up, and treatment rooms. In addition, implementation of this positioning system has allowed development of a more convenient and comfortable system of immobilization for patients with neoplasms of the brain and head and neck, in which a cast of the shoulders and head replaces a full torso cast. This also permits omission of casts for treatment of lesions of the abdomen and pelvis, resulting in improved patient comfort and ease of positioning. Finally, the three-point set-up system allows accurate positioning of the height of the patient, a critical parameter in dynamic treatment with focused fan beams.

Immobilization casts, when needed, are made from a fiberglass material (Lightcast II) that hardens under ultraviolet light. The casts are made on the patient, then bisected in the sagittal plane for lateral head and neck treatments to accommodate the vertical pion treatment beam. Special oblique casts are made for specific treatment situations. The casts are rigid, yet comfortable for the patients, and they provide reproducible immobility. With on-site CT scanning, appropriate approximations of field centers may be obtained from "scanogram" images, and use of a line-laser system in the CT scanner permits marking and tattooing of the patient's skin, indicating the direction of movement through the CT scanner and the plane of the individual scans. These marks permit accuracy in subsequent repositioning of the patient and alignment of beam-shaping devices.

After CT scanning and preparation of bolus and collimator designs, patient and field positions are checked by orthodiagraphic films obtained at final simulation. This technique, which is necessary to confirm the alignment of fields treated with the non-diverging, static pion beam, consists of timed exposure radiographs taken with very narrow collimation along a central axis of the beam while the patient is moved along an axis perpendicular to that of beam collimation. The result is a film showing no divergence in the direction of patient movement, and a pair of such films provides confirmation, in x and y dimensions, of the accuracy of collimator shape. The possibility of installing an x-ray tube in the beam area for port films verification is being explored.

Lengthy treatment times and set-ups necessitate patient positioning and alignment of beam-shaping devices in a staging area, thus reducing beam-off time while patients are exchanged within the treatment room. This exchange time is routinely on the order of five minutes due to further improvement in the table and trolley system in use for the last three years. Improved maneuverability and decreased weight have resulted in more rapid transport with less patient displacement. The impact of attention to the technique of patient immobilization, simulation, and transport is apparent in the excellent correlation of simulation films with post-treatment

port films obtained by orthodiagraphic scanning through the treatment collimator, and in the predictability of in vivo dosimetric measurements, which are obtained in every patient.

All aspects of treatment planning, dosimetric confirmation, channel tuning, and hardware and software interfacing have been implemented successfully in the treatment of several patients with dynamic scanning (see Physics). Further refinement of this technique and development of necessary treatment planning computer codes for nonhomogeneous treatment volumes are major priorities for the next year. In the interim, static beam therapy will continue to be routine, as will standardized localizing radiographic procedures, including simulation and port-checks by orthodiagraphic scanning as well as in vivo dosimetry in all cases.

Patient safety has been a primary concern in the design of Phase I-II trials and has dictated a conservative approach in the incrementation of doses and volumes. Table 4 shows the evolution of large field pion radiotherapy from 1976 through 1980 for both initial and cone-down volumes. The trend toward increasing volumes and doses reflects increasing familiarity with normal tissue tolerance and patterns of tumor recurrence. Average doses for 1980 are somewhat decreased from 1979 and reflect increasing treatment volumes and an increasing proportion of patients receiving low dose (1000-1600 π rad) pion irradiation of cone-down volumes in the brain, and the combination of large-field conventional irradiation with cone-down pion irradiation in the pancreas.

Treatment policies are outlined in Table 5. Maximum daily doses of 125 π rad are given for most sites, including brain, head and neck, and pelvis. Minimum doses at the periphery of treatment volumes are routinely 80 percent of the maximum dose. A brief experience with static treatment planning to a minimum of 90 percent resulted in greater acute and chronic normal tissue reactions, presumably related to the increased volume of normal tissue receiving relatively high dose irradiation, and has been abandoned; this technique will be possible with dynamic treatment planning. A notable exception to the routine daily dose of 125 π rad is in the treatment of pancreatic carcinoma. For these patients, 160 π rad is given daily in two treatments divided by a minimum of six hours. One hundred π rad maximum is given to a volume encompassing the entire pancreas, tumor, and regional nodes through AP:PA opposed ports, followed at six hours by an additional 60 π rad maximum through an anterior portal to the site of radiographically demonstrable disease. A total of 3840 π rad is delivered to the site of gross disease in 4 1/2 weeks, followed by an additional 2400 rad/3 weeks photon irradiation to the entire liver, pancreas and tumor. The other example of routine combination of conventional and pion irradiation is in the treatment of malignant astrocytomas in which conventional megavoltage irradiation of the whole brain to doses of 4200-4500 rad/4-5 weeks is combined with pion irradiation of cone-down volumes to doses of 1200-1500 π rad maximum in 2-3 weeks.

This report details clinical observations of the 196 patients who have received pion irradiation, with particular emphasis on a group of 96 patients treated with curative intent and followed for a minimum of one year. Table 6 details the patient population of interest (excluding 23 patients treated since January 1, 1981). Thirty-three patients treated between June 1980 and November 1980 are included in the analysis of survival and local

TABLE 4
EVOLUTION OF PIGN THERAPY

<u>Year</u>	<u>Number of Patients</u>	<u>Volume (initial) cc</u>	<u>Volume (cone) cc</u>	<u>Dose (Initial) τ Rad Max.</u>	<u>Dose (Cone) π Rad Max.</u>
1976-1977	34	715	572	2450	2827
1978	41	1137	654	2682	3864
1979	49	1540	783	3542	4274
1980	43	1894	672	3233	4070

TABLE 5
TREATMENT POLICY

<u>Site</u>	<u>Maximum Dose (π rad)</u>	<u>Minimum Dose (π rad)</u>	<u>Fractions</u>	<u>Days</u>
Pelvis*	4500	3600	36	50
Brain*				
Whole	2750	2200	22	32
Cone-down	4500	3600	36	50
Pancreas**				
Whole	2400	1920	24	35
Cone-down	3840	3072	24	35
Esophagus*				
Wide Field	3500	2800	28	38
Cone-down	4500	3600	36	50
Lung				
Wide Field	3250	2600	26	35
Cone-down	4500	3600	36	50

*May be treated by conventional wide-field irradiation and pion boost (approx. 1500 π rad max./12 fx/2½ weeks).

**Combined with planned external beam conventional therapy.

TABLE 6
PION PATIENTS 1974-1980

Total Cases	173
Follow-up < 1 year	33
Exclusions:	
Skin Metastases	9
Distant Metastases	15
Low Dose Pilot	-
Low Dose Beam	10
Low Dose Medical	<u>3</u>
Total Exclusions	44
Total Curative Cases	129

control, but excluded from the analysis of chronic effects because of insufficient follow-up time. Of 173 patients treated prior to 1981 (including one with simultaneous primary lesions of the prostate and urinary bladder), 9 patients treated in Phase I trials for cutaneous metastases and 15 patients with known distant metastases at time of treatment are excluded from the population treated with curative intent. In addition, 20 patients receiving less than 2700 π rad maximum, that dose at which complete tumor regression was first noted, are excluded for reasons including deliberately planned low doses in conjunction with Phase I studies, machine malfunction, and interruption of treatment for medical reasons. Table 7 shows the distribution of patients treated with curative intent before November 1980 according to treatment modality. Except for six patients receiving cone-down pion irradiation to the brain, all patients received a minimum of 2700 π rad, although only 90 were treated with pions alone. Only 49 were treated to dose levels currently thought to approximate tolerance doses of relevant normal tissues.

Data regarding 129 patients (with 130 primary lesions) treated with curative intent have been analyzed with respect to survival, local control and acute reactions, while 96, followed for more than one year, are analyzed with regard to chronic reactions. Separate analyses are reported for patients receiving less than 4000 π rad maximum and those treated to higher doses.

Tables 8 and 9 show crude survival and local control statistics for the group of 129 patients treated with curative intent. In each of these tables is a separate analysis of six patients treated for high-grade gliomas using a planned combination of conventional whole brain irradiation and pion irradiation (<2000 π rad) of cone-down volumes. The data are also shown in Figures 5 and 6. Patients with primary neoplasms of the head and neck comprise the largest single group, with 38 cases, followed by glioma, 36; prostate, 21; and pancreas, 16. The "other" category includes four patients with transitional carcinomas of the urinary bladder, and two each with carcinomas of the esophagus and lung. Four patients with carcinoma of the rectum were treated, as were individual patients with carcinoma of the stomach and skin. Three patients were treated for advanced carcinoma of the uterine cervix. Also in the "other" category is one patient with carcinoma of the anus and one patient with an ethesioneuroepithelioma. Three of four patients with bladder lesions had local control, although one expired of unrelated, intercurrent GI bleeding, while the third survives with local persistence. One patient with a Pancoast tumor survives without evidence of disease at three years, but the second patient with lung cancer expired with local recurrence at two years after therapy. Both patients with esophageal carcinoma expired, although one was free of tumor at autopsy, having died as a result of sequelae of chronic alcoholism. Two patients with rectal carcinoma expired with metastatic disease, although one was free of local disease at autopsy. Two others survive without evidence of disease. The patient with stomach cancer died of local recurrence, while a patient with a large basal cell carcinoma of the face, invading bone, remains free of disease at two years. One patient with Stage IIIB carcinoma of the cervix expired with lung metastases and apparent small bowel necrosis one year after combined pion and interstitial template irradiation. Review of autopsy material in determining the role of irradiation in the small bowel injury is pending. Another patient expired of progressive local disease and uremia, while the third has local persistence of disease. The patient with anal carcinoma and the patient with ethesioneuroepithelioma are alive with no evidence of disease at ten months.

TABLE 7

130 TUMORS TREATED WITH CURATIVE INTENT

Pions alone	90*
Pions XRT	29
Pions + Surgery	<u>11</u>
Total	130

*89 patients, one with simultaneous prostate and bladder primaries.

TABLE 8

SURVIVAL OF PION PATIENTS TREATED WITH
CURATIVE INTENT BY SITE AND DOSE

	<u><2000 π^- rad</u>	<u><4000 π^- rad</u>	<u>>4000 π^- rad</u>	<u>Total</u>
Head & Neck	-	6/12	10/26	16/38 (42%)
Brain	4/6	3/16	7/14	14/36 (39%)
Prostate	-	4/5	15/16	19/21 (90%)
Pancreas	-	5/11	0/5	5/16 (31%)
Other	-	5/9	5/10	10/19 (53%)

TABLE 9

LOCAL CONTROL IN PION PATIENTS TREATED WITH
CURATIVE INTENT BY SITE AND DOSE

	<u><2000 π^- rad</u>	<u><4000 π^- rad</u>	<u>>4000 π^- rad</u>	<u>Total</u>
Head & Neck	-	6/12	13/26	19/38 (50%)
Brain	1/6	2/16	3/14	6/36 (17%)
Prostate	-	4/5	15/16	19/21 (90%)
Pancreas	-	0/11	0/5	0/16 (0%)
Other	-	5/9	5/10	10/19 (53%)

130 Tumors Treated with Pion Radiotherapy
with Curative Intent — Survival

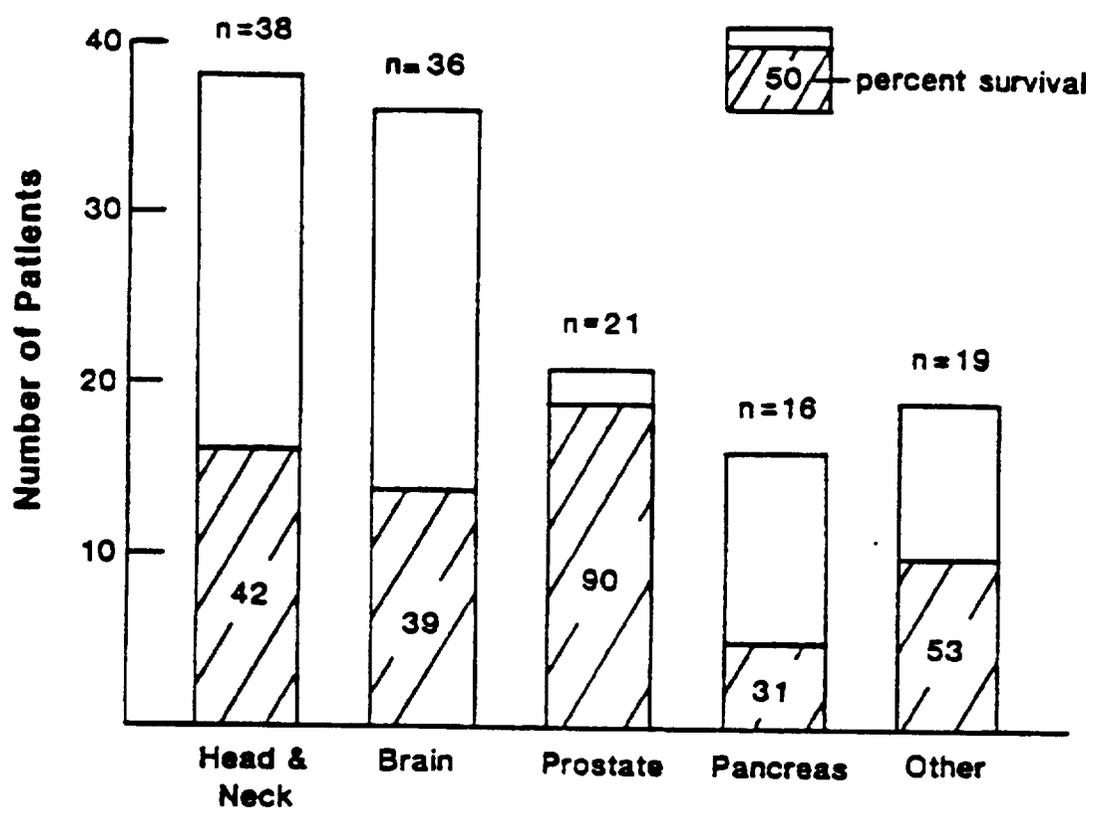


Figure 5. Survival of patients given pion radiotherapy with curative intent

130 Tumors Treated with Pion Radiotherapy
with Curative Intent - Local Control

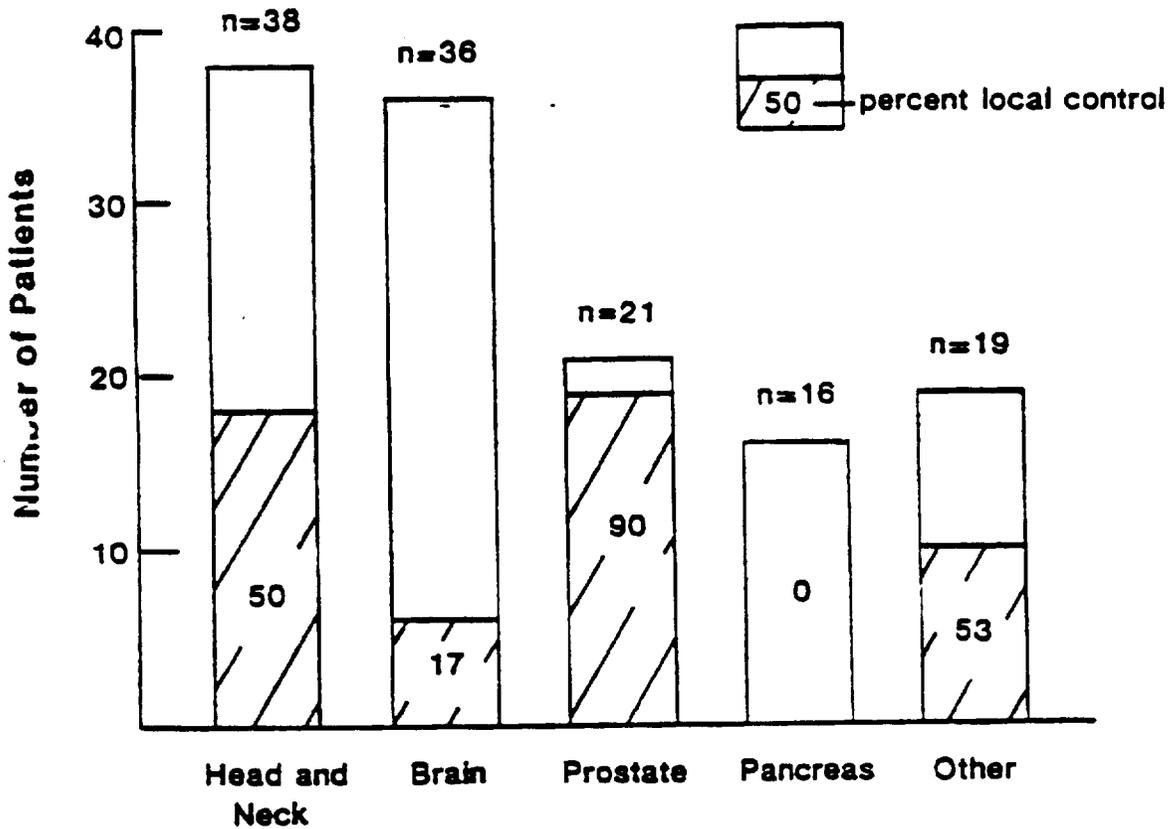


Figure 6. Local control for patients given pion radiotherapy with curative intent

Crude survival rates are 90, 42, 39 and 31 percent for patients with prostate, head and neck, brain, and pancreatic tumors, respectively, with corresponding local control statistics of 90, 50, 17, and 0 percent. Local control is scored in the case of glioma only if the patient has stable neurologic symptoms, no steroid dependence, and no evidence of contrast enhancement or mass effect on CT scan. Local control is scored in the case of pancreatic carcinoma only if there is resolution of tumor mass as documented by CT scanning or autopsy confirmation.

Acute reactions recorded for the group of patients treated with curative intent are shown in Table 10. Acute reactions are scored on a scale of 0-4 as follows: 0 - nil; 1 - skin erythema, mucosal injection, mild dysuria or diarrhea < 4 stools per day, etc.; 2 - dry desquamation, patchy mucositis, moderate dysuria, diarrhea with mucus (≥ 5 stools per day), etc.; 3 - moist desquamation, confluent mucositis, severe dysuria with bladder spasms, diarrhea with blood, etc.; and 4 - acute necrosis. Average acute reaction scores were obtained by summing severities of all reactions for individual anatomic sites as follows: head and neck - mucosa, skin, salivary glands; pelvis - skin, rectum, bladder, thorax - skin, dysphagia; abdomen - nausea, diarrhea; brain - skin, and dividing by the number of scoring criteria for each category (e.g. skin, oral mucosa, and salivary gland = 3 criteria for head and neck). The analysis shows a trend to more severe reactions at all sites in the higher dose range, although it must be noted that these data ignore such potentially contributory factors as dose per fraction, hyperfractionation, and volume. Of note is the observation that the average acute reaction score in 11 patients (10 with carcinoma of the head and neck and one with stomach cancer) receiving more than 5000 π rad maximum was 2.2.

A separate evaluation of acute toxicity data in head and neck patients was performed to examine the importance of volume, daily dose, and total dose. Figure 7 shows the distribution of 36 patients treated before July 1980, receiving 3000 π rad or more for neoplasms of the head and neck with summation of acute reactions recorded for skin, mucosa, and salivary glands. Average values for fraction size, treatment volume, and total dose were calculated for each level of acute injury and plotted with a line fitted to the data by the method of least squares. These data are shown in Figures 8, 9 and 10 and suggest that acute reactions are relatively independent of fraction size and treatment volume, at least within the ranges employed, but increase in proportion to total dose. The acute tolerance of skin and mucosa is approximately 4500 π rad in seven weeks for usual treatment volumes, with acute reactions increasing rapidly above this dose.

Table 11 shows a compilation of all patients treated with pions and subsequently scored as having severe chronic reactions (Grade III or greater, according to the late effects scoring system of EORTC/RTOG). Only four patients had such chronic effects related to pion irradiation alone. Case [redacted], a [redacted]-year-old female had chronic, severe laryngeal edema after 5000 π rad for a T₄ squamous carcinoma of the larynx. Patient [redacted], Case [redacted] had severely symptomatic pulmonary fibrosis after 4000 π rad for a large adenocarcinoma of the lung. Patient [redacted] (Case [redacted]) developed necrosis of a portion of the pharyngeal wall four months after 4600 π rad for a T₃N₂M₀ squamous carcinoma of the base of tongue. Patient [redacted] (Case [redacted]) received 4950 π rad in 140 π rad increments for a large pelvic recurrence of cloacogenic carcinoma of the anus. Ten months later he developed small bowel

TABLE 10

ACUTE INJURY RELATED TO PION IRRADIATION IN DOSES $>2700 \pi^-$ RAD
BY SITE AND DOSE RANGE*

<u>Dose Range</u>	<u>Site</u>	<u>Number of Patients</u>	<u>Average Acute Reaction Score</u>
$<4000 \pi^-$ rad	Head & Neck	14	1.7
	Pelvis	10	1.4
	Thorax	3	1.2
	Abdomen	11	0.9
	Brain	10	1.1
$>4000 \pi^-$ rad	Head & Neck	26	1.9
	Pelvis	22	1.6
	Thorax	1	1.5
	Abdomen	6	1.1
	Brain	20	1.5

*See text for explanation of scoring system.

ACUTE REACTIONS IN 36 PATIENTS RECEIVING PIONS TO THE HEAD & NECK

Moseley, Robert D., Jr., M.D.

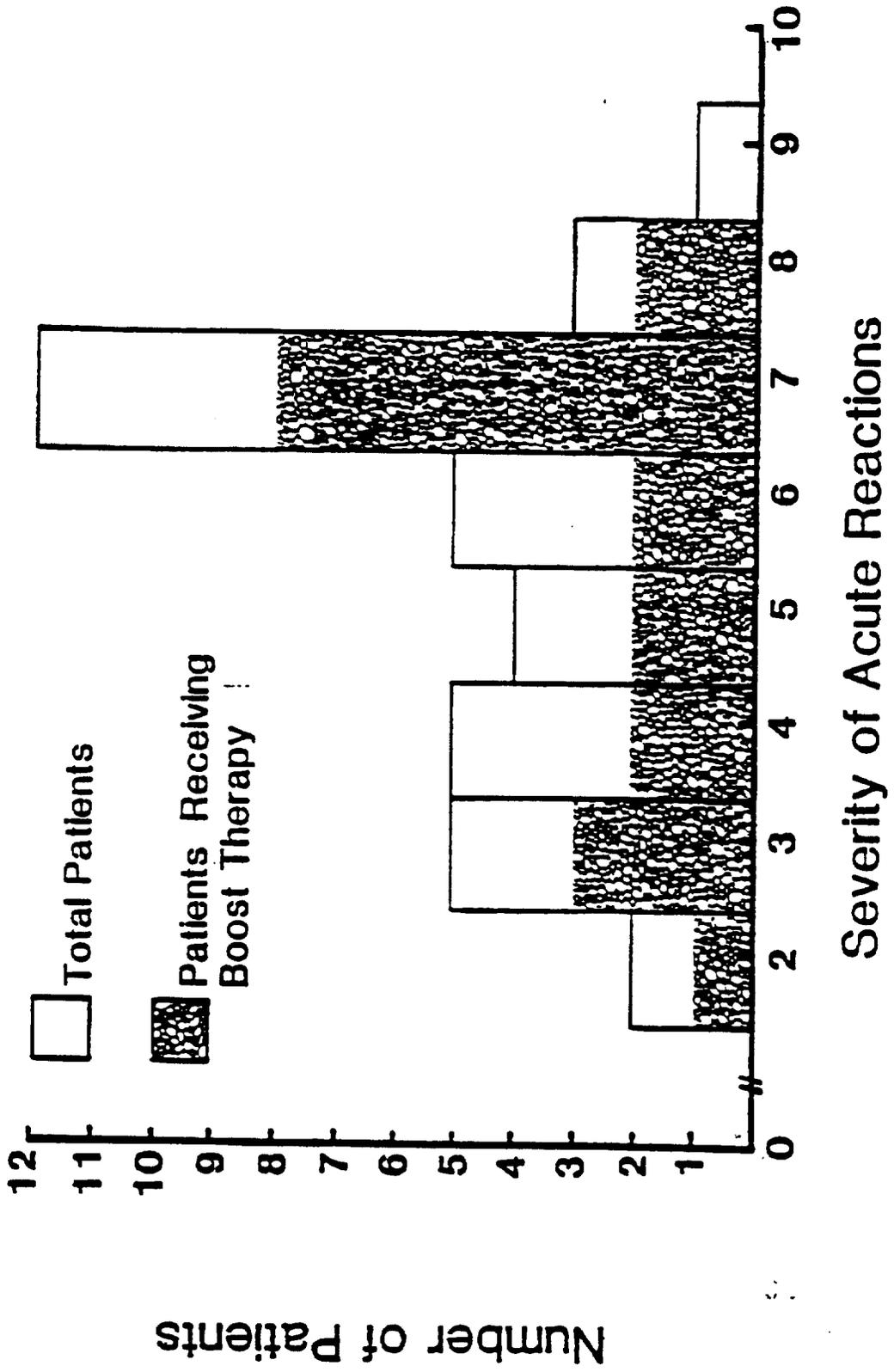


Figure 7. Summation of acute skin, mucosa, and salivary gland reactions to pion therapy in 36 patients

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HEAD & NEC ACUTE REACTIONS BY AVG. FRACTION SIZE

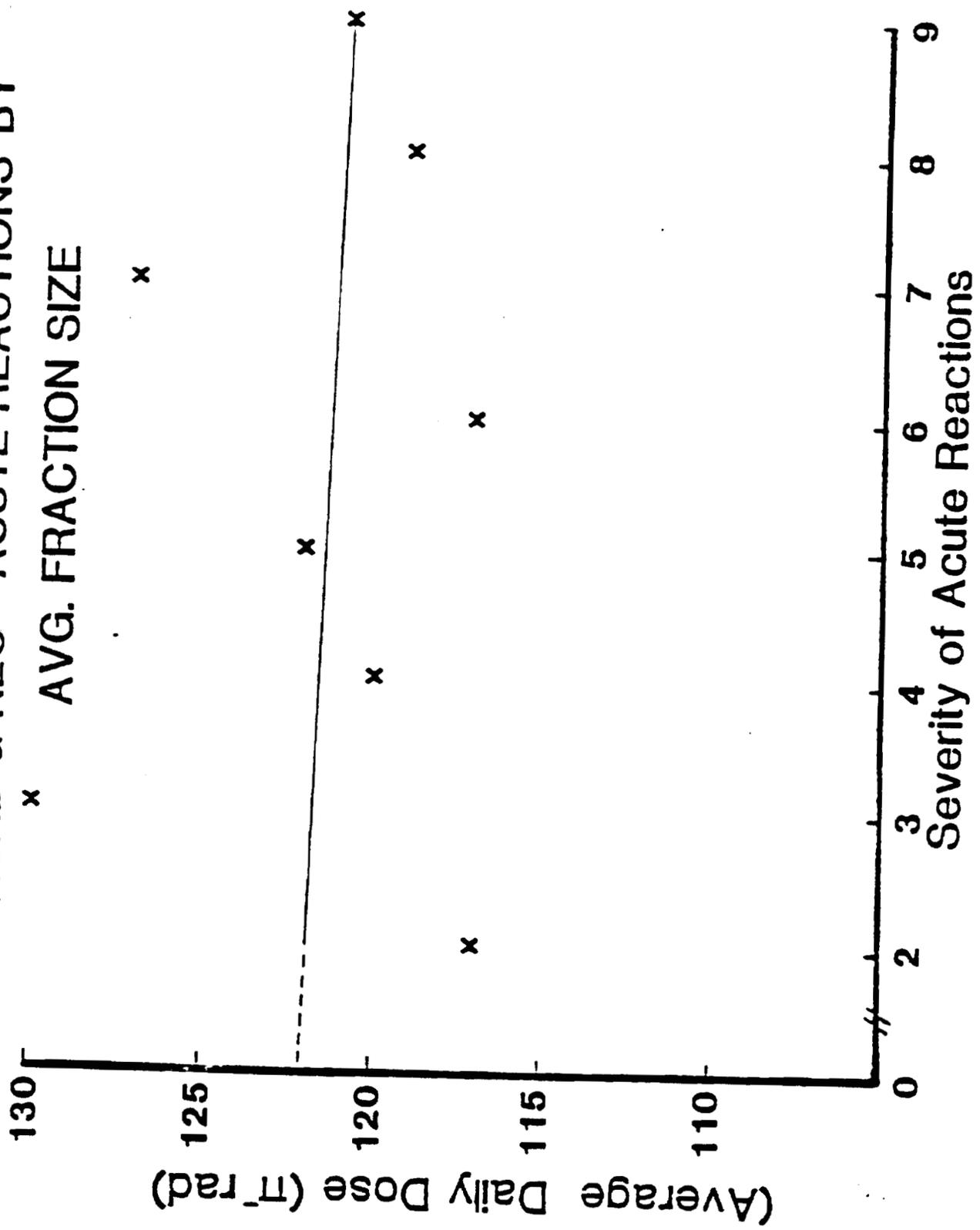


Figure 8. Correlation of acute reactions with fraction size in head and neck

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HEAD & NECK ACUTE REACTIONS BY TREATMENT VOLUME

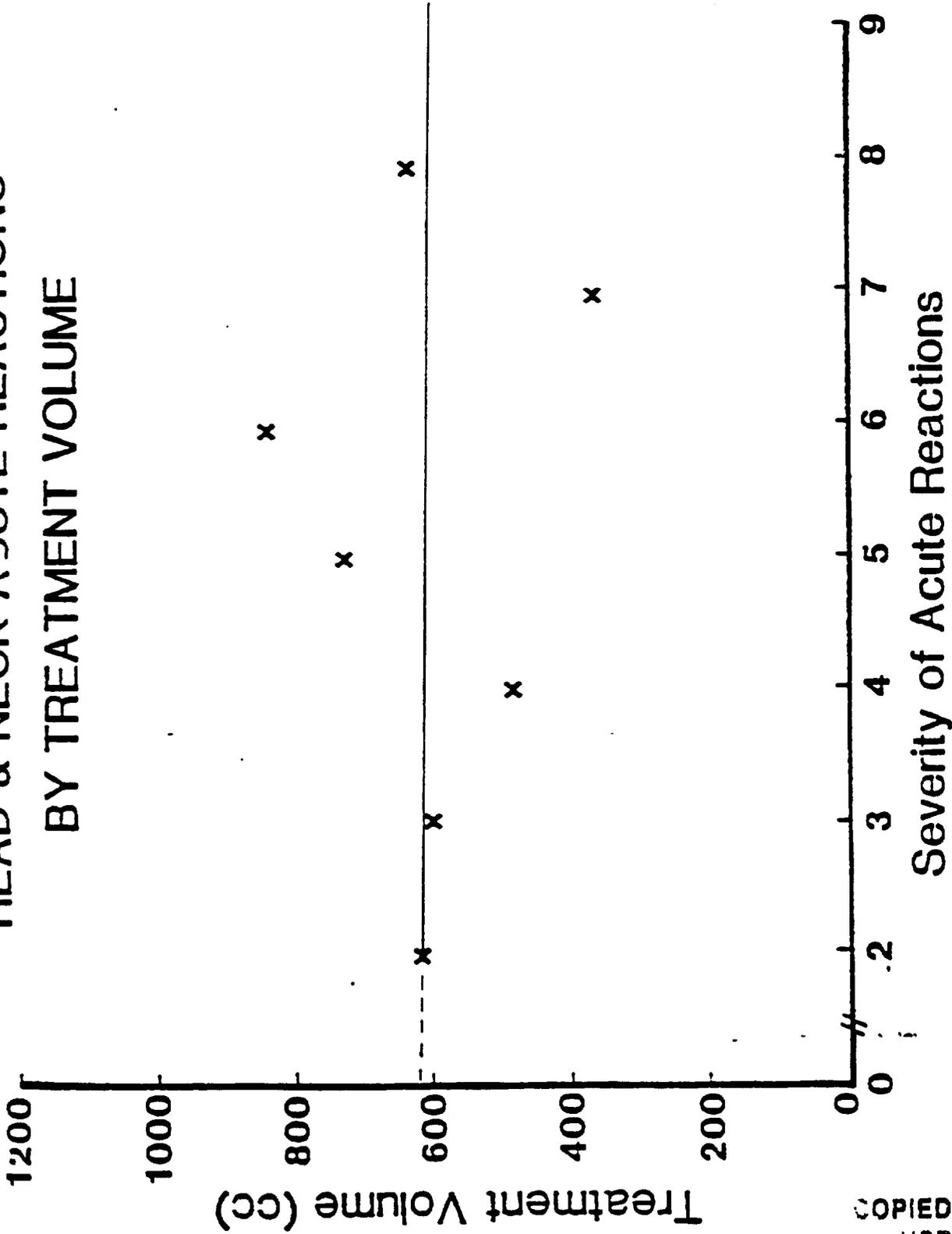


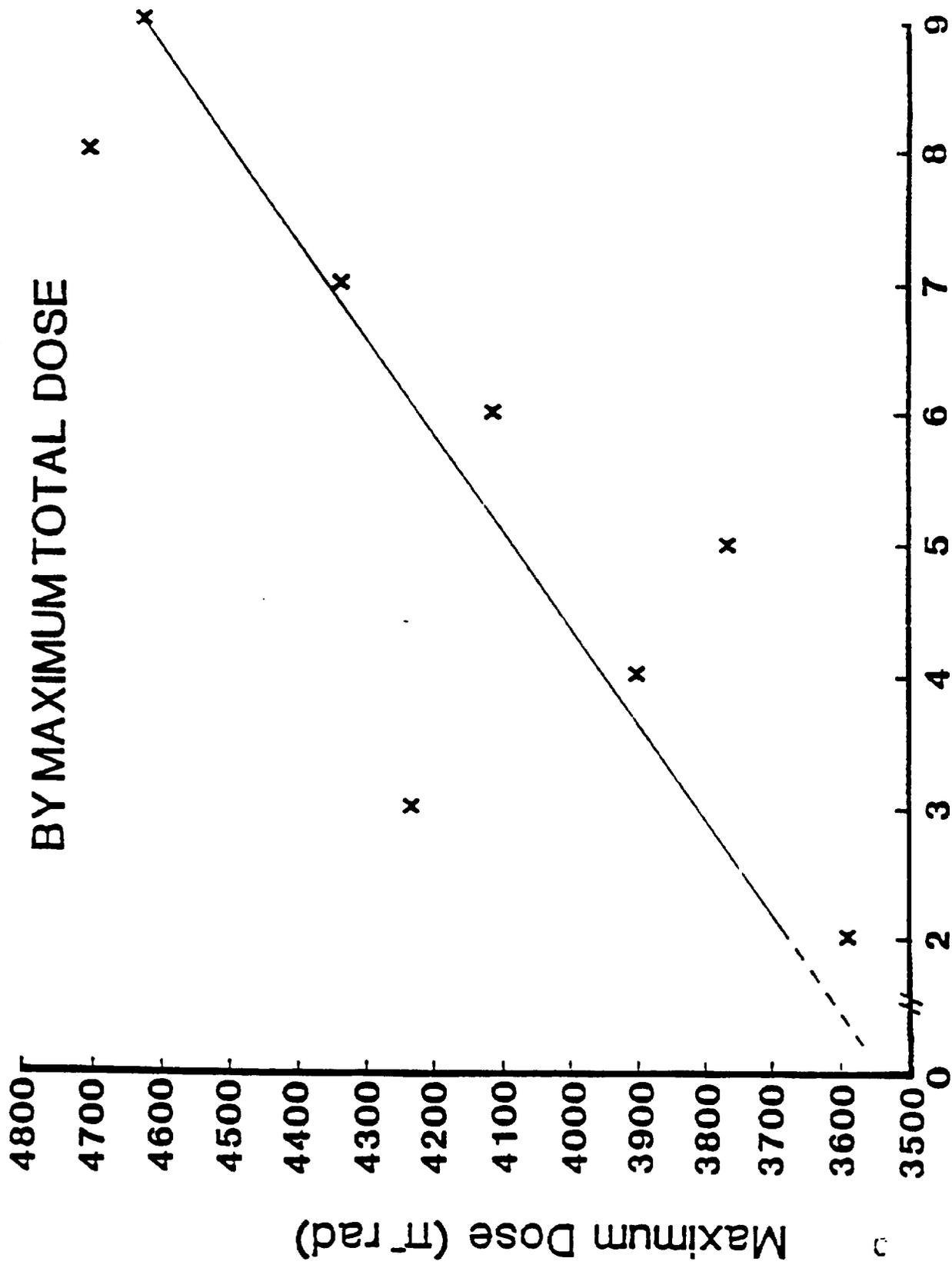
Figure 9. Correlation of acute reactions with treatment volume in head and neck

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HEAD & NECK ACUTE REACTIONS BY MAXIMUM TOTAL DOSE



Severity of Acute Reactions

Figure 10. Correlation of acute reactions with maximum total dose in head and neck

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TABLE 11

SEVERE CHRONIC REACTIONS IN PION IRRADIATED PATIENTS

<u>Disease Site</u>	<u>Case Number</u>	<u>Type of Reaction</u>	<u>Comment</u>
Bladder		Vesico-vaginal fistula	Persistent disease
Rectum		Hematochezia	Persistent disease
Anus (Recurrent)		Small bowel injury	PIONS ONLY
Prostate		Lymphedema	Previous lymphadenectomy
Cervix	135	Small bowel necrosis	Implant + pions
Head & Neck		Skin atrophy	XRT + pions
		Laryngeal edema	
Head & Neck		Mucosal necrosis	Implant + pions
Head & Neck		Mucosal necrosis	Surgery + pions
Head & Neck		Laryngeal edema	XRT + pions
Head & Neck		Skin atrophy	Previous surgery
Head & Neck		Subcutaneous fibrosis	Surgery + pions
Head & Neck	99	Flap necrosis	Surgery + pions
Head & Neck		Edema	Persistent disease
Head & Neck		Laryngeal edema	PIONS ONLY
Head & Neck		Mucosal necrosis	Implant + pions
Head & Neck		Mucosal necrosis	PIONS ONLY
Lung		Pulmonary fibrosis	PIONS ONLY

obstruction and bleeding, necessitating ileostomy. Three patients had chronic reactions that were co-existent with persistent disease, and one patient, with a history of multiple previous surgeries for a large basal carcinoma of the face, developed skin atrophy after subsequent pion irradiation. Three patients (Cases [redacted] and [redacted]) developed mucosal necrosis after combined therapy with pions and supplemental interstitial implants or surgery; however, healing occurred in each case. Six additional patients developed severe chronic reactions after a combination of pion therapy with surgery or with conventional irradiation. Two of these patients are presumed to have expired from treatment-related complications. C.H. (Case #99) exsanguinated from a tracheal-innominate artery fistula two weeks after salvage composite resection for tonsillar carcinoma persistent after 5000 π rad. Patient G.C. (Case #135) developed small bowel obstruction and necrosis one year after 4500 π and 2500 rad by template implant for Stage IIIB carcinoma of the cervix. Thirteen patients treated for glioma have been autopsied, and, although all had gross or microscopic evidence of residual tumor, none had pathognomonic histological evidence of radiation injury to normal brain.

Table 12 shows a comparison of average chronic reaction scores for various treatment sites and for doses less than or greater than 4000 π rad in a population of patients receiving pion irradiation alone and followed for a minimum of one year. The group of patients receiving therapy for pelvic primaries has been analyzed for chronic effects as related to treatment planning policy, i.e., whether the minimum tumor dose was determined as 80 percent or 90 percent of maximum. The average chronic reaction scores for patients treated at 80 percent is 0.6 (n = 6), while it is 1.2 (n = 3) for those treated to 90 percent. All patients received 4000-4500 π rad at 115-125 π rad per fraction. Four patients treated with pions alone for prostate cancer had rectal bleeding at 9-12 months after therapy, and two, both treated at 90 percent, developed mild to moderate rectal strictures after 4500 π rad in 125 π rad fractions. These data suggest that in the dose range above 4000 π rad, chronic injury increases disproportionately in comparison to acute injury and may manifest itself only after periods of 9-12 months.

Observations of acute reactions and the pattern of increasing severity of chronic reactions with higher dose and longer follow-up indicate that present dose-fractionation schedules should not be modified until additional follow-up of patients treated in this fashion is available. Two studies are underway to further delineate chronic effects of pions. Thirteen patients treated for glioma have been autopsied, and the brains have been examined in detail, correlating gross and microscopic findings with precise isodose contours. A second study, just approved by the Human Research Committee of the University of New Mexico, will involve sigmoidoscopy and biopsy of rectal mucosa of age-matched pion and conventionally irradiated patients with prostate cancer and will compare in a blinded fashion, microscopic morphology based on the system described by Black *et al.*¹⁴ in an attempt to establish relative biological effectiveness (RBE) for chronic injury in a normal human tissue. Sunder Mehta, M.D., of the Division of Gastroenterology, Department of Medicine, is a collaborating investigator in this study.

iii. Publications

(1) Bush, Steven E., and Kligerman, M.M.: Pion radiotherapy for cancer of the pancreas. Cancer Clinical Trials, in press.

TABLE 12

CHRONIC INJURY RELATED TO PION IRRADIATION ALONE IN
DOSES $>2700 \pi^-$ RAD BY SITE AND DOSE

<u>Dose Range</u>	<u>Site</u>	<u>Average Chronic Reaction Score</u>
$<4000 \pi^-$ rad	Head & Neck	0.7
	Pelvis	0.5
	Other	1.4
$>4000 \pi^-$ rad	Head & Neck	0.9
	Pelvis	0.9
	Other	0.7

- (2) Bush, Steven E.; Smith, Alfred R.; St. Patrick M.; Smith, Nancy; Stark, Richard; and Pannell, Alison: Clinical results of pion radiotherapy at LAMPF. Proceedings, Second International Meeting on Progress in Radio-Oncology, in press.
- (3) Khan, K.M.; Bush, S.; Herzon, F.; and Kligerman M.M.: Pi meson radiotherapy for advanced head and neck neoplasms: Summary results. Head and Neck Surgery, in press.
- (4) Kligerman, M.M.: Potential for therapeutic gain similar to pions by daily combinations of neutrons and low-LET radiations. Medical Hypotheses 5: 257-264, 1979.
- (5) Kligerman, M.M.; Bush, S.; Kondo, M.; Wilson, S.; and Smith, A.R.: Results of Phase I-II trials of pion radiotherapy. Proceedings of the Second Rome International Symposium on Biological Bases and Clinical Implications of Radioresistance, in press.
- (6) Kligerman, M.M.; Sala, J.M.; Smith, A.R.; Knapp, E.A.; Tsujii, H.; Bagshaw, M.A.; and Wilson, S.: Tissue reaction and tumor response with negative pi mesons. Journal of the Canadian Association of Radiologists 31: 13-18, 1980.
- (7) Kligerman, M.M.; Sala, J.M.; Wilson, S.; and Yuhas, J.M.: Investigation of pion treated human skin nodules for therapeutic gain. International Journal of Radiation Oncology, Biology and Physics 4: 263-265, 1978.
- (8) Kligerman, M.; Tsujii, H.; Bagshaw, M.; Wilson, S.; Black, W.; Mettler, F.; and Hogstrom, K.: Current observations of pion radiation therapy at LAMPF. Treatment of Radioresistant Cancers, M. Abe, K. Sakamoto, and T. L. Phillips, eds. Amsterdam: Elsevier/North-Holland Biomedical Press, pp. 145-157, 1979.
- (9) Kligerman, M.M.; von Essen, C.F.; Khan, M.K.; Smith, A.R.; Sternhagen, C.J.; and Sala, J.M.: Experience with pion radiotherapy. Cancer 43: 1043-1051, 1979.
- (10) Kligerman, M.M.; Wilson, S.; Sala, J.; von Essen, C.; Tsujii, H.; Dembo, J.; and Khan, M.: Results of clinical applications of negative pions at Los Alamos. High LET Particles in Clinical Radiotherapy. Oxford: Pergamon Press, pp. 61-65, 1979.
- (11) Sala, J.M., and Kligerman, M.M.: Clinical experience with negative pi mesons and other high-LET radiations. Advances in Medical Oncology, Research and Education Vol. 6, Basis for Cancer Therapy 2, M. Moore, ed. Oxford: Pergamon Press, pp. 215-221, 1979.
- (12) Tsujii, H.; Bagshaw, M.; Smith, A.; von Essen, C.; Mettler, F.; and Kligerman, M.: Localization of structures for pion radiotherapy by computerized tomography and orthodiagraphic projection. International Journal of Radiation Oncology, Biology and Physics 6: 319-325, 1980.

3. Specific Aims

a. To conduct non-randomized trials of pion radiotherapy in the management of high-grade gliomas (astrocytoma Grade III and IV), and inoperable or unresectable carcinoma of the pancreas, esophagus, lung and uterine cervix (Stage III, IVA), comparing pion therapy results with best conventional treatment results published in the literature over the past 5-10 years, as a means of rapidly identifying those sites for which Phase III trials are most appropriate.

b. To proceed as rapidly as is warranted by data from Phase II trials, in which patients have been treated to optimal dose with systematic technique, to design of Phase III studies.

c. To continue observations of acute and chronic effects of pions on normal human tissues including, but not restricted to, direct observations in the clinic, serial radiographic follow-up (particularly using CT scanning), analysis of appropriate biopsy material, and examination and correlation of autopsy findings with dose distribution.

d. To perfect available techniques and develop new techniques to assure optimal delivery and monitoring of patient treatment including, but not restricted to, methods of immobilization, positioning, and port simulation; application of CT scanning in definition of tumor volumes; monitoring of changes in external and internal body habitus; in vivo dosimetric measurement; and routine implementation of dynamic treatment techniques.

e. To maintain, expand, and upgrade the data base containing demographic, staging, treatment, and follow-up data on all pion patients, as well as to implement such a system for conventionally irradiated patients at CRTC/Albuquerque as an intramural comparison group for pion-related clinical observations.

f. To foster relationships with institutions and individual physicians as referral sources of patients for the study and sites for dissemination of pion-related patient care technology.

g. To maintain close cooperation with pion projects underway at the TRIUMF accelerator in Vancouver and SIN in Villigen, Switzerland, and to coordinate protocol design and correlate clinical observations to obtain the maximum amount of information in the shortest possible time.

4. Methods of Procedure

a. General

i. Protocol design and implementation. The assessment of potential efficacy of pion radiotherapy necessitates evaluation of the modality in treatment of multiple tumor types and sites. Locally bulky and necrotic tumors and those that are deep-seated and/or in close proximity to radiosensitive normal

tissues might most reasonably be expected to respond more favorably to irradiation than to photon treatment. Some anatomic sites in which lesions arise and in which local control of the neoplasm is known to be a significant factor in limiting survival include brain, lung, esophagus, and uterine cervix. Decisions regarding the feasibility and usefulness of randomized trials for these sites will be delayed pending acquisition of additional data.

Protocol design for the pion radiotherapy program necessitates consideration not only of ideal experimental design but also of relevant endpoints for such technologically intensive clinical investigation and practical and logistic limitations inherent in such an effort. Consideration must be given to such factors as appropriate "control" groups, optimization of therapeutic technique in both experimental and control arms of the study, uniformity of treatment technique during the anticipated accession period, adequacy of patient numbers, and adequacy and reliability of beam production. The implicit premise that warrants the use of pion radiotherapy is that otherwise incurable patients may be curable when treated by the experimental modality. Confirmation of the premise necessitates treatment and evaluation of adequate numbers of patients with tumors at multiple sites for which the theoretical advantages of pion therapy are anticipated and for which failure of local control is an established impediment to improved survival.

ii. Statistical considerations. Statistical considerations regarding the proposed Phase II trials are outlined in Table 14. The estimates of the number of patients necessary for each site are predicted upon calculations according to the methods described by Schoenfeld.¹⁵ The major purpose of the proposed studies is to evaluate pion radiotherapy in the management of several disease sites which represent significant public health problems and for which failure of local control is recognized as a significant impediment in curative management. The Phase II trials will be used as a guide to the design of Phase III studies for those disease sites showing some promise of improved results and no evidence of unacceptable morbidity.

Statistical assumptions considered in the estimate of necessary patients include an estimate of local control or proportion of surviving patients at a defined interval following treatment and an arbitrary estimate of "significant" improvement. These proportions have been obtained from the published literature regarding results with conventional therapy and from a conservative estimate that 20 percent improvement with pions is "significant." In addition, factors are considered regarding the acceptability of (1) proceeding to Phase III trials in the case in which the experimental modality is not actually superior, or (2) rejecting such trials when the experimental modality actually represents true improvement. The probabilities accepted for these Phase II trials are 25 percent for (1) and 10 percent for (2).

iii. Anticipated accession. Based upon previous experience and anticipated accelerator operating schedules, it is expected that approximately 70 patients will be treated annually (Table 15). An additional complicating factor has been the cyclic operating schedule of the LAMPF accelerator, which dictated that all patients intended to receive a definitive, full-course series of pion treatments must be identified within a maximum of 2-3 weeks before an

TABLE 14

ANTICIPATED NUMBER OF PATIENTS
NECESSARY FOR NONRANDOMIZED STUDIES

<u>Site/Stage</u>	<u>Parameter Evaluated</u>	<u>Reference</u>	<u>P₀</u>	<u>P₁</u>	<u>C₁</u>	<u>C₂</u>	<u>N</u>
Cervix III	LC	49, 50, 52	.50	.70	.25	.1	21
Cervix IV	LC	49, 51	.25	.45	.25	.1	22
Pancreas	PS 1	66, 67	.40	.60	.25	.1	23
Esophagus	PS 1	80, 81, 83	.40	.60	.25	.1	23
Lung	PS 1	98, 104, 109	.40	.60	.25	.1	23
Glioma III	PS 1.5	86	.55	.75	.25	.1	20
Glioma IV	PS 1.5	86	.25	.45	.25	.1	<u>22</u>
TOTAL							154

- LC = local control
- PS 1 = proportion surviving at 1 yr
- PS 1.5 = proportion surviving at 1.5 yrs
- P₀ = probability of local control with best conventional therapy
- P₁ = probability of local control assuming "significant" improvement with pion radiotherapy
- C₁ = probability of accepting a treatment for Phase III trials that is no better than conventional
- C₂ = probability of rejecting a superior treatment for Phase III trials
- N = number of patients necessary to complete pilot study

TABLE 15
ANTICIPATED TREATMENTS/YEAR

Ports/Year, Assuming:

27	weeks of operation/yr
<u>x5.5</u>	days of operation/wk
149	days/yr
<u>x16</u>	hrs/day
2376	hours/year
<u>x2.53</u>	ports/hour (avg 7/80-11/80)
6011	ports/yr (100% efficiency)
<u>x.71</u>	daytime-evening efficiency
4268	ports/year

Ports/Treatment Course, Assuming:

28	fx/treatment course (avg 1/80-3/81)
<u>x2.17</u>	port/tx (avg 1/80-3/81)
60.1	ports/treatment course

$$4268 \text{ ports/year} \div 60.1 \text{ ports/treatment course}$$

$$= 71 \text{ treatment courses/yr}$$

anticipated operating cycle and have all necessary diagnostic evaluation and treatment planning completed by the beginning of the cycle. Two major changes in policy have resulted in more continuous accessions and increased patient through-put. First, the accelerator operating schedule has been modified to allow more or less continuous operation for the funded portion of each fiscal year. This allows much greater flexibility in recruitment of "definitive" patients. In addition, an increasing number of patients are receiving abbreviated courses of pion therapy in which boosting doses of approximately 1500-2000 π rad are delivered to localized volumes of radiographically demonstrable tumor in conjunction with planned supplementary conventional radiotherapy. This approach has been used primarily in treatment of high-grade gliomas and unresectable pancreatic cancer, with such patients being entered on study at any time during the treatment cycle when available positions exist in the treatment schedule. The treatment of cone-down volumes, particularly for deep-seated neoplasms, is especially attractive in considering the theoretical benefits of improved dose distribution. Protocol changes suggested previously involving assessment of re-oxygenation with completion of therapy with standard photons and the use of shorter overall fractionation times improve patient accession.

In light of the need to evaluate multiple sites and types of neoplasms and the necessity for large numbers of patients treated in a uniform manner in randomized trials as well as inherent limitations on patient through-put, it is necessary to consider alternative approaches to collection of data useful in deciding the future of pion radiotherapy. The method selected is nonrandomized trials in those sites with extremely poor survival rates with conventional therapy.

Nonrandomized trials will be continued under RTOG protocol 79-23 for those patients with high-grade glioma (Astrocytoma Grade III and IV), inoperable esophageal carcinoma, inoperable epidermoid carcinoma of the lung, carcinoma of the uterine cervix (Stages III and IVA), and inoperable adenocarcinoma of the pancreas. With the exception of Stage III cervical carcinoma, the anticipated five-year survival in each of these diseases is approximately 10 percent or less, and any significant trend toward improved survival after pion therapy should be apparent with treatment of a moderate number of cases and with relatively short follow-up. We do not believe it to be appropriate to proceed to Phase III trials in all sites until adequate numbers of patients with each disease have been treated in a systematic fashion to tolerance doses and analysis can be completed regarding unexpectedly low survival rates or unacceptable morbidity as compared to conventional therapy. In addition, it is necessary to compare optimal pion therapy with optimal conventional treatment to obtain meaningful results, and this dictates the necessity for routine dynamic pion therapy for most sites outside the head and neck. Such capability is now available.

Adequacy of patient numbers is an essential aspect of the clinical program if the proposed studies are to be completed within three years. Patient accession has shown a steady pattern of growth as a result of improved cooperation with the medical community within New Mexico and development of closer ties with referring physicians in other states (Table 16). The necessity for recruitment from a wide population base follows from the narrow time-frame for accession with cyclic beam operation and protocol restrictions, particularly regarding limitation of sites to be treated and performance status.

TABLE 16

PION REFERRALS BY STATE

Arizona	1
California	31
Colorado	18
District of Columbia	1
Massachusetts	4
Minnesota	6
Missouri	6
Montana	3
New Jersey	1
New Mexico	99
Albuquerque (78)	
Other communities (21)	
New York	10
Ohio	5
Pennsylvania	3
Texas	7
Utah	5
Wisconsin	1
Wyoming	<u>2</u>
TOTAL	203

With an increase in accelerator intensity, approximately 15 more patients can be accessed annually. A log of rejections has been maintained since the inception of the program, and analysis of the last three years showed approximately 35 referrals per year of patients who would have been eligible for study, but were rejected because of the maximum number of patients had been accessed for treatment or because of beam down-time constraints. Therefore, we anticipate no difficulty in accessing 70 patients per year, as proposed in this application.

The clinical trials outlined below are all active at The CRTC, with the approval of the NCI, the RTOG, and the Human Research Review Committees of the University of New Mexico and the Los Alamos National Laboratory.

Carcinoma of the uterine cervix

i. Introduction. Although of declining incidence, advanced stage carcinoma of the uterine cervix continues to be refractory to satisfactory management by external irradiation and conventional radium systems and, therefore, continues to be a significant source of morbidity and mortality. The published five-year survival rates for Stage III and IV cervical carcinomas vary substantially, as shown in Table 18.

A major source of failure of conventional treatment is in the failure to control local-regional disease. Jampolis presented a detailed analysis of sites of failure after definitive radiotherapy and showed central and regional (pelvic) failures in 33 percent of patients with Stage IIIA and IIIB disease.⁵⁰ Eighteen percent of patients in these groups developed distant metastases alone. Failures were ascribed to unfavorable geometry for intracavitary radium and inability to deliver doses in excess of 7000 rad due to intolerance of pelvic organs. Tak also reported 33 percent pelvic failures in Stage III patients.⁵² In Stage IV disease this pattern is even more striking. Million reported a series of 53 patients with bladder invasion, with 36 of 41 recurrences of disease in the pelvis.⁵¹ Prempre reported local failure in only 5 of 31 patients with Stage IIIB disease treated with a combination of external irradiation and parametrial radium needle implant.^{53,54} The complication rate was only 3 percent, and the apparent improvement in local control was ascribed to increased local dose.

(1) Para-aortic nodes. Systematic surgical staging of patients with carcinoma of the cervix has shown that approximately 35 percent of patients with Stage III and 50 percent of patients with Stage IV disease have involvement of para-aortic lymph nodes.⁵⁵ In a study of 103 patients having lymphangiography and subsequent surgical exploration, accuracy of 98 percent was obtained for histologic confirmation of a definitely positive lymphangiogram.⁵⁶ False negative studies occurred in 22 percent of proven involvement. False positive rates as high as 50 percent have been reported.⁵⁵

Because of the frequency of para-aortic lymphadenopathy in advanced stage cervix cancer, various groups have studied extended field irradiation in an attempt to improve survival.⁵⁷⁻⁶⁰ In a selected group of "evaluable" patients, Wharton⁵⁹ reported 69 percent of failures were distant metastases and the remainder were local pelvic recurrences, suggesting that aggressive therapy might contribute to improved survival in only about one-third

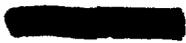


TABLE 18

FIVE-YEAR SURVIVAL FOR ADVANCED CARCINOMA OF THE UTERINE CERVIX

	Institution			
	<u>Royal Marsden</u> ⁴⁹	<u>M.D. Andersen</u> ^{50,51}	<u>Tufts</u> ⁵²	<u>Maryland</u> ^{53,54}
III	16%	50%	42%	65% (3-yr survival)
IV	6%	11-14%	23%	--

of those patients with nodal involvement. Low para-aortic failure as initial site of relapse has been reported.⁵⁴ Overall, survival in patients initially staged IIIB and IVA and treated with extended field radiotherapy for documented nodal disease is only about 10-15 percent;⁵⁶⁻⁵⁸ however, substantial mortality in several series has been related to treatment complications.

(2) Complications of conventional irradiation. With standardized techniques of conventional treatment, complications such as proctitis, fistula formation, bowel necrosis, and ureteral obstruction may be expected in 5-10 percent of cases.^{52,54} The uniform experience with wide-field irradiation, particularly after surgical staging, has been a marked increase in frequency and severity of complications involving the GI tract.^{50,58,59} El Senoussi⁵⁷ reported a detailed analysis of dose and volume factors as related to complications. Complications, including fistulae, sigmoid obstruction, and small bowel injury, occurred in 62 percent of patients receiving extended field irradiation for Stage IIIB and IVA disease. Increased incidence of complications was related both to large volumes (6000-7000 cm³) and high doses of external therapy (greater than 5000 rad) necessary in treatment of advanced local disease and para-aortic nodes.

(3) Hyperbaric oxygen. Randomized clinical trials have been published comparing results of irradiation of advanced cervix cancer in air or hyperbaric oxygen.⁶¹⁻⁶³ Improved local control for patients with IIB, III and IVA was obtained in each study for hyperbaric oxygen. In studies reported by Watson⁶¹ and Dische,⁶² this translated into a statistically significant survival advantage for patients with Stage III disease treated with hyperbaric oxygen.

ii. Rationale and objectives. Pi meson radiotherapy is proposed as a potential means of improving local control in primary advanced stage (III, IVA) or locally recurrent (following surgery alone) squamous cell carcinoma of the uterine cervix and associated bulky lymphadenopathy and, thus, improving survival. Anticipated benefits are:

(1) Improved dose distribution with decreased volume of normal tissue receiving high dose and, therefore, decreased risk of serious morbidity.

(2) High-LET radiation effect on hypoxic cell fraction in sites of bulky disease, a proven source of local failure, and a mechanism of potential therapeutic gain corroborated by favorable results with hyperbaric oxygen therapy.

Objectives of the study include determination of:

- (1) Tumor response,
- (2) Response of regional nodal metastases,
- (3) Incidence of locally persistent or recurrent disease and time to recurrence.
- (4) Incidence of distant metastases,
- (5) Patient survival,
- (6) Acute and late effects of pions on normal tissues and incidence of morbidity, and
- (7) Optimal dose-volume, relationship and technique in pion treatment of pelvic and regional nodal disease.

iii. Protocol. This study is proposed for inclusion in a pilot study under RTOG 79-23 (see Appendix A), a protocol previously approved by the RTOG and NCI for Phase II studies of pion radiotherapy.

Eligibility requirements are: biopsy-proven squamous cell carcinoma of the uterine cervix, Stage III or IVA by FIGO or A staging system, or locally recurrent disease following surgical therapy and other criteria of eligibility as defined in the protocol (see Appendix A, RTOG 79-23, p. 3).

All patients will have initial diagnostic evaluation including medical history and physical examination; chest x-ray and CT or tomograms of the chest as indicated; liver function tests and CT or radionuclide liver scan as indicated; CT of the entire pelvis and para-aortic region to the renal hila; IVP; bipedal lymphangiography; CBC; blood chemistry screening panel, including renal function tests; and urinalysis. Examination under anesthesia, including cystoscopy and sigmoidoscopy, will be performed by the study team before therapy. Additional studies, e.g., bone scans, blood studies, cultures, barium enema, etc., will be performed as indicated.

Consistent with the objective of improved local control of sites of bulky disease, pion irradiation will be given to such sites of disease in the pelvis or para-aortic region as documented by complete diagnostic evaluation.

(1) Pion radiotherapy alone. Patients receiving pion irradiation alone will receive a minimum dose of 2800 π rad (3500 π rad maximum) to the pelvis and regional nodes at a minimum distance of 2-3 cm outside documented gross disease and/or encompassing regional nodal groups at known risk, using anterior and posterior opposed fields and abutted fields as necessary. Boosting doses of 800 π rad minimum (1000 π rad maximum) will be given to sites of bulky disease. Daily fractions will be 100 π rad minimum (125 π rad maximum), with doses of 500 π rad to 600 π rad minimum per week. A single interruption of one week may occur during the planned course of therapy, as necessitated by beam operating schedule.

(2) Pion radiotherapy in combination with conventional irradiation. Patients accessed to the study in excess of 2½ weeks before the initiation of a treatment cycle or less than 7 weeks before the end of a cycle or who have mitigating social or medical circumstances may receive planned combined conventional and pion irradiation. Depending upon time of accession, pion boosting therapy will be given to sites of bulky disease before or after conventional irradiation of regions requiring prophylactic treatment. The dose of pion irradiation will be 1200 to 1600 π rad minimum tumor dose (1500-2000 π rad maximum) in 12-16 fractions over 2½-3 weeks. The minimum dose will be prescribed at the margin of radiographically demonstrable gross disease. Supplementary conventional irradiation will be given by megavoltage equipment, using four-field or equivalent technique to pelvis and appropriate para-aortic volumes to a dose of 4500 rad in 180 rad daily fractions over 5 weeks.

Follow-up data will be collected in accordance with RTOG 79-23 (see Appendix A).

(3) Endpoints. Numbers of patients necessary to assure, on statistical basis, the acceptance for further testing by Phase III trials of a potentially superior treatment have been determined by the method of Schoenfeld.¹⁵ Table 14 contains the details of pertinent statistical assumptions. It is anticipated that approximately 43 appropriate patients will be accessed and treated over the next 2-3 years. About 20 such patients are evaluated and treated annually at the CRTC/Albuquerque, and additional patients are regularly referred from Loma Linda University (James Slater, M.D.) and New York Medical College (Hugh R.K. Barber, M.D.).

e. Carcinoma of the pancreas

i. Introduction. Adenocarcinoma of the pancreas has demonstrated an alarming increase in incidence over the last 40 years¹³ and continues to present as advanced disease refractory to adequate local management by any therapeutic modality (Table 19).

(1) Surgery for pancreatic carcinoma. Reported five-year survival after primary surgical therapy (Whipple procedure or total pancreatectomy) ranges from less than 1 percent to 5 percent for unselected groups of patients.^{64,65} In fact, only 7-20 percent of patients are candidates for radical surgical extirpation of pancreatic carcinoma at the time of diagnosis, and survival in this relatively favorable group is only 5-15 percent.^{64,72} Inadequacy of surgical treatment is related in part to high operative mortality (16-30 percent)^{64,65,73} and to frequent local recurrence. Thirteen of 26 patients who survived attempted surgical excision in the report of Tepper⁶⁴ subsequently developed local recurrence. This may be, in part, because the standard Whipple procedure does not remove all involved node groups in about one-third of patients with resectable carcinoma of the head of pancreas.⁷⁴ In addition, multicentricity is reported in as many as one-third of such cases.⁷³ As a result, most surgical intervention is purely palliative and associated with median survival in the range of 6-7 months.^{64,65} Appropriate palliative surgery may include gastrojejunostomy as well as biliary bypass, as 11-26 percent of patients will subsequently develop GI obstruction during the course of their disease.⁶⁵

(2) Radiotherapy for pancreatic carcinoma. Traditionally, radiotherapy has been used for palliation only; Miller and Fuller⁷¹ described favorable response of symptoms to doses of 3600 to 6000 rad but median survival of only 6.6 months and "excellent" palliation in only 10 percent of cases. Moertel showed improvement with a combination of 3500-4000 rad with 5-FU giving a mean survival of 10.4 months.⁷⁵ Occasional cures have obtained with interstitial brachytherapy, although most locally unresectable lesions are associated with regional adenopathy of other evidence of local-regional spread, rendering them unsuitable for cure by this means.⁶⁸ Improved survival has been reported with high-dose conventional irradiation by Halsam⁶⁶ and Dobelbower.⁶⁷ Halsam reported a median survival of about 9 months and 21 percent 30-month survival in a group of 29 patients receiving 6000 rad over 10 weeks in split course treatment. Dobelbower reported a median survival of 12 months and approximately 10 percent, three-year survival in a group of 40 patients receiving 5900-7000 rad in 7-9 weeks. Five of 48 patients failed to complete planned treatment. Seven of 27 patients at risk greater than 6 months developed upper GI bleeding presumed secondary to radiation gastritis. Only 9 of 40 patients in this study reportedly developed metastatic disease.

TABLE 19

SURVIVAL AND LOCAL CONTROL IN UNRESECTABLE ADENOCARCINOMA OF THE PANCREAS

<u>Treatment Modality</u>	<u>Local Failure (%)</u>	<u>Median Survival (months)</u>	<u>Five-year Survival (%)</u>	<u>Reference</u>
Radical surgery	50	11	10-15	64, 65
High-dose external irradiation	63	9-12	(unk)	66, 67
Interstitial irradiation	71	7	1	68
Neutron irradiation	45	9	(unk)	69, 70
Palliative only	100	6	0	64, 65, 71

(3) High-LET radiotherapy for pancreatic carcinoma.

Because of difficulty controlling local disease in unresectable pancreatic carcinoma, various new radiation modalities have been employed, including neutrons^{69,70} and pions.⁷⁶ Al-Abdullah et al.⁶⁹ presented a comparison of conventional irradiation, fast neutron irradiation and ¹⁹⁸Au implantation, with respective median survival of about 6, 8, and 9 months. Three-year survival was 3, 14, and 12 percent. Kaul et al.⁷⁰ reported a median survival of 9 months and 5 percent at two years in a group of 31 patients receiving neutron radiotherapy. Eleven patients developed late complications, eight of which were related to severe GI injury and two of which were fatal. Fourteen patients had progression of local disease, and the liver was the most commonly implicated site of distant metastasis. This finding has been confirmed in a series of 18 patients receiving pion radiotherapy, 14 of whom developed distant disease with liver involvement in 10 cases.⁷⁶

ii. Rationale and objectives. Pion radiotherapy is proposed as a potential means to improve local control in biopsy-proven, regionally localized, unresectable adenocarcinoma of the pancreas. The anticipated benefits are:

(1) A favorable dose distribution advantage for pion irradiation over conventional irradiation, allowing delivery of high dose to the tumor with minimal increased risk to dose limiting normal tissues, including G.I. tract, spinal cord, kidneys, and liver.

(2) A potential benefit related to the high-LET component of the beam as corroborated by early reports of favorable responses of pancreatic carcinoma to fast neutron irradiation.

Objectives of the study include determination of:

- (1) Tumor response by serial examination, CT scanning and other appropriate radiographic studies,
- (2) Sites of progression of disease,
- (3) Time to progression of disease,
- (4) Median and actuarial survival,
- (5) Effects of pion irradiation on normal tissues with particular attention to late injury, and
- (6) Optimal dose-volume relationships and technique of pion radiotherapy for this site.

iii. Protocol. A Phase II trial of combined pion and conventional irradiation for treatment of unresectable pancreas cancer will be continued under RTOG 79-23.

Eligibility requirements are: biopsy-proven adenocarcinoma of the pancreas with contiguous or regional nodal spread to peri-pancreatic or para-aortic nodes (AJC stages T3/T4 or any T/N1-3) deemed unsuitable for resection by the referring surgeon and without distant intra-abdominal spread; a surgical procedure to include biliary and, when possible, GI bypass procedures, inspection and biopsy of the liver, and inspection and biopsy, when appropriate, of mesentery, peritoneum, or other intra-abdominal structures; no known distant metastases; and other criteria of eligibility according to the protocol (see Appendix A, RTOG 79-23, p. 3).

[REDACTED]

All patients will have initial diagnostic including routine history and physical examination, chest x-ray and tomograms of the chest as indicated; liver function tests, both contrast and non-contrast CT scan of the entire upper abdomen with liver; radioisotope liver-spleen scan; upper GI series; IVP; CBC; CEA; and urinalysis. All reports will be reviewed in detail to assure anatomic localization of abdominal disease. Additional studies including cholangiography, blood studies, etc., will be obtained as indicated.

A treatment regimen previously tested in eight patients fulfilling criteria of eligibility will be continued. A planned combination of pion irradiation to the pancreas and sites of radiographically demonstrable disease and moderate dose conventional irradiation of the entire liver, pancreas, tumor and regional nodes is to be employed. Depending upon time of accession during the treatment cycle, pion irradiation will precede or succeed conventional therapy. The pion component of the treatment includes a dose of 1920 rads minimum dose (2400 rads maximum) delivered in 24 fractions over five weeks to a volume encompassing the entire pancreas, tumor, and regional nodes (usually about 1200 cm³) via evenly weighted anterior and posterior opposed ports. An additional dose of 1152 rads minimum (1440 rads maximum), prescribed at the periphery of the radiographically demonstrable mass on CT scan, is delivered over the same time period through a single anterior field (approximately 300 cm³). The two treatments are spaced a minimum of six hours apart, but both volumes are treated daily. Conventional supervoltage irradiation of the entire liver and pion irradiated volume is delivered through anterior and posterior opposed fields to a dose of 2400 rad in 150 rad fractions over 3½ weeks.

Follow-up data will be collected in accordance with RTOG 79-23.

Twenty-three patients are necessary to assure testing of pion radiotherapy as a potentially superior method of treatment of pancreatic carcinoma according to the method of Schoenfeld,¹⁵ based upon statistical assumptions shown in Table 14. Eight patients have been accessed to this pilot study since July 1980, and increased accessions are anticipated.

f. Carcinoma of the esophagus

i. Introduction. Carcinoma of the esophagus is relatively uncommon, accounting for about 3 percent of newly diagnosed cancer, but associated with very poor prognosis for local control or survival. Surgery alone, radiotherapy alone or as a pre-operative adjuvant and radiation in combination with chemotherapy have all been employed in the attempted cure of esophageal carcinoma with variable, and mostly unsatisfactory results (Table 20).

(1) Conventional therapy for carcinoma of the esophagus. Surgical excision of esophageal carcinoma is a procedure associated with significant operative mortality and unsatisfactory survival rates. Postoperative mortality of 5-18 percent has been reported^{77,79} and long-term survival, even accounting for the relatively favorable lesions and general status of patients selected for surgery, is only about 7-17 percent.^{77,78} Between 30 and 50 percent of unselected patients are suitable for palliation only.⁸⁰⁻⁸³ Pre-operative radiotherapy has been employed in an attempt to render otherwise inoperable lesions suitable for resection. Even after doses of 3000-4000 rad,

TABLE 20
 LOCAL CONTROL AND SURVIVAL IN CARCINOMA OF THE ESOPHAGUS

<u>Treatment Modality</u>	<u>Local Failure (%)</u>	<u>Median Survival (months)</u>	<u>Five-year Survival (%)</u>	<u>Reference</u>
Surgery	60-70	12	7-17	77, 78
Pre-op XRT	80-93	9-12	4-13	79-81
Radical XRT	40-80	9-12	4-20	80-83
XRT + chemotherapy	>50	6-11	unknown	84, 85
Palliative	>99	4-6	0	80, 82, 84

only 73 percent of patients planned for operation were operable and only 73 percent were resectable in a group of 56 patients reported. No significant differences in survival are noted for patients treated with surgery alone, pre-operative radiotherapy with surgery, or radiotherapy alone. 7-83

Although about 30 percent of patients develop distant metastases, failure of therapy is most often related to failure to eradicate disease in the primary site. This is evidenced by local failure rates between 40 and 95 percent.⁷⁷⁻⁸⁵ Survival is dependent upon size of primary lesion,⁸⁰⁻⁸² histology,⁷⁷ site of primary,⁸⁰ and radiation dose.⁸¹ Elkon⁸² showed a 25 percent local failure rate in patients with lesions less than 5 cm in length and 64 percent local failure in larger tumors. Kinoshita⁷⁷ showed 10-year survival following surgery alone of 3.3, 10.3 and 46.0 percent for poorly, moderately and well differentiated carcinomas respectively. Hussey⁸⁰ showed two-year survival rates of 17, 5, and 11 percent for lesions of the cervical, mid-thoracic, and distal esophagus respectively. The optimal dose range reported by Beatty⁸¹ is 1600-1700 rets, with 28 percent 2-year survival in this group. Two-year survival for patients receiving doses of 1100-1599 rets was 15 percent.

(2) Complications of conventional therapy. Operative mortality of 5-18 percent has been reported for primary surgical management.^{77,79} Radiation-related complications include injury to lung, heart, and spinal cord. Incidence of severe chronic reactions is approximately 5 percent.⁸² Approximately two-thirds of patients will develop esophageal stricture after radiotherapy; however, only about 25 percent of these strictures are benign.⁸¹

ii. Rationale and objectives. Pion radiotherapy is proposed as a potential means of improving local control and, therefore, survival in inoperable and unresectable carcinoma of the esophagus. The anticipated benefits are:

- (1) Favorable dose distribution allowing high dose to the esophagus with minimization of radiation dose to spinal cord, heart, and lungs.
- (2) High-LET radiation effect on bulky, ulcerated, hypoxic primary lesions.

Objectives include determination of:

- (1) Primary tumor response,
 - (2) Frequency and timing of local recurrence,
 - (3) Frequency of distant metastases,
 - (4) Frequency of regional nodal spread of disease,
 - (5) Median and actuarial survival,
 - (6) Effect of pion irradiation on normal tissues,
- and
- (7) Optimal dose-volume relationships and technique of pion radiotherapy.

iii. Protocol. A Phase II trial of pion radiotherapy alone or in planned combination with conventional radiotherapy for inoperable or unresectable carcinoma of the esophagus will be undertaken under the existing protocol RTOG 79-23 (see Appendix A).

Eligibility requirements are: biopsy-proven carcinoma of the esophagus determined by the referring surgeon to be inoperable or unresectable; no evidence of distant metastasis, including involvement of celiac lymph nodes; and other criteria of eligibility according to the protocol (see Appendix A, RTOG 79-23, p. 3).

All patients will have initial diagnostic evaluation consisting of routine history and physical examination, chest x-ray and whole lung tomograms as indicated, CT scan of the entire thorax, contrast-enhanced and noncontrast CT scan of the liver with detail of the celiac axis, upper GI series with esophograms, liver function tests, CBC, urinalysis, radionuclide liver-spleen scan, and bone scan. Additional evaluation will be performed as indicated. Fiberoptic esophagoscopy will be performed in all cases.

Depending upon time of accession relative to treatment cycle, patients will receive pion therapy alone or as boosting therapy in combination with planned conventional radiotherapy to volumes requiring prophylactic doses.

(1) Pion radiotherapy alone. Pion radiotherapy will be given to a dose of 2800 π rad minimum tumor dose (3500 π rad maximum) in 100 π rad fractions over six weeks to a volume encompassing gross tumor, with 5 cm superior and inferior margins overlying radiographically normal esophagus. Treatment technique will entail anterior and posterior opposed fields alone or in combination with oblique fields to obtain optimal normal tissue sparing. Boosting doses of 800 π rad minimum (1000 π rad maximum) will be given in 8 fractions over 1½-2 weeks to the site of bulk disease, with the minimum tumor dose prescribed at the margin of radiographically demonstrable gross disease. Interruption of treatment by up to one week may be necessitated by beam scheduling.

(2) Combined pion and conventional radiotherapy. Patients accessed to the protocol more than 2½ weeks before a scheduled treatment cycle or less than 7 weeks before the conclusion of a cycle will be treated with planned combined therapy. Conventional treatment will precede or succeed pion therapy, depending upon time of accession. The conventional therapy portion of treatment will entail treatment of the primary lesion with appropriate margins, using anterior and posterior fields with wedge-filtered oblique fields as necessary to optimize dose distributions. Regional nodes in the mediastinum, celiac area, and supraclavicular fossae judged to be at risk will be included in this treatment volume. The dose at the isocenter will be 4500 rad in 25 fractions over 5 weeks (180 rad/fraction), with all fields treated daily. The pion component of therapy will entail 1200-1500 π rad minimum (1500-1875 π rad maximum) in 12 to 15 fractions of 100 π rad minimum tumor dose (125 π rad maximum) over 2½-3 weeks to a volume in which the minimum tumor dose will be delivered to the margin of radiographically demonstrable disease.

Follow-up data from either arm will be collected in accordance with RTOG 79-23.

(3) Endpoints. Twenty-three patients have been determined as necessary to provide the statistical basis for acceptance or rejection of pion treatment for testing in a Phase III randomized trial based on the methods of Schoenfeld¹⁵ (see Table 14). Patients have not been actively

sought for treatment of esophageal carcinoma, so precise assessment of numbers of patients potentially available is impossible. It is anticipated that the requisite number of patients for this pilot study can be accessed in 3 to 3 years.

g. High-grade glioma - astrocytoma III and IV

i. Introduction. The high-grade or malignant gliomata comprise an exceptionally virulent group of diseases, refractory to control by any treatment modality. These lesions are generally considered to be uniformly lethal and demonstrate a pattern of relentless local progression and only very rarely, distant metastasis.

(1) Conventional therapy for high-grade glioma. The standard treatment for high-grade glioma has been attempted surgical excision with post-operative radiotherapy.⁸⁸⁻⁹⁰ This form of treatment has been demonstrated to be superior to surgery alone in prospective randomized trials.⁹⁰ Survival statistics vary, depending upon histology, with five-year survival of approximately 20 percent in Grade III lesions treated with excision and high dose irradiation,^{86,88} but only occasional survival with Grade IV tumors, i.e., glioblastoma multiforme.^{86-88,91} As a result of such poor survival statistics, a variety of experimental therapy has been investigated, including chemotherapy,^{90,92,93} radiation sensitizers,⁹⁴ high-LET irradiation,⁹¹ and altered fractionation and dose schedules.^{86,95} A summary of these results is presented in Table 21.

Despite aggressive therapy, median survival continues to be measured in weeks, with statistics ranging from about 6-17 weeks for palliative therapy to about 45-50 weeks for combined groups of patients with Grade III and Grade IV lesions.^{87-90,92,93} Death is almost invariably related directly to progression of primary disease or to debilitating secondary effects of uncontrolled disease in the central nervous system. Distant metastases are very rarely encountered outside the CNS, although spread within the brain may be extensive and difficult to assess clinically. Spread within the brain is by direct extension or seeding, and about 25 percent of supratentorial lesions show crossing to the contralateral hemisphere at the thalamus or corpus callosum.⁹⁵

(2) Results of experimental therapy. Several experimental approaches to improve local control in high-grade gliomas have been explored. Chemotherapy, most often with nitrosoureas, has been studied by the Brain Tumor Study Group^{90,93} and by individual institutions.⁹² In studies by Walker, et al.^{90,93} addition of semustine (MeCCNU) or carmustine (BCNU) to post-operative radiotherapy did not produce a statistically significant change in survival, although significance was demonstrated for the difference between patients receiving semustine alone or carmustine plus radiotherapy. Lomustine (CCNU), in combination with surgery and radiotherapy, produced median survival of 11.5 months, comparable to that reported with surgery and radiotherapy alone.

Metronidazole with low-dose radiotherapy (3000 rad) resulted in 26-week median survival in patients with Grade IV tumors. Similar results were observed with hyperfractionated irradiation with doses up to 4000 rad in one week.⁹⁶ Salazar and Rubin reported median survival of 204

TABLE 21
LOCAL CONTROL AND SURVIVAL IN HIGH-GRADE GLIOMAS

<u>Treatment Modality</u>	<u>Tumor Grade</u>	<u>Median Survival (wks)</u>	<u>Five-year Survival (%)</u>	<u>Reference</u>
Surgery alone	III IV	6	0	87
XRT alone	III IV	? 13	? 0	- 87
Surgery + post-op XRT	III IV	91-230 42-57	26 1	86, 88 86, 88
Surgery • XRT + chemotherapy	III IV	45-47	0	90, 92, 93
XRT + radiosensitizer	III IV	N.A. 26	N.A. 0	94
Neutron XRT	III IV	50	0	91
"Very-high-dose" XRT • surgery	III IV	204* 56	35 0	86 86
Palliative	III IV	6-17	0	87, 90

*Data based on 6 cases.⁸⁶

weeks and 57 weeks for Grade III and IV tumors, respectively, following protracted, "very-high-dose" irradiation to doses as high as 8000 rad.⁹⁵ The dose response phenomenon is confirmed by the results of Walker.⁹⁷

Neutron radiotherapy has been used in treatment of high-grade gliomas on the presumption that tumor hypoxia was a contributing factor in failure to control disease locally and that this could be overcome by high-LET radiation. Caterall confirmed previous experience with fast neutron irradiation of the brain in that no improvement in survival could be determined for the experimental modality, but that patients died with absence of disease or minimal microscopic involvement and coagulative necrosis in almost 70 percent of cases following 1300-1560 neutron rad.⁹¹

ii. Rationale and objectives. Pion radiotherapy is proposed as a means of improving local control and survival in treatment of biopsy-proven high-grade glioma, astrocytoma Grade III and IV. The anticipated benefits are:

(1) Improved dose distribution over conventional radiations, permitting delivery of higher doses in regions of brain known to be involved by tumor, thus taking advantage of the known dose-response relationships for this disease.

(2) High-LET effect on hypoxic cell fraction, attempting to obtain the same advantage in tumor control found with neutron therapy, but sparing the toxicity.

Objectives of the study include determination of:

- (1) Tumor response by serial CT scanning,
- (2) Time to recurrence and criteria of diagnosis of recurrence, including CT diagnosis of tumor recurrence and brain necrosis,
- (3) Median and disease-free survival,
- (4) Acute and chronic effects of pion irradiation on normal tissues based on systematic study of autopsy materials, and
- (5) Optimal dose-volume relationships and technique of pion radiotherapy for this site.

iii. Protocol. Continuation of Phase II, non-randomized trial of pion radiotherapy alone or in planned combination with conventional radiotherapy for biopsy-proven high-grade glioma (astrocytoma Grade III and IV) will be undertaken under the existing protocol RTOG 79-23 (see Appendix A).

Eligibility requirements are: biopsy-proven high-grade glioma (astrocytoma Grade III and IV) with or without resection of primary lesion, and other criteria of eligibility according to the protocol (see Appendix A, RTOG 79-23, p. 3).

All patients will have initial diagnostic evaluation, including routine history and physical examination, contrast-enhanced and noncontrast CT scans of the whole brain, chest x-ray, urinalysis, CBC, and blood chemistry screening panel. All pre-operative CT scans, arteriograms, or other pertinent studies, including operative reports, will be reviewed in detail by the study team.

Depending upon time of accession and mitigating social or medical circumstances, patients will receive pion radiotherapy alone or in planned combination with conventional megavoltage radiotherapy to the whole brain.

(1) Pion radiotherapy alone. Pion radiotherapy will be given to the whole brain to a dose of 2200 π rad minimum tumor dose (2750 π rad maximum) in 22 fractions of 100 π rad minimum over 4-4½ weeks. The minimum tumor dose will be prescribed at the surface of the brain. Boosting doses of 1400 π rad minimum (1750 π rad maximum) will be given in 14 fractions of 100 π rad minimum over 2½-3 weeks to sites of radiographically demonstrable disease. Both whole brain and boosting treatment will be given by opposed lateral fields. The minimum dose for cone-down volumes will be prescribed to a volume encompassing regions of obvious postsurgical defect, contrast enhancement, and surrounding regions of low density. In cases of supratentorial glioma in which involvement of midline structures is of concern, the cone-down volume will include the medial portion of the contralateral hemisphere at the level of involvement.

(2) Combined conventional and pion radiotherapy. Patients accessed to the study before two weeks in advance of the anticipated start of a treatment cycle or less than four weeks before the conclusion of a cycle will receive full course conventional, megavoltage irradiation of the whole brain in combination with pion irradiation of the site of gross disease. Whole brain irradiation will be given using megavoltage x-rays or ⁶⁰Co gamma rays to doses of 4400-5000 rad in 4½-5½ weeks with daily fractions of 180-200 rad via lateral opposed fields with appropriate blocking. Pion irradiation will precede or succeed conventional irradiation, depending upon accession time and will be given in doses of 1200-1500 π rad minimum (1500-1875 π rad maximum) in daily fractions of 100 π rad minimum over 2½-3 weeks. The volume for cone-down will be the same as described in the previous section for pion radiotherapy alone.

For patients accessed between four to seven weeks before the end of a cycle, boosting therapy will be given as described; however, a portion of the whole brain treatment may also be given by pion therapy as described above. The exact dose would be dictated by beam availability and accession time, and any difference in equivalent dose between that given to the whole brain with pion irradiation (corrected in comparison to conventional dose by an RBE = 1.6) would be supplemented by conventional treatment of the whole brain.

(3) Endpoints. Twenty Grade III and twenty-two Grade IV patients are expected to be necessary to specify, within defined statistical assumptions, the basis for acceptance or rejection of pion radiotherapy for testing in randomized Phase III trials for those diseases. The statistical assumptions are shown in Table 14, and calculations are according to the methods of Schoenfeld.¹⁵ Given present rates of accession of patients with those diseases, it is anticipated the requisite number of patients will be accrued within 2-2½ years.

h. Inoperable carcinoma of the lung

i. Introduction. Carcinoma of the lung is the most common neoplasm among males in the United States.¹³ Unfortunately, the disease is often nonsymptomatic and is difficult to detect by any simple screening

method resulting in presentation of advanced stage, inoperable lesions in the large majority of cases. Approximately 40 percent of carcinoma of the lung is of epidermoid histology.^{98,99}

Surgery is widely held to be the preferred treatment for early and operable lesions.¹⁰¹⁻¹⁰² Nevertheless, only about 25-33 percent of all patients are suitable candidates for operation because of local or distant spread of carcinoma or intercurrent medical factors, and of these, only about 33 percent are resectable. Therefore, five-year survival statistics for surgical management of unselected patients with lung cancer, may be expected to fall in the range of 5-10 percent. Since the majority of lesions are inoperable, external beam radiotherapy has become a mainstay of the management of this disease.

(1) Conventional radiotherapy of lung cancer. The curative potential of irradiation in management of localized tumors of the type suitable for surgical management has been reported by Smart.¹⁰³ The five-year survival of 23 percent reported in that series is far superior to other radiotherapy series in which two-to-five-year survival rates from 6-15 percent are obtained in treatment of advanced disease.^{98,100,101,104,105} Local control, median and long-term survival for several recent series are presented in Table 22.

A dose-response relationship for unresectable, non-oat cell carcinoma of the lung has been demonstrated by Perez.⁹⁹ He showed a variation in incidence of local recurrence, with or without concomitant distant disease, from 64 percent at a dose of 4000 rad/4 weeks to 38 percent at 6000 rad in six weeks. This observation was particularly notable in the subpopulation of patients with squamous cell carcinoma, in whom 47 percent local failure occurred at a dose of 4000 rad, but only 28 percent of patients had local failure after doses in excess of 5000 rad. This difference may apparently translate into a survival advantage for patients treated to higher dose. Petrovich reported a median survival of 12 months in patients receiving a minimum of 1600 ret, although only 30-35 percent of patients receiving lower doses survived this period.¹⁰⁶

Complications of conventional radiotherapy for lung cancer are predictable and generally mild. Acute esophagitis is relatively common but late esophageal stricture occurs in <2 percent of cases.¹⁰⁰ Radiographic evidence of pulmonary parenchymal injury is relatively common as a late observation, although it is rarely of clinical significance if appropriate treatment planning and dose selection have been used.¹⁰⁷

(2) Local failure versus metastatic spread. The exceptionally poor prognosis of carcinoma of the lung has often been ascribed to the tendency of the disease to metastasize early, especially to the liver, bones, and brain.^{99-101,108} An autopsy series by Matthews showed that locally persistent disease alone occurred in only 24 of 73 patients (of a total group of 202) in whom autopsy evidence of residual cancer was documented after early post-operative death following "curative" resection for lung cancer.¹⁰⁹ Of note, 22 of these 24 cases had epidermoid carcinoma. Overall rates at metastasis following radiotherapy for inoperable, non-oat cell carcinoma are approximately 50-60 percent.^{98,99,101,108} Perhaps the most significant pattern in relation to pattern of relapse is the observation that squamous cell carcinomas tend to remain localized for longer periods and, as a possible result, show higher

TABLE 22

LOCAL CONTROL AND SURVIVAL FOLLOWING
RADIATION THERAPY FOR INOPERABLE LUNG CANCER

<u>Study</u>	<u>Local Failure</u>	<u>Median Survival</u>	<u>Five-year Survival</u>
Perez ⁹⁸	42-63	10	N.A.
Holsti ¹⁰⁴	N.A.	11	7
Coy ¹⁰⁰	45-75	12	10
Eisert ¹⁰¹	64	6	N.A.

rates of local relapse. Perez showed that distant metastasis occurred in about 28-38 percent of patients with squamous cell tumors, but 53-72 percent of those had large cell or adenocarcinoma.⁹⁸ Shin documented that 60 percent of failures after irradiation for adenocarcinoma occurred at distant sites.¹⁰⁸ Overall, patients treated with high dose (i.e., >5000 rad/5 weeks) have isolated local recurrence in about 25 percent of cases, regardless of histology.⁹⁸ This translates into substantial absolute numbers of patients with local failure as a primary problem, as well as an unpredictable number in whom distant disease might not develop if adequate local control were achieved. The potential advantage of pion radiotherapy would be greatest for epidermoid carcinoma in which fewer distant metastases occur and for which local control is a correspondingly greater problem.

ii. Rationale and objectives. Pion radiotherapy is proposed as a means of improving local control and, therefore, survival for inoperable and unresectable, epidermoid carcinoma of the lung. The anticipated benefits are:

- (1) The favorable dose distribution advantage of pions, potentially permitting increased local dose to sites of gross disease and, thereby, obtaining the demonstrated advantage of dose-related response in these lesions.
- (2) High-LET effect upon hypoxic cell fraction of large, necrotic primary tumors and regional nodal disease.

Objectives include determination of:

- (1) Tumor response including comparison of chest x-ray and CT scanning in assessment of response,
- (2) Time to disease progression and radiographic criteria for progression.
- (3) Response of regional nodal disease,
- (4) Incidence of metastatic disease,
- (5) Survival,
- (6) Reactions of normal tissues to pion irradiation with particular attention to late effects in heart, lung, and spinal cord, and
- (7) Optimal dose-volume relationships and technique in treatment of these diseases.

iii. Protocol. Patients with inoperable or unresectable epidermoid carcinoma of the lung without known distant metastasis will be treated in a non-randomized, Phase II trial under the existing protocol RTOG 79-23 (see Appendix A).

Eligibility requirements are: biopsy-proven epidermoid carcinoma of the lung deemed inoperable or unresectable by the referring surgeon, no known distant metastases, and other criteria of eligibility according to the protocol (see Appendix A, RTOG 79-23, p. 3).

All patients will have initial diagnostic evaluation, including routine history and physical examination, chest x-ray, chest tomograms as indicated, and CT scan of the entire thorax. Metastatic evaluation will include radionuclide liver and bone scans; contrast enhanced and nonenhanced CT of the whole brain; liver function tests; CBC; blood chemistry screening

panel; and urinalysis. Pulmonary function tests will be performed as indicated, as will additional radiographic procedures, blood studies, and cultures, etc.

Treatment will consist of full course pion irradiation. Initial treatment volumes will include the primary tumor, all grossly involved regional nodes and a margin of at least 3 cm to the next echelon of clinically uninvolved nodes. Prophylactic irradiation of uninvolved supraclavicular nodes will not be delivered with pions, although a contralateral hilum may be included in the tumor volume should there be involvement of the ipsilateral hilum or lower mediastinum. Beam direction will be tailored on an individual basis, depending upon site and extent of disease, to optimize normal tissue sparing. A minimum dose at 2600 π rad (3250 π rad maximum) will be prescribed to this volume, to be delivered in 26 daily fractions of 100 π rad minimum (125 π rad maximum) over 4½-5 weeks. A boosting dose of 800-1000 π rad minimum (1000-1250 π rad maximum) will be delivered subsequently to sites of bulky disease in the primary or regional nodes. Eight to 10 daily fractions of 100 π rad minimum (125 π rad maximum) will be delivered over 1½-2 weeks to a volume in which the minimum dose is delivered at the periphery of radiographically demonstrable disease. Up to one week interruption of therapy may occur due to scheduling of beam operation.

iv. Endpoints. Twenty-three patients are anticipated as necessary to determine, within specified statistical assumptions, the basis of acceptance or rejection of implementation of a Phase III randomized trial for this group of diseases (see Table 14). The necessary number of patients would be accrued within 2-2½ years.

6. Anticipated Results

Results of pion radiotherapy in the first group of 175 patients treated with this modality are presented in the Detailed Report. Clinical data are entered on a computerized data base (DATATRIEVE) at the time of completion of primary therapy and at each subsequent follow-up visit for purposes of retrospective evaluation and correlation of clinical and treatment parameters, with subsequent observations regarding tumor and normal tissue responses, patterns of recurrence, survival, and other resultant data. In randomized trials, these data may be used directly in testing the hypothesis that pion radiotherapy is superior to conventional radiotherapy. In nonrandomized trials, to be implemented for those disease sites with extremely poor survival, the data collected will be analyzed with particular attention to local control statistics. Based on statistical analysis according to the methods of Schoenfeld,¹⁵ of data collected on appropriate numbers of patients in each disease category, statistically sound recommendations may be made regarding the appropriateness of implementing Phase III, randomized trials for individual sites. Such recommendations are based upon assumptions regarding the results of conventional therapy and the acceptability of submitting to randomized trials a treatment that may prove no better than conventional therapy or rejecting for testing a treatment that is actually superior.

Although collection of definitive data regarding local control and survival are the main endpoints of this project, data regarding all acute and chronic reactions of normal tissues will be scrupulously monitored and recorded to optimize treatment technique and to reject methods with unacceptable complication rates.

Data collected in the clinical aspect of the project will be reviewed in light of observations in the biology portion of the project with particular attention to the anatomic distribution of acute and late normal tissue reactions and sites of tumor recurrence as related to predicted and observed RBE and degrees of isoeffectiveness of various treatment beams. Late effects studies on normal tissues in animals will be taken as guidelines in the evaluation of tolerance of normal human tissues and in design of alternative time-dose-fractionation schedules should clinical results or accelerator operating schedules indicate the need.

Clinical data will be correlated with physics data, either calculated or measured, in optimization of techniques of treatment planning. In vivo dosimetry will continue to be a major method of confirming the reliability of individual beam shaping appliances in the delivery of the prescribed treatment.

6. Significance

The clinical study is the central aspect of the entire project. The ultimate aim of the project, i.e., improved control of advanced cancers with resultant improved survival, will be demonstrated in the clinical results, although optimization of these results will be obtained only by meticulous attention to the biological and physical parameters of pion radiotherapy and continuous correlation of clinical findings with basic observations.

7. Human Subjects

Complete information on protection of human subjects, including the consent forms used for this project, is contained in the protocols of Appendix A. All protocols implemented under this program, as well as any significant subsequent modifications, are first reviewed and approved by the University of New Mexico Human Research Review Committee, the joint Los Alamos National Laboratory/Los Alamos Medical Center Human Research Review Committee, the Lovelace-Bataan Medical Center Human Research Review Committee, the Veterans Administration Research and Education Committee, the UNM Radiological Safety Committee's Human Uses Subcommittee, the Pion Radiotherapy Program External Advisory Committee, the Radiation Therapy Oncology Group, and the National Cancer Institute Clinical Investigations Branch. Progress reports are submitted to each unit as required. All necessary rules and regulations are followed as required by each group.

8. Facilities Available

Outpatient facilities of the University of New Mexico Cancer Research and Treatment Center in Albuquerque, the Pion Biomedical Facility of the Clinton P. Anderson Meson Physics Facility in Los Alamos, and the Los Alamos Medical Center in Los Alamos (which includes housing for patients), as well as inpatient facilities of the UNM Hospital, the Los Alamos Medical Center, the Veterans Administration Hospital, and the Lovelace-Bataan Medical Center are available to this project. Details on these facilities are provided in Section II.

9. Collaborative Arrangements

Close coordination is maintained with the pion program principal investigators at the Swiss Institute for Nuclear Research in Villigen (Carl F. von Essen, M.D.) and TRIUMF in Vancouver, British Columbia (George Goodman, M.D.), and considerable cross-transfer of technology is in progress. In addition, the guidance of a select group of radiotherapists is available to the project in the form of the Pion Radiotherapy Program External Advisory Committee (see Section III).

Considerable effort has been devoted to strengthening relationships with referring institutions throughout the country, with emphasis on those organizations with significant numbers of patients in the anatomic sites under study. The University of Southern California/Loma Linda University Community Radiation Oncology Program (a group of 16 institutions in the Los Angeles metropolitan area) has exhibited considerable interest in providing a major referral source for the project, and during the past treatment cycle referred 35 percent of patients accepted for treatment, most of them with gliomas. H.R.K. Barber, M.D., gynecologic oncologist of Lennox Hill Hospital in New York City, has expressed considerable interest in pion therapy of advanced uterine cervix cases, and has referred five of eight such patients treated with pions to date.

As the studies progress, follow-up patients are beginning to accumulate in and near large metropolitan areas (notably, Los Angeles, New York, and Denver), and a concerted effort will be instituted to have the CRTC radiation oncologists follow them on some occasions in their home locale in concert with the referring physician. It is anticipated this will result in closer communication with the referring physicians and increased interest on their part in future referrals, as well as contribute to improved quality control for cases randomized to conventional therapy at participating institutions.

Dual caseload credit is issued by the RTOG to member institutions contributing patients to the pion radiotherapy trials, which has helped referrals. This practice is expected to continue.

B. Physics1. Investigators

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Robert Hilko, Ph.D.	Developmental Physicist, UNM/Los Alamos
TBA	Biomedical Engineer, UNM/Los Alamos
TBA	Treatment Planning Physicist, UNM/Los Alamos
TBA	Treatment Planning Technician, UNM/Los Alamos
TBA	Research Technologist, UNM/Los Alamos
James N. Bradbury, Ph.D.	Group Leader, MP-3, LANL
Michael Paciotti, Ph.D.	Physicist, MP-3, LANL
J. Wing	Engineer, MP-3, LANL
P. Berardo, Ph.D.	Physicist, MP-3, LANL
B. Swenson	Programmer
O. Rivera	Mechanical Technician
TBA (4)	

2. Introduction

a. Objective. The primary objective of this program component is to continue support of the proposed clinical pion therapy program by development of pion physics, calculations, measurements, techniques, methodology, hardware, and software, to fully optimize the delivery of pion therapy. In addition, the physics program is directed toward the support of the proposed radiation biology program. These objectives will be met by a unified and integrated effort by both the UNM and LANL physics groups working together toward total support of the program project.

b. Background. Because of the unique nature of the pion itself and of the pion transport system, the physics program began essentially at ground zero when the first pion treatment of patients began at LAMPF. Very little technology or experience from conventional or neutron therapy programs is applicable to pion therapy. The program began with treatment of skin nodules then advanced to treatment of superficial tumors and finally to the treatment of large deep-seated tumors at a variety of anatomical sites. This program required the development of a large variety of pion beams, treatment delivery systems, beam shaping devices, treatment planning techniques, dosimetry systems, in-vivo dosimetry systems, and calculational techniques. Due to the combined efforts of the LANL basic physics and support group and the UNM clinical physics group, the clinical program has advanced rapidly to a highly developed and sophisticated state. Although still in its infancy, the delivery of pion therapy is comparable in precision and accuracy to that of conventional radiation therapy in the best institutions. Therefore, the physics group is confident of its ability to support clinical trials for the program project. The background for each specific physics area is presented in the detailed progress reports for individual projects of the physics component.

c. Rationale. Negative pi mesons offer the possibility of both physical and biological advantages over conventional radiation therapy

modalities. This program project proposes to explore these advantages by treating large, deep-seated tumors in a variety of anatomic sites with pions in Phase II clinical trials. To adequately test the efficacy of pions, it is imperative that the advantages of pions be fully exploited, i.e., the pion therapy must be highly optimized. Systems must be developed, tested, and implemented to provide for optimum dose delivery and measurement so that meaningful clinical results can be obtained. The problems of pions (their production, transport, delivery, measurement, and calculation) are significantly different from those of conventional and neutron beams, and require substantial continued technology development. The necessary technology must be developed in conjunction with the on-going clinical and biological pion research effort.

d. Progress report

(1) Beam tuning and channel development. The objective of this component of the physics effort is to develop therapy beams for both static and dynamic treatments and to document the beams for use in the three-dimensional treatment planning code. The biomedical channel at LAMPF is shown in Figure 11.

(a) Beam tunes. The catalog of broad beams for static treatments has been expanded to provide fields with transverse dimensions up to 20 cm at each of three momenta corresponding to nominal depth penetration of 12 cm, 16 cm, and 23 cm. Fan beams for dynamic treatments have been prepared at several channel momenta, and extensive beam tuning and dosimetry have been performed.

Several conflicting factors were considered in upgrading the quality of the fan tunes, and some compromise was necessary. The size of the beam waist (y-plane) determines how versatile the tune will be for field-shaping in the scan dimension. Sizes range from 3.8 cm to 4.5 cm (FWHM) for the beam measured in water at depth. The location of the waist determines the maximum useful range-shifter stroke and the ability to shape the scan plane at different depths. It was decided to locate the beam waist in air at 100 cm from the effective edge of the last quadrupole. This 100-cm point is usually the bottom of the treatment volume. The effect of multiple scattering is to move the waist in water upward to approximately the center of the treatment volume. In this way, good edge sharpness is maintained all the way to the bottom of the treatment volume.

Other factors include the beam size and uniformity in the long dimension (x) of the fan. Several sizes were considered at each momentum to maximize average dose rate. In this plane the divergence has been reduced to ease treatment planning problems. It is possible to vary several parameter correlations with the position x. They are momentum vs. x, momentum spread vs. x, y-size vs. x, and electron-muon (e- μ) contamination vs. x. Two polarity configurations were investigated; one of these is better in terms of limiting the spatial separation of the contamination from the pions, an effect originating through the action of the wedge degrader on the different components. The effect gives non-uniformity beam quality along x and is also present in the static treatment tunes.

(b) Muon contamination, measurement, and calculation.

The objective of this work is to provide input to PIPLAN which uses measured beam data with particles identified by position, angle, momentum, and type, i.e., pion, muon, or electron. The muon beam contains several components corresponding to regions in the channel in which the pions decay. Muons originating from π decays between the target and the early part of the channel are clearly separated by time-of-flight in Figure 12. These "cloud" muons are produced by pions that would not necessarily be accepted by the channel and are therefore enhanced. Muons from forward decays up to the last bend are also separable by time-of-flight, filling the valley between the cloud muon peak and the pion peak. Some of the decays occurring between the last bend magnet and the channel exit are also separable from pions by time-of-flight and also reside in the valley. Table 23 gives measured beam composition from time-of-flight data.

Muons from decays in the last portion of the channel form a large "halo" around the pion beam. As pion field sizes have increased, this "halo" has become an increasingly larger fraction of the beam. These muons are primarily contained within the pion time-of-flight peak, and other methods must be used to separate them. An experimental method has been developed for detecting these $\pi \rightarrow \mu$ decays which uses the wire chambers before and after the beam-shaping section of the channel where decays cannot be identified by time-of-flight. The matrix transformation from the upper wire chambers to the lower wire chamber predicts the output trajectory from the measured trajectory at the upper chambers. These differences are formed for each event as follows:

$$\begin{aligned}\Delta_X &= X_{\text{measured}} - X_{\text{predicted}} \\ \Delta_\theta &= \theta_{\text{measured}} - \theta_{\text{predicted}} \\ \Delta_Y &= Y_{\text{measured}} - Y_{\text{predicted}} \\ \Delta_\phi &= \phi_{\text{measured}} - \phi_{\text{predicted}}\end{aligned}$$

The distributions of the Δ 's are Gaussian with long tails that can be identified as muons from decays in the region between the chambers. The widths of the pion central regions are typically 1-2 cm rms and 10-20 mr rms. Multiple scattering due to material in the beam such as the wire chambers themselves contributes to the widths. The channel has no vacuum system but has helium bags throughout most of its length.

The accuracy and limitations of this method were explored with the ray-tracing code DECAY TURTLE¹¹⁰ modified for this problem. A time-of-flight calculation was added to the code so that the muon component not identified by time-of-flight could be examined separately. The observed widths of the Δ distributions are largely explained by multiple scattering. Some reduction of material in the beam is possible, and recently slightly reduced widths were observed. The limitation of this experimental "kink" detection method is that some pions are incorrectly flagged as muons.

The TURTLE code also predicts muon fractions from distributions from decays late in the channel. Sample results from the TURTLE code are shown in Table 24.

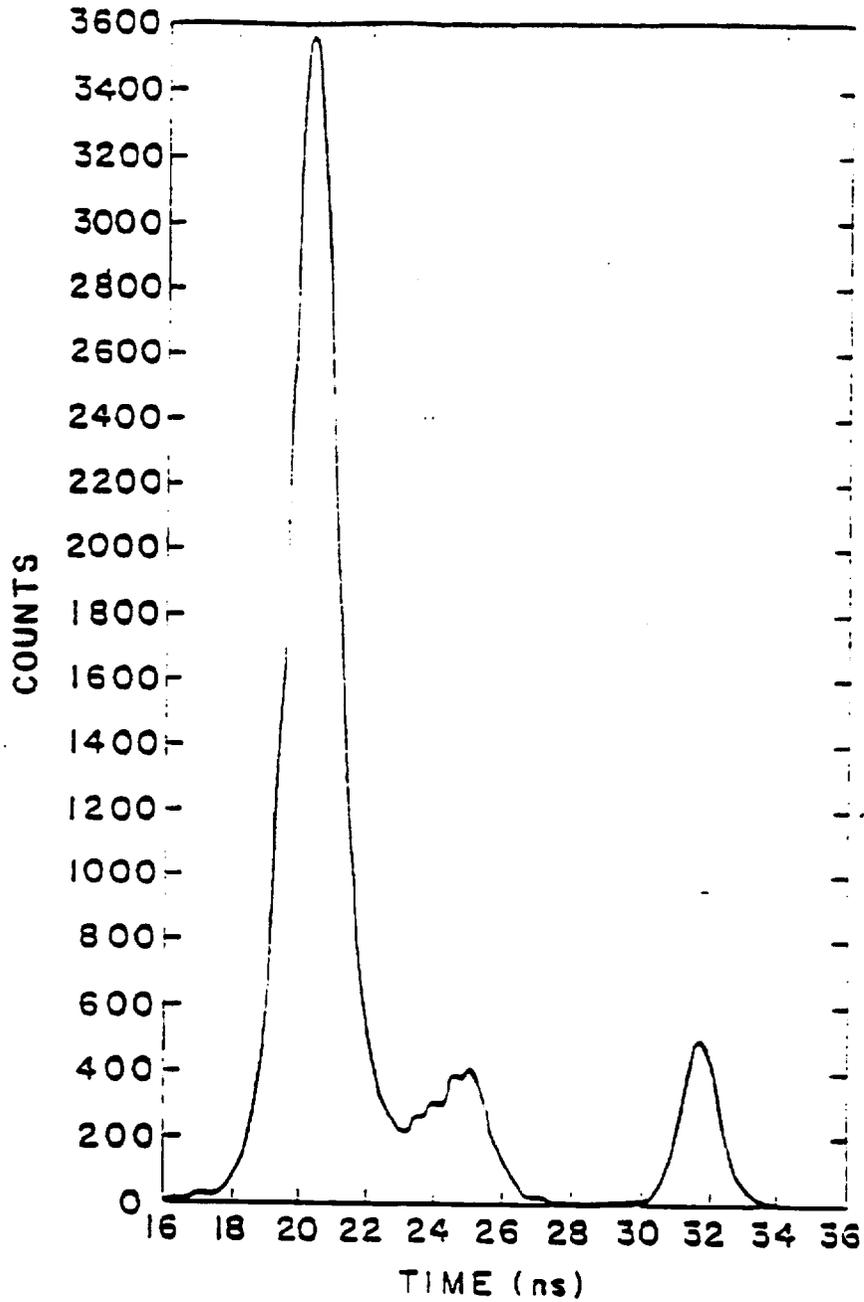


Figure 12. Time-of-flight distribution for 167 MeV/c negative beam using 40 ns chopped proton beam (width of pion region fit is 0.75 ns)

TABLE 23

BEAM COMPOSITION FROM TIME-OF-FLIGHT DATA
(MUONS FROM LATE DECAYS NOT SEPARATED FROM PIONS)

<u>Momentum (MeV/c)</u>	<u>π^- and μ^- From Late Decays (%)</u>	<u>Cloud μ^- and μ^- From Mid-Channel Decays (%)</u>	<u>e^- (%)</u>
150	71	15	14
167	75	16	9
190	81	12	7

TABLE 24

TURTLE RESULTS FOR MUONS WITHIN THE PION TIME-OF-FLIGHT PEAK
AND HITTING 40 x 40-CM SCINTILLATOR

<u>Beam Type-Treatment Mode</u>	<u>Pion Beam Size FWHM(cm)</u>		<u>Momentum MeV/c</u>	<u>$\frac{\mu}{\pi}$</u>	<u>$\frac{\mu}{\pi}$ On Axis</u>
	<u>X</u>	<u>Y</u>			
Broad-static	16	15	150	0.18	0.051
Broad-static	17	20	150	0.18	0.074
Broad-static	16	15	167	0.19	0.060
Broad-static	20	23	157	0.18	0.092
Broad-static	18	16	190	0.20	0.094
Broad-static	22	22	190	0.20	0.14
Fan-dynamic	23	3	167	0.18	0.025
Spot-dynamic	5	7	167	0.21	0.018

The muons are required to fall within the acceptance of the tuning apparatus limited by a 40 x 40 time-of-flight scintillator. Thus 18 to 21 percent of the particles within the pion time-of-flight are muons. This fraction is added to the muons already identified in Table 23. Still another 20 percent muon component misses the counter and is not observed by the tuning equipment. Other than possible whole-body dose, the only interest in these muons is in the calibration of the monitor chamber for absolute PIPLAN dose calculations, where the beam composition for all particles passing through the monitor chamber must be estimated.

The last column of Table 24 gives the μ/π ratio on the z axis for the decays late in the channel. The range of values is large but the ratio is smallest for the spot beam. Here beam purification is possible by collimating out the extended muon halo.

(c) Biomed channel production target. The biomedical channel pyrocarbon target is now nearly optimum. The target in Figure 13 was developed by MP-Division and other laboratory groups. Its use in connection with beam reproducibility is discussed elsewhere.¹¹¹ Figure 14 is a demonstration of the targeting geometry for control of electron contamination. By moving the assembly up and down, the average graphite converter thickness seen by decay π^0 γ rays is varied. The e^- fraction varies linearly with converter thickness. The converter thickness is measured directly by the target scan procedure, and the operator is instructed by the program where to set the target vertically to maintain constant e^- contamination.

(d) Beam profile monitor. A multiwire chamber has been constructed and tested for use as a beam profile monitor. It operates in the full pion beam but with reduced wire gain. The readout system, a LAMPF design, senses peak wire current during each beam pulse and displays each axis, x and y, on an oscilloscope. It is a useful addition but is not envisioned as a built-in device. The most useful location for a monitor would be at the patient, which is impossible. An on-line monitor could be implemented using quadrants or sectors located within the argon monitor ionization chamber.

(e) Patient beam tune characterization. A large dosimetry effort has been directed toward providing the characterization of a large variety of patient beams. All treatment beams derive from three basic beam penetrations: 12, 16, and 23 gm/cm². Using these three beams, any tumor between the skin surface and 23 gm/cm² in depth can be reached by using the appropriate bolus designed to cause the pions to stop in the prescribed target volume.

There are three types of beams:

- (i) Broad, essentially parallel beams used for static treatments;
- (ii) Beams focused in one dimension and broad in the perpendicular dimension used for one-dimensional dynamic treatments; and
- (iii) Beams focused in two dimensions used for two-dimensional dynamic treatments.

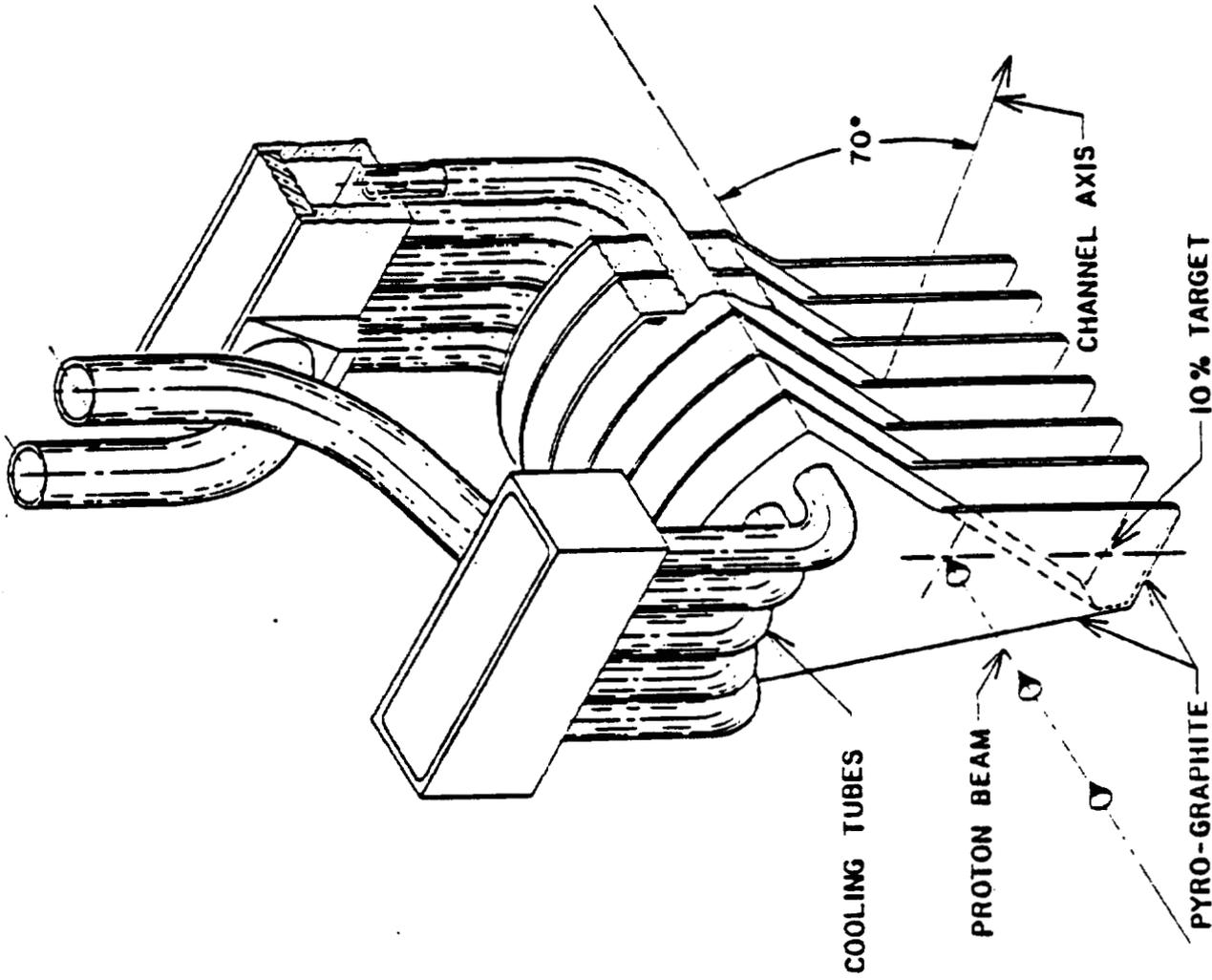


Figure 13. Pyrolytic graphite ($\rho = 2.2 \text{ g/cm}^3$) water-cooled target using copper tubes brazed to graphite

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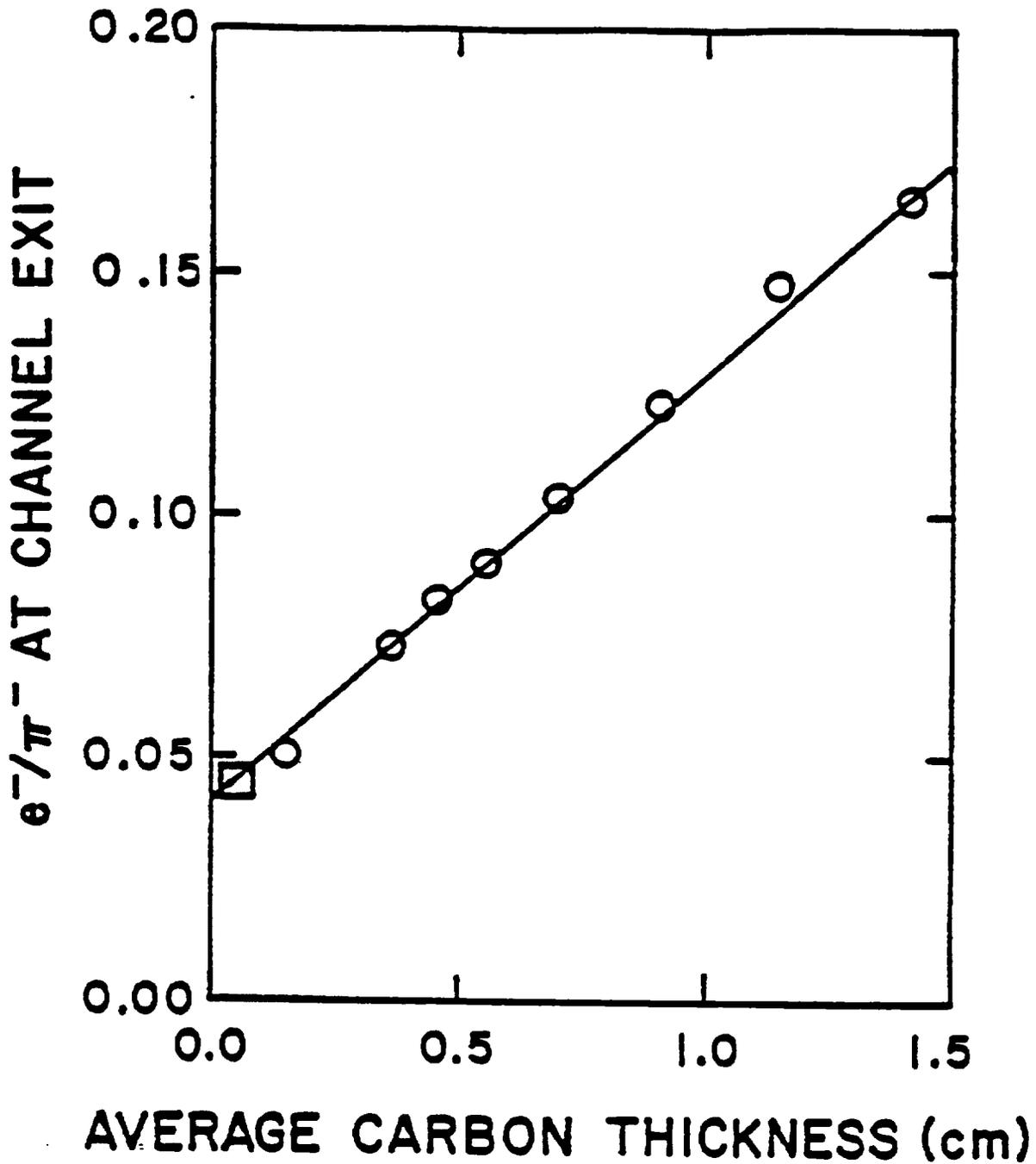


Figure 14. Electron fraction at 167 MeV/c measured at the exit of the channel as a function of the average graphite ($\rho = 2.2 \text{ g/cm}^3$) converter thickness for π^+ γ rays

For the static beams, three beam sizes (small, medium, and large) have been developed and characterized for each penetration. One focused beam of each type will be developed and characterized for each penetration.

Table 25 gives the catalog of patient beam tunes.

For each penetration, the A, B, C series are the small, medium, and large beams for static treatments, the F tunes are beams focused in one dimension (fan beams), and the S tunes are beams focused in two dimensions (spot beams).

The beam size for each tune used for static treatments defines the maximum field size that can be treated with that tune. Target volumes requiring larger field sizes are treated using combinations of abutted fields. Since there is no limit to the number of fields that can be abutted there is no limit to the target volume size (in the lateral dimension) that can be treated.

The dose rates for the pion therapy beams are a function of the beam momentum, the beam tune (size) for a given momentum, and the size of the spread peak region. Typical dose rates for the beams in use range from .02 to .03 rad/min/liter for each microampere of proton beam current on the biomedical pion target. In the summer of 1982, the proton beam current will be raised to 750 microamperes, resulting in about 600 microamperes of proton current on the biomedical pion target, yielding dose rates from 12 to 18 rad/min/liter. The design current for the LAMPF accelerator is 1000 microamperes. The average treatment volume is about two liters for single parallel-opposed pairs of fields. However, some patients require two or three pairs of parallel-opposed fields (abutting) during each treatment cycle so that the overall average treatment volume is probably closer to 2.5 liters.

(2) Development of range-modulation functions. The narrow Bragg peaks of the pion beams are spread in depth by the use of a dynamic range-shifter. The range-shifter is computer-controlled and can be programmed to produce spread peaks of varying dimension and shape. The range-shifter varies the thickness of a low viscosity oil ($\rho = 0.9 \text{ g/cm}^3$) in the beam path according to a prescribed time function.

The period of a range-shifter cycle is 10 seconds. The range-shifter is programmed to give stopping pion distributions ranging in depth from 3 to 14 cm in 1-cm intervals. A series of such range-modulation functions has been developed for each momentum (148, 167, and 190 MeV/c). This is necessary because the peak-to-plateau ratio, beam contamination (electrons and muons), and momentum spread (resulting in differences in the full-width-half-maximum of the spread peak) are different for each momentum. During the next year, range modulation functions will be developed for each individual tune so that the differences in beam divergence will also be taken into account.

For each spread peak it is possible to tailor the slope of the physical dose, and consequently the distribution of stopping pions. It is possible to produce spread peaks with uniform total dose, uniform high-LET dose, or uniform biologically effective dose.

TABLE 25
 PATIENT BEAM TUNES

<u>Name</u>	<u>MeV/C</u>	<u>Penetration*</u>	<u>Beam Size (x·y)</u>	<u>Rad/Min/Microamp (8 cm spread peak)</u>
12A	148	11.6	8 x 8	0.034
12B	148	11.6	12 x 15	0.016
12C	148	11.6	17 x 17	0.010
12F	148		TBC**	
12S	148		TBC	
16A	167	16.1	10 x 8	0.032
16B	167	16.1	11 x 14	0.020
16C	167	16.1	18 x 17	0.014
16F	167	15.7	18 x 3	0.052
16S	167		TBC	
23A	190	22.9	11 x 9	0.024
23B	190	22.9	12 x 17	0.012
23C	190	22.9	14 x 19	0.009
23F	190		TBC	
23S	190		TBC	

* Measured with range-shifter at minimum thickness.

**To be characterized.

In the fall of 1980, the range-modulation functions were completely redesigned, and these new functions have been in use since that time. The old range-modulation functions were designed according to the criterion that the fraction of high-LET radiation from stopping pions (>50 keV/micron) must be above a minimum value of 10 percent of the total dose throughout the spread peak. This minimum value was established by early biological experiments which indicated that this amount of high LET resulted in uniform RBE across the spread peak. This criterion resulted in spread pion peaks with relatively flat total dose for peaks spread to about 9 cm. For large spread peaks, the total dose became lower in the distal peak, resulting in a slope from 100 percent (proximal peak) to 70 percent (distal peak) for 14-cm spread peaks. In practice, most pion treatments are accomplished by use of parallel-opposed overlapping ports, which results in uniformity in both the total physical (absorbed) dose and in the resultant biologically effective dose. However, there are always special cases when opposed fields cannot be used, and a single field is utilized. In these cases, there was concern that the effective dose was not uniform over the target volume. Experiments were performed on these peaks using multicellular tumor spheroids, which indicated that the biological effect was indeed uniform for single fields; however, the prevailing opinion is that the sensitivity of these biological systems prevents resolution of biological effect below a level of 20 percent change. Calculations and measurements showed that the ratio of high- and low-LET dose varied across these spread peaks to an extent that differences of approximately 20 percent in the biological effect across the spread peaks was possible. Experiments performed by Raju at LAMPF, using gel tubes with single cells in suspension, confirmed the predictions. Therefore, it was decided to redesign the shaping of the spread peaks in such a way as to accomplish greater uniformity in biological effect for single-field treatments.

The range-modulation function describes the thickness of a bellows-controlled column of oil in the beam path versus time. The range-modulation function development code takes measured, central axis, unmodulated total and high-LET distributions and, applying time-weights, offsets each curve by prescribed shifts in depth; sums all the offset curves together; and renormalizes to obtain the resultant modulated total and high-LET depth-dose curves. The program then uses an RBE model to calculate the effective dose. The user operates interactively with the program, which requests input values of various parameters needed in the calculation, calculates the function, and then displays the resultant depth-dose curves (effective, total, and high LET). The user may choose to perform the calculation again, changing any or all of the input parameters. This process is repeated until the desired uniformity of effective dose is obtained.

The RBE is assumed to be a linear function of the fraction of dose delivered at high LET for the ranges of high LET in our beams:

$$RBE = 1.0 + RBF (D_H/D_L)_N \cdot F(RMF),$$

where RBF is an RBE factor assigned to a standard treatment (10 x 10-cm collimator, 10-cm range-modulation function, 4500 rad in 35 fractions), $(D_H/D_L)_N$ is the ratio of the high-to-low-LET dose normalized to 1.0 at the point of maximum LET, and $F(RMF)$ is a function of the size of the spread peak. At points where the high-LET dose approaches zero, i.e., in the plateau and post peak, the RBE approaches 1.0, the low-LET value. The value 0.6 has been assigned to the RBE

factor (RBF) so that for the standard treatment field the RBE = 1.6 at the point in the distal peak where D_H is maximum. For spread peaks less than 10 cm, the ratio D_H/D_T will, in general, increase, because there is less low-LET plateau dose folded into the peak region. However, for smaller spread peaks, the neutron component of the dose will decrease, thereby offsetting somewhat the increase in charged particle high-LET dose. For spread peaks larger than 10 cm, the opposite occurs: the charged particle high-LET dose will decrease, while the neutron component will increase. Therefore, the function $F(RMF)$ is 1.0 for a 10-cm spread peak and will increase slightly for smaller peaks and decrease slightly for larger peaks. The maximum RBE for any spread peak is not expected to vary more than ± 10 percent from 1.6 due to the effect discussed above.

Because of the complicated nature of these effects and the great difficulty in accurately predicting them, $F(RMF)$ has to be determined from radiobiology experiments. Some of these experiments have been performed and the results are discussed under Biology. The biology data are being analyzed using the Kellerer-Rossi model. The program calculates the cell survival curves for any point in the depth-dose curve produced by the LAMPF range-modulation development program as shown in Figure 15. These are calculated curves for a 9-cm spread peak, 13 x 11-cm collimator. The lower curve is the high-LET dose, the middle curve is the total dose, and the upper curve is the effective dose calculated from the model described above. The RBE at the maximum of the high-LET curve is 1.6, and the RBE at the proximal peak (7.0-cm depth) is 1.2; both of these numbers are uncorrected for $F(RMF)$. A series of such curves has been calculated for each penetration used for patient treatments (12, 16, and 23 cm penetrations).

(3) Dosimetry

(a) Patient dosimetry systems. An automated data-acquisition and analysis system has been developed for dosimetry measurements on the pion therapy beam using a PDP-11/70 computer and CAMAC interface. Initialization, test and monitor programs allow the user to set the physical limits of scanner travel, test the data lines, calibrate the analog signals for the scanner position, and monitor the analog-versus-digital values of the scanner position during operation. Data-acquisition programs scan the ionization chamber in one, two, and three dimensions. Many options are available to the user in selecting the scan parameters and in changing some of these parameters during scanning. Data-analysis programs provide reproduction of stored data, comparison of linear scans, beam profiles along any line of a planar or volume scan, and isodose distributions from any planar scan or from any plane of a volume scan. Other programs summarize stored data files and search for specific data according to the user's instruments.

A multiple ionization chamber array (MICA) system, with associated software control, has been developed for dosimetry measurements. This system increases dosimetry data-acquisition rates by a factor equal to the number of data channels in use. The system has been tested and used with a linear array of 10 ionization chambers. In principle any number of chambers can be used in linear, planar, or volume arrays. The system was put into routine use in the summer of 1981.

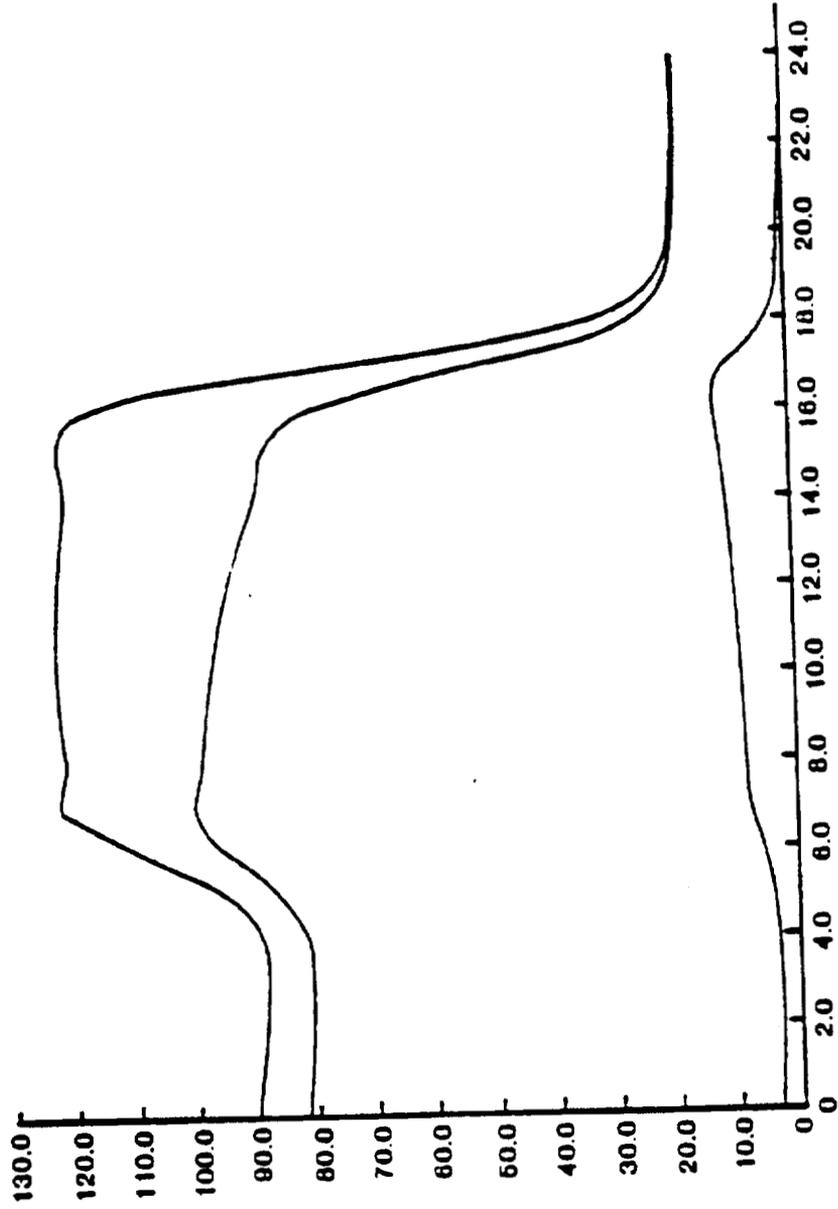


Figure 15. Calculated depth-dose curves for 9-cm spread peak

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(b) Patient dosimetry techniques. The object of patient dosimetry is to determine the central-axis depth dose and the output calibration (rad/monitor unit) at the maximum of the peak dose, using the beam tune, range-modulation function, and collimator assigned to a particular patient field with the geometry (air gaps) between appliances and between the collimator and water phantom the same as that expected for the actual patient treatment. Also, the water phantom is positioned so that the maximum pion penetration (peak of the unmodulated Bragg peak) is located at 100 cm quadrupole tumor distance (QTD), thus simulating the geometry of patient treatment.

The output calibrations are necessary for daily calculation for each patient treatment. The channel is calibrated each morning and daily treatments are adjusted to this calibration. The depth-dose curves are used as input to a code which uses the collimator geometry, multiple scattering, beam emittance, and uncollimated beam dosimetry to calculate isodose distributions, in water, for a plane corresponding to a CT slice in the patient. These isodose distributions are then folded into the bolus design and CT data to calculate an isodose distribution on the patient.

In general, measurements must be made on each patient field because changes in collimator area and shape change the shape and magnitude of the resulting depth-dose profile. These changes are complicated, occurring both in the plateau and peak regions of the dose profile, and are difficult to predict. All measurements are made with a small (0.1 cc) thimble ionization chamber in combination with an electrometer and an automated positioning device (scanner and electrometer are interfaced with the PD 11/70 computer and are controlled by a group of dosimetry software codes that are initiated by a series of positions on a button panel). The chamber walls are made of Shonka A-150 plastic, and methane-based tissue equivalent gas flows through the chamber during measurements.

In addition to specific patient treatment measurements, routine measurements are also made to determine the integrity (constancy) of the individual beam tunes used for patient treatment. These tunes are subject to variations due to target or magnet (there are 11 magnets in the channel) changes. These measurements consist of x and y beam profiles taken in the center of a 9-cm range modulated peak.

Each patient has, on the average, three treatment fields, which include multiple treatment fields and cone-downs. The dosimetry for each treatment field requires approximately two hours with two people required to perform the measurements. Therefore, for 20 patients per cycle about 240 man-hours are required for patient dosimetry. The direct measurement of each patient field thus requires a substantial effort. To eliminate a large part of this effort, an extensive program of measurements has been performed on every beam tune used for patient treatments in order to establish a data base from which to extract a model, based on fitting parameters, for prediction of the depth dose and calibration at the peak of the depth-dose profile for any given beam tune, range-modulation function, and collimator.

(c) Patient dosimetry models. To eliminate a large fraction of the manpower and beam time used in the measurement of dosimetry for each patient field, a project of extensive measurements has been undertaken

from which models will be extracted that will predict the depth dose for any given beam tune, collimator, and range-modulation function. In addition, these models will predict the beam output for any given set of the above parameters.

For each of nine beam tunes (a small, medium, and large treatment field for 12-, 16-, and 23-cm penetrations) measurements were made for five collimator sizes and without a collimator, using an unmodulated beam and beams modulated to produce spread peaks of five different sizes ranging in size from 3 cm to the maximum allowable spread peak for a given penetration. Range-modulation functions that produce spread peaks ranging in size from 3 cm to 14 cm in 1-cm steps are available. The unmodulated depth-dose curves were analyzed to determine the collimator effects. Typical depth-dose curves are shown in Figure 16 for a 16-cm penetrating beam using collimators with openings of 5 x 5, 14 x 14, and 18 x 17 cm and no collimator. These curves have been normalized at the peak of the distribution.

Collimator effects are seen to be strongest in the plateau of the depth-dose curves, but are also evident in the post peak region. These effects are thought to be primarily due to neutrons. Pions stopping in the collimator generate a neutron spectra, which becomes a component of the total beam incident upon the phantom, causing increases in the plateau dose, the increase being inversely proportional to the size of the collimator opening. The post peak dose is reduced because pions that previously stopped at depth in the phantom and produced fast neutrons which contributed to the central axis dose at depth are now being stopped in the collimator.

An analysis of these data, which consists of a parameterization of the effects, produces analytical expressions containing coefficients fixed by curve fitting, which permits the calculation of collimator effects for any collimator size. Therefore, a depth-dose curve can be calculated for any collimator size. This collimator-corrected curve can then be entered into a computer file accessed by the code that calculates the spread peak distribution resulting from the action of a range-shifter in the beam path (see Development of Range-Modulation Functions). This process then results in a calculated depth-dose distribution for any spread peak using any collimator opening.

Examples of these calculations compared to measurements are shown in Figures 17, 18, and 19. Concurrent with these calculations and measurements, the beam output (rad/monitor unit) was also determined for various collimator sizes and range-modulation functions. An analysis of these data results in curves such as those shown in Figure 20, which enables one to find the beam output for any combination of collimators and spread peaks. The structure in the curves for the 10-, 12-, and 14-cm spread peaks for small field sizes is due to collimator-neutron effects.

(d) Microdosimetry. Accurate microdosimetry data are required as input to the algorithms used in the calculations of RBE, pion effective dose, and range-shifter functions. Such data are obtained from a variety of experimental techniques, including Rossi chamber proportional counters, solid state detectors (totally depleted lithium-drifted silicon), and aluminum activation measurements.

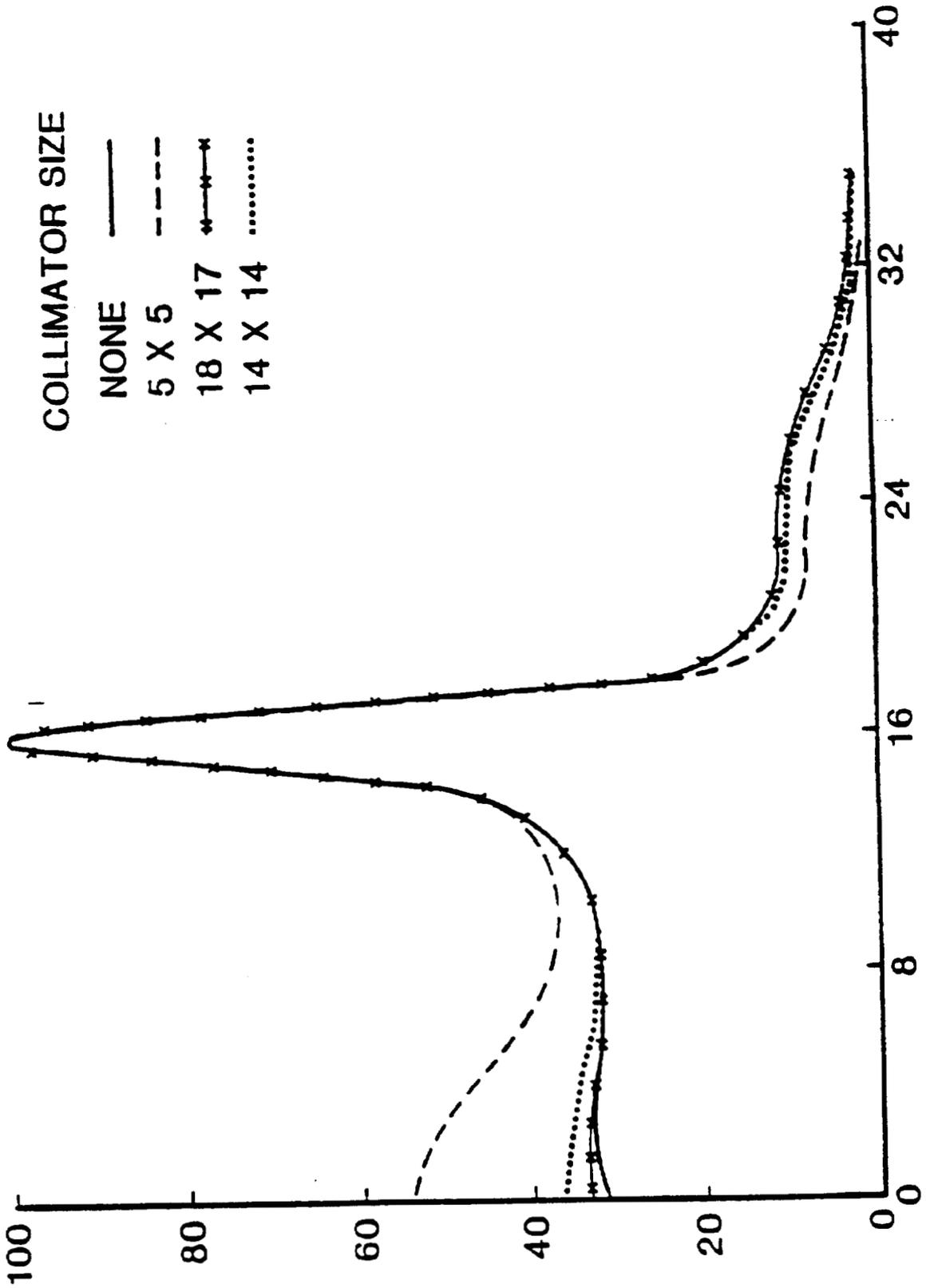
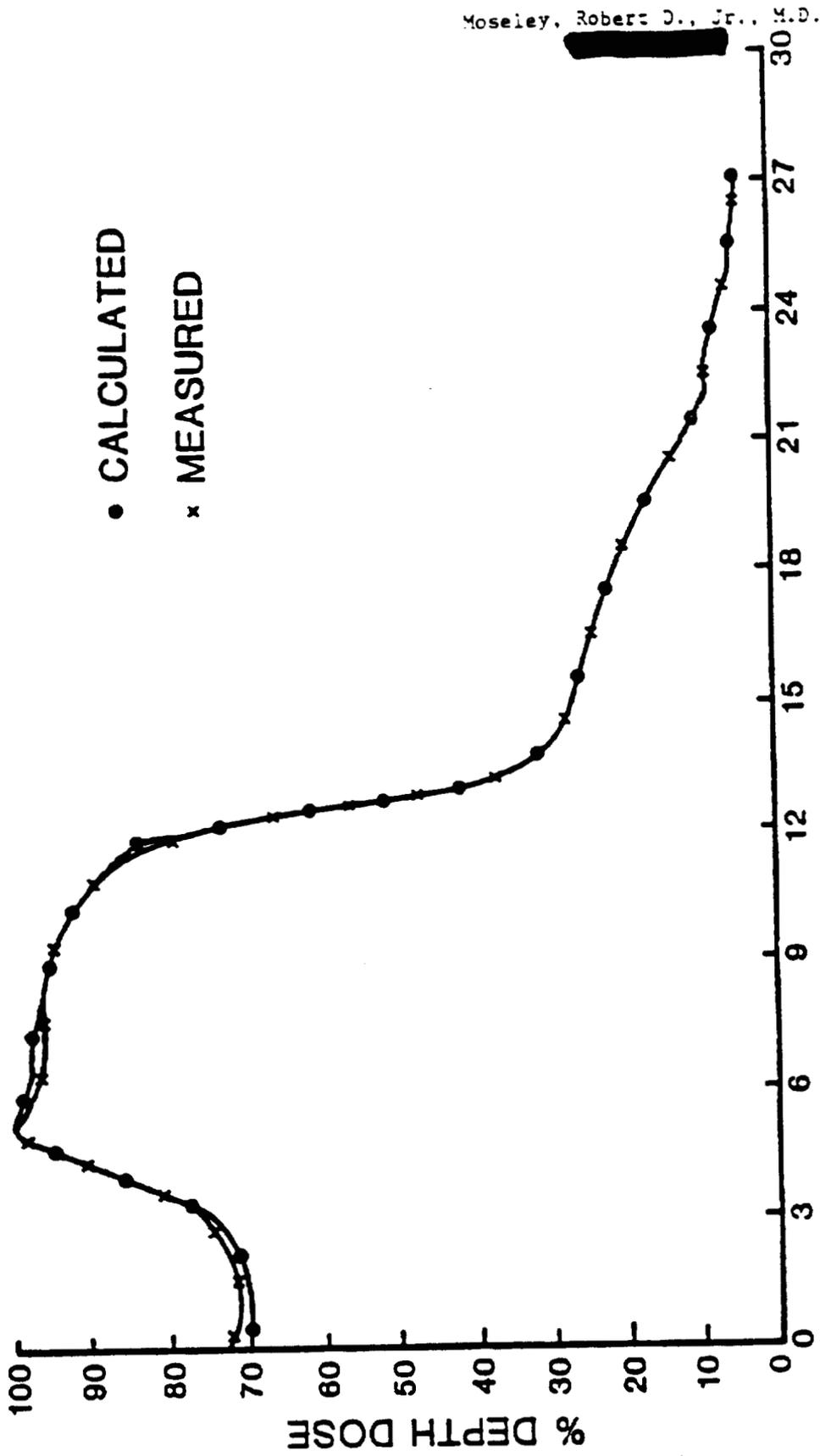


Figure 16. Depth-dose curves for 16-cm penetrating beam with varying collimation and no collimation

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17 X 17 CM COLLIMATOR 7 CM RANGE MODULATION FUNCTION

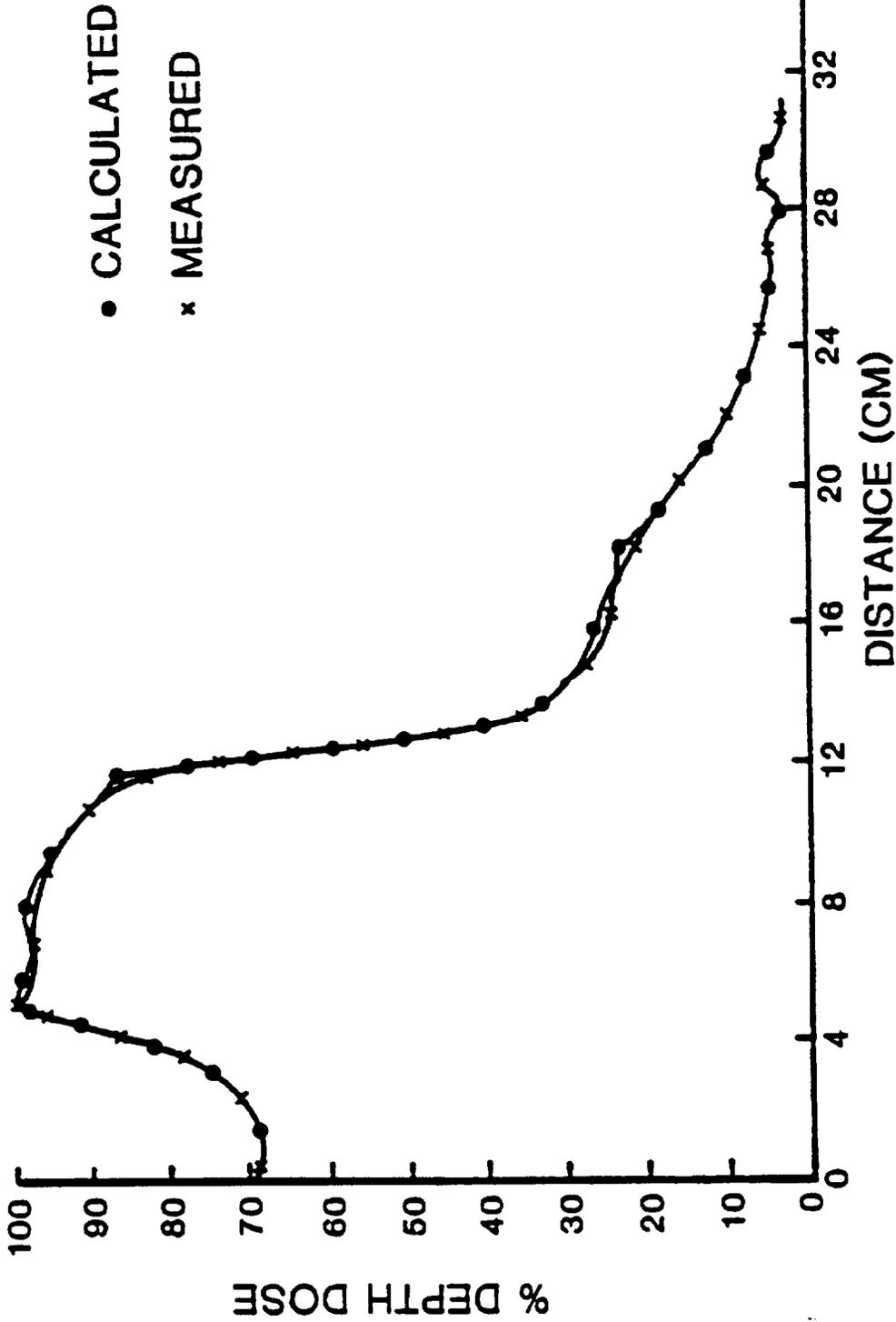


Moseley, Robert D., Jr., M.D.

Figure 17. Calculated depth-dose distribution for 17 x 17-cm collimator, 7-cm spread peak
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23 X 21 CM COLLIMATOR 5 CM RANGE MODULATION FUNCTION



Moseley, Robert D., Jr., M.D.

Figure 18. Calculated depth-dose distribution for 23 x 21-cm collimator, 5-cm spread peak

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7 X 7 CM COLLIMATOR 9 CM RANGE MODULATION FUNCTION

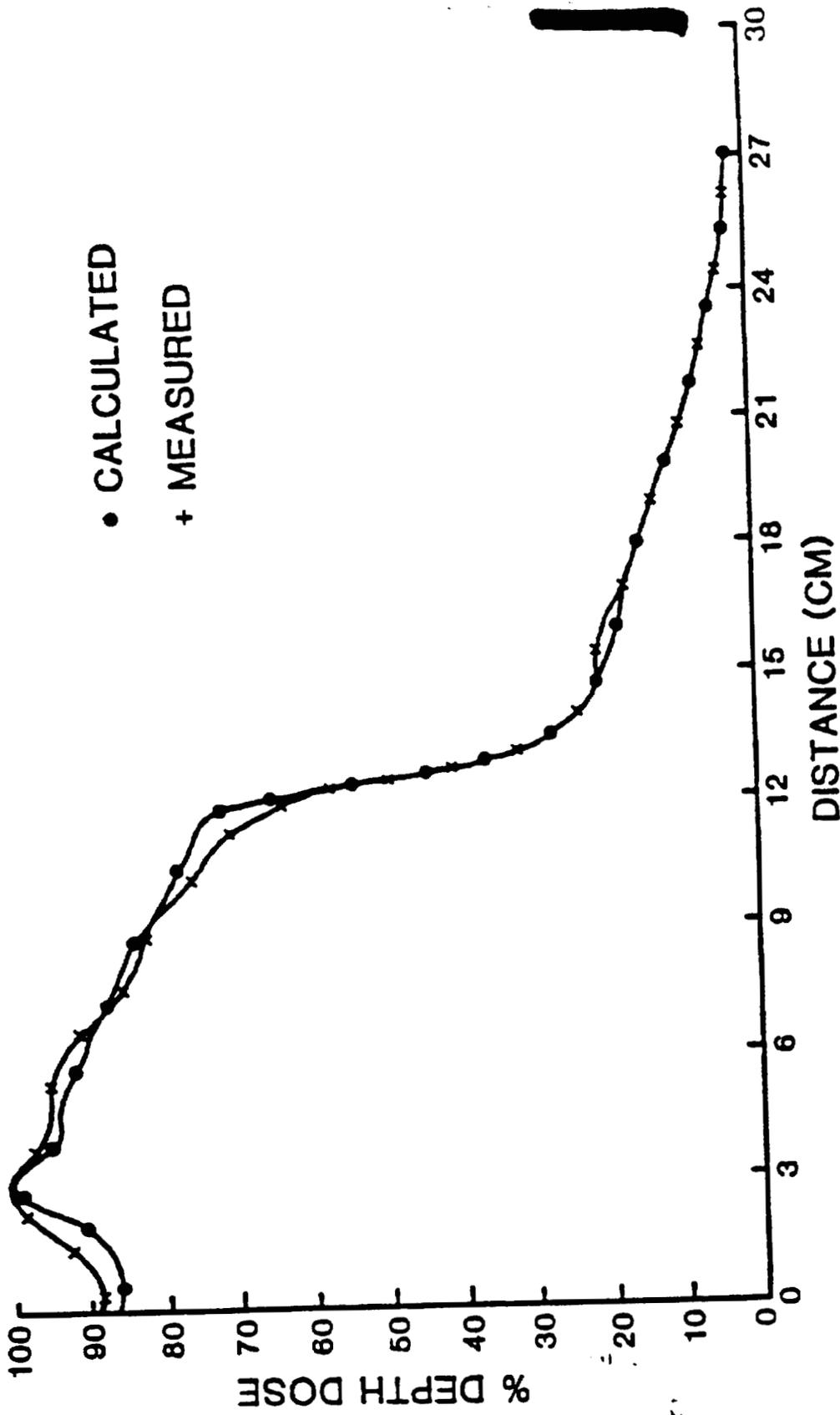


Figure 19. Calculated depth-dose distribution for 7 x 7-cm collimator, 9-cm spread peak
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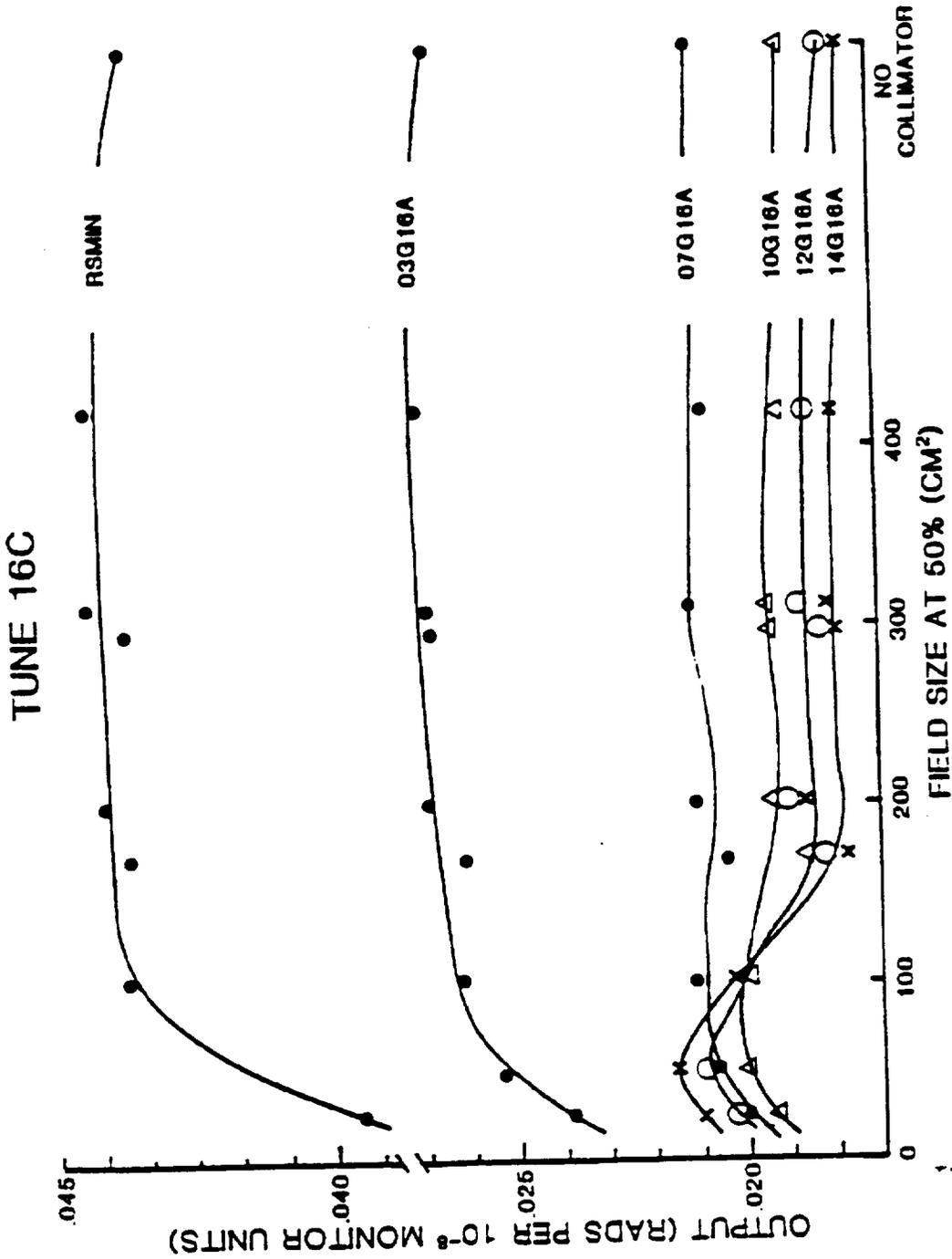


Figure 20. Beam output for varied collimation and range modulation (16-cm penetration)

For the pion beam microdosimetry studies, a simple data acquisition system was designed using a commercial (EG&G) 4" Rossi-type proportional chamber. This system does not require any gas-flow system or extensive electronics. It is similar to the more complicated method used previously, except that its use is limited to beams of very low intensity. Results from this system compare favorably with data from the more complicated system. Hence, it can be used to characterize selected pion beams during normally scheduled periods of low-intensity operation of the linear accelerator. This has greatly simplified the method for obtaining microdosimetric data on beams used for radio-biological and clinical experiments.

The Rossi chamber measurements are used as the primary source of microdosimetric data. Such techniques have been used to accurately measure linear energy and LET spectra for various types of ionizing radiation, including x-rays, neutrons, heavy ions, and pions. Rossi chamber measurements, however, are time-consuming, and adequate amounts of beam time are not available for use of this technique in characterizing all of the therapy beam tunes. Instead, one or two Rossi chamber spectra are obtained for each beam tune, with additional data obtained from either solid state detectors or aluminum activation. The latter two techniques permit rapid data collection. They are limited, however, by the fact that absolute normalization of the data requires accurate knowledge of pion and neutron cross-sections plus stopping powers of heavy ions. Such information is not completely available. Instead, LET information obtained through these two techniques is normalized (i.e., high-LET rad/total rad, or high-LET dose/ monitor unit) by comparison with the Rossi chamber data. In this manner, complete information on the spatial variations (in both the z-dimension and the transverse x-y plane) of the high-LET dose for all therapy beams is obtained.

For most purposes, such as the calculation of pion effective doses, high-LET dose has been arbitrarily defined as that fraction of the dose with LET $>50 \text{ keV}/\mu\text{m}$. An RBE model has been developed that can accurately fit the results of radiobiological experiments using such information. For more exacting purposes, however, complete LET spectra, obtained from Rossi chamber measurements, are used.

Using the techniques described above, microdosimetric data have been obtained for the various static beams, fan beams, and range-shifter modulated beams used for patient treatments.

(e) Beam shaping and inhomogeneity compensation.

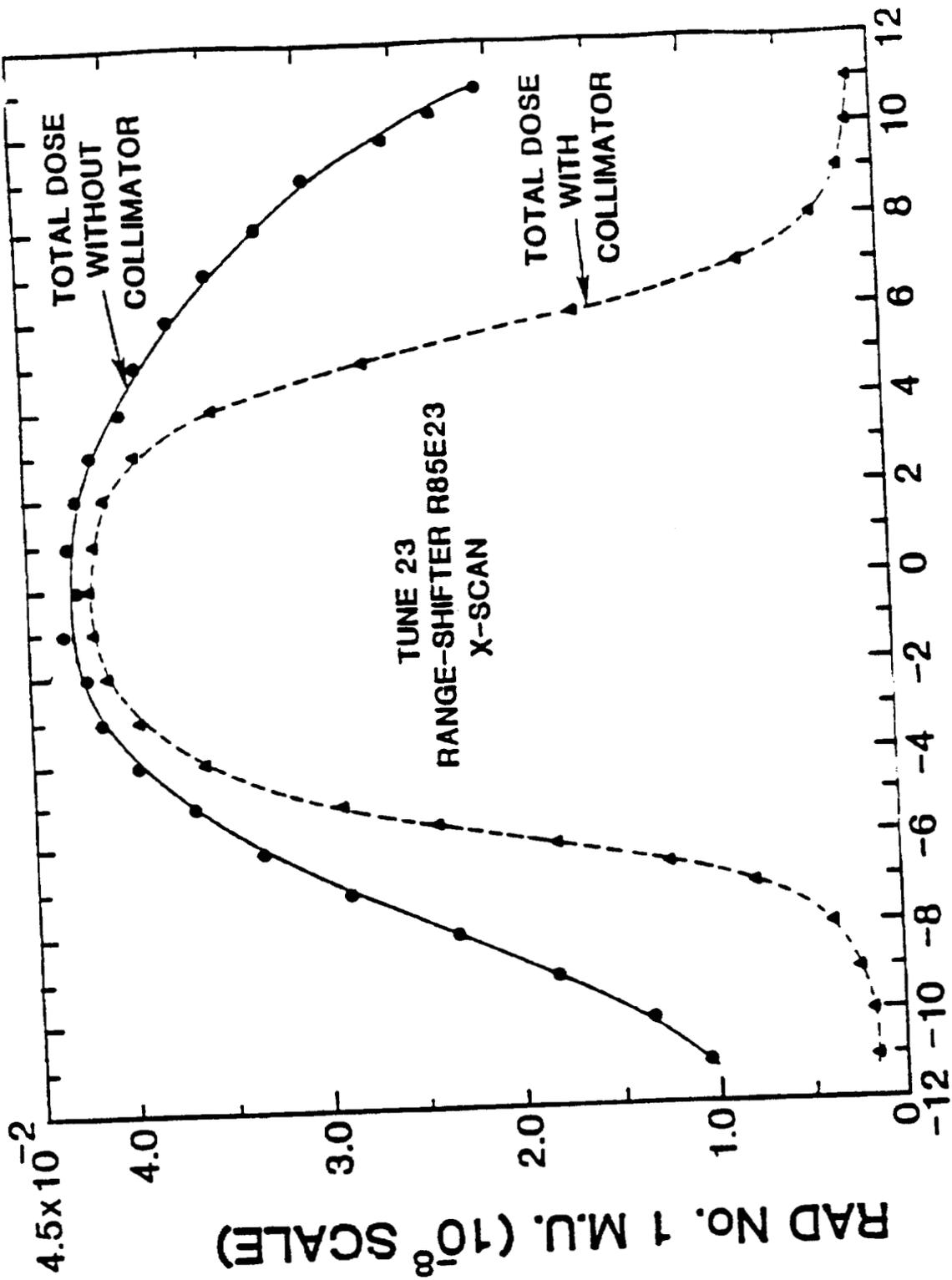
After the development of beams to be used in patient treatments, the major effort has been to tailor these beams for individual treatment situations. We have studied the effect of inhomogeneities, compensating bolus, collimation, and air gaps between patient treatment devices. The physical advantage of pions over conventional radiations lies in the ability to concentrate the peak pion dose on the tumor and deliver less dose to the adjacent normal tissue. To realize this advantage, the influence of tissue inhomogeneities upon the dose distribution must be understood so that adequate compensation can be made to shape the stopping pions in the direction of the beam. In addition, collimation must be properly designed so that the dose is restricted to the treatment volume in the plane perpendicular to the incident beam.

Beam shaping in the transverse dimensions for patient treatments is achieved by use of collimators individually designed for each patient. These collimators are made from a low-melting point alloy (50.0 percent bismuth, 26.7 percent lead, 13.3 percent tin, and 10.0 percent cadmium) with a density $\rho = 9.4 \text{ g/cm}^3$. The collimators are made with a thickness for each momentum sufficient to completely stop the incident pions outside the treatment aperture. Figure 21 shows typical beam profiles with and without collimation. These beam profiles were measured in the center of an 8.5-cm spread peak. The asymmetry in the uncollimated x-profile is due to the different phase space of pions, muons, and electrons. The distribution of muons and electrons is shifted toward the x-axis. The channel is tuned to give a symmetrical dose profile after collimation.

Collimation also alters the depth-dose distributions. Pions stopping in the collimator give rise to fast neutrons. The depth-dose spectra of those neutrons emitted in the forward direction is superimposed upon the depth dose of the pion beam causing a rise in the first few centimeters of the plateau. The relative effect increases with decreasing size of the aperture in the collimator because more pions are being stopped. Also, there is an effect in the stopping region: some off-axis pions stopping the collimator would have contributed neutron dose to the peak region. Therefore, these two mechanisms, neutrons produced in the collimator and the consequent loss of peak neutron dose, result in altered depth dose profiles such as those shown in Figure 22 for a 170-MeV/c range-shifted beam. The increased plateau dose, consisting of some fraction of neutrons having a high RBE, is not a clinical problem because in most cases this portion of the curve falls within the beam-shaping bolus which is placed between the patient and the collimator.

Compensation is the technique of modifying the pion beam so that the peak dose is constrained between the distal and proximal surfaces of the target volume. The penetration of the beam to the distal surface of the treatment volume can be controlled by using bolus. The bolus must be designed to compensate for all geometrical and tissue inhomogeneities in the beam path. The proximal edge of the peak dose is controlled by properly modulating the pion peak width using a range-shifter. When treatments are done with large, essentially parallel beams, the proximal edge of the peak region cannot be varied once the distal edge is defined, and a spread peak width is chosen to cover the maximum extent (depth) of the treatment volume. With dynamic treatments, in which the patient is scanned beneath a narrow focused beam (focused in either one or two dimensions), the proximal edge of the spread peak region can be varied, and the treatment volume will be more precisely outlined by the stopping pion region. Dynamic treatments are discussed later in this report.

Before treatment planning can begin it is necessary to understand the effects of tissue inhomogeneities lying in the paths of treatment beams and to determine whether bolus can adequately compensate for inhomogeneities. Measurements of the effects of inhomogeneities and compensation bolus in clinical pion beams have been made. Tissue inhomogeneities such as bone or lung alter the dose distributions from those predicted from homogeneous unit-density tissue because of variations in the pion linear stopping power, multiple scattering, and secondary particle emission. The main influence of these inhomogeneities is distal to the inhomogeneity interface, where the pion range has been altered, distorting the shape of the dose distribution in the stopping region. When inhomogeneities are located in the stopping



DISTANCE ALONG X-AXIS IN WATER (cm)

Figure 21. Typical beam profiles with and without collimation (8.5-cm spread peak)

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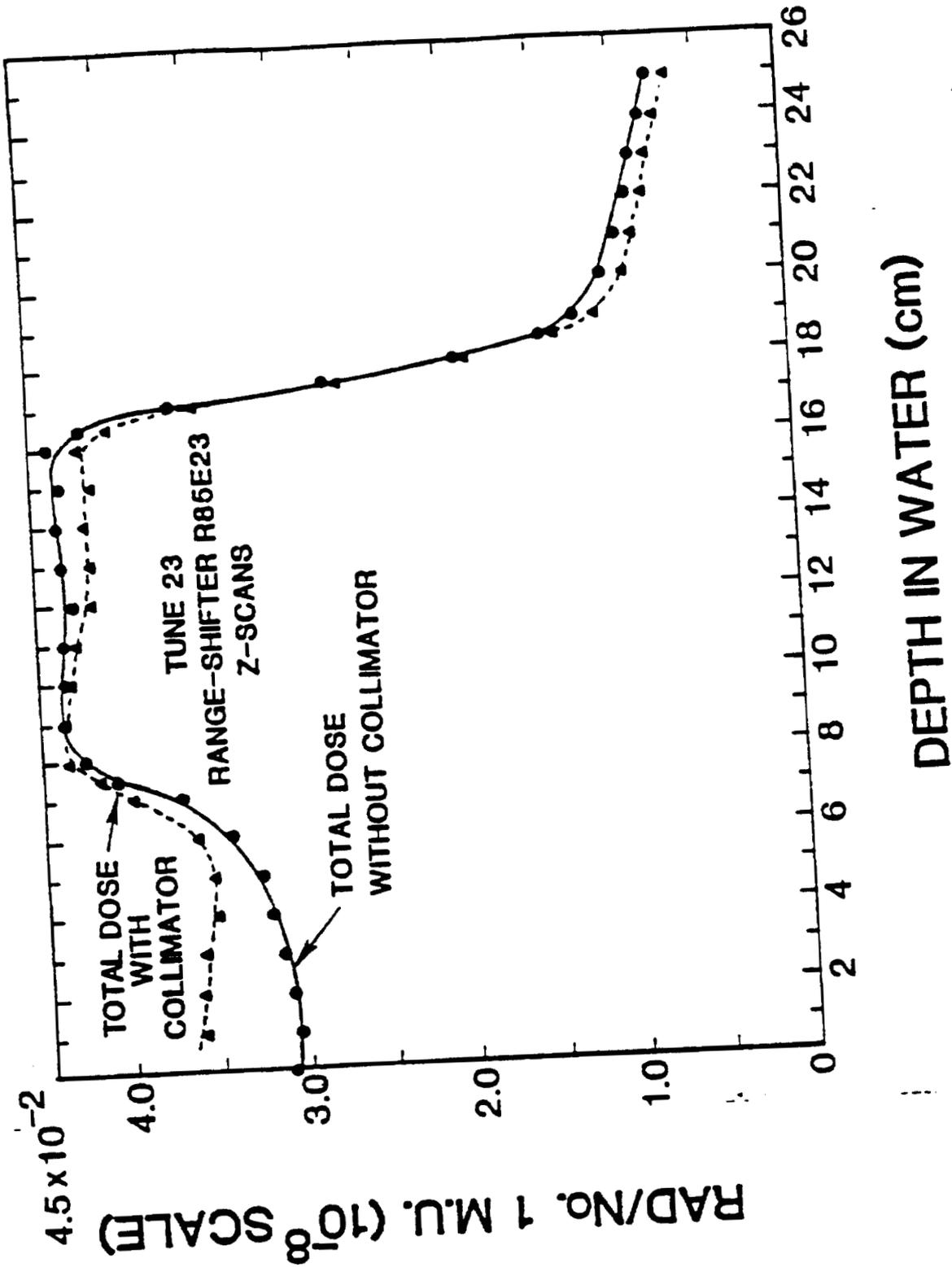


Figure 22. Altered depth-dose profiles from neutrons produced in collimator and consequent loss of peak neutron dose

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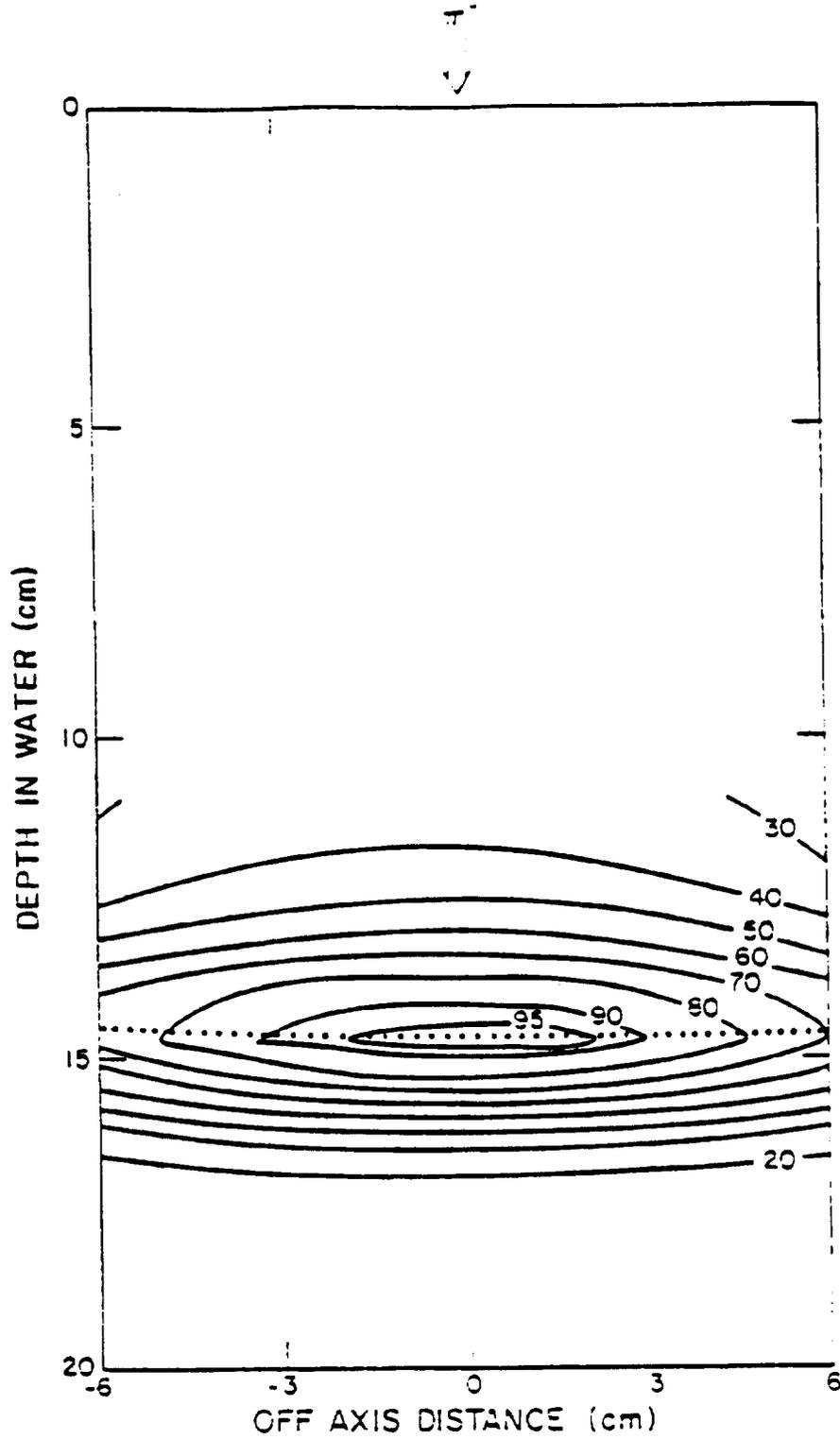
region of the pion beams, additional dose modifications could occur because of density effects or changes in the secondary charged particle spectra.

Measurements have been made for inhomogeneity and bolus compensation for pion beams of different energy; variation of the inhomogeneity depth beneath the surface; air and Teflon inhomogeneities to simulate lung and bone; bolus compensation using a parallel beam model; and bolus-inhomogeneity misalignment. Examples of such measurements are shown in Figures 23 through 26. Figure 23 shows a typical iso-ionization distribution for an open beam. The dotted line in the peak region is a ridge that connects the depth-dose peaks for various off-axis distances. Figure 24 compares the open-beam ridge (dotted line) with the ridge (dashed line) under a Teflon inhomogeneity. The Teflon block is 2 cm thick by 4 cm wide in cross-section and is located 0.5 cm beneath the water surface. The peak ionization has been shifted forward beneath the Teflon. A comparable inhomogeneity in a patient could grossly underdose the distal boundary of the target volume.

In addition to the displacement of peaks due to inhomogeneities there is a change in the peak dose rate. This effect is seen in Figure 25, where the incident pion beam passes through an 11 x 9-cm elliptical collimator and an 8 x 4 x 4-cm Teflon block, located along the beam axis 1 cm below the water surface. Note the forward shift of the pion peak, due to the Teflon. By translating the Teflon peak back to the original peak position (a shift of 3.24 cm), one observes that the peak dose under Teflon is a few percent less than the peak dose without Teflon. This decrease occurs because there are fewer scattered pions in the peak, since pions not incident on the Teflon stop deeper than the shifted peak. Some of these pions have undergone multiple scattering to the rear of the central peak, and they contribute additional dose there.

The ability to compensate for the Teflon inhomogeneity using a parallel beam bolus correction model is seen in Figure 26. The bolus is 3.5-cm paraffin with a 8 x 4-cm rectangular hole directly above the Teflon. The shape and magnitude of the peak in the depth-dose curve has been restored to the original. Similar results have been obtained with air inhomogeneities. Such measurements indicate that it is possible to predict the effect of inhomogeneities and to compensate for these effects in treatment planning.

In designing patient bolus, one must compensate for skin contour, tumor shape, tissue inhomogeneities, movement of anatomy due to breathing, and changes in anatomy due to fluctuations in bowel gas, and bladder or rectal filling. At the present time anatomy changes are handled by prescribing target volumes that will encompass expected deviations. Considerable effort has been expended in developing casting and immobilization techniques that minimize patient movement during treatment and that reproduce the treatment positions from day to day. Patient motion is not as critical as for heavier ion beams because of the greater multiple scattering of pions which leads to beam edges that are less sharp. However, these same properties prevent pion beams from being as precisely shaped to conform to target volumes, especially in the presence of sharp gradients in the target surface in the direction of the beam.



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Figure 23. Typical iso-ionization distribution for open pion beam

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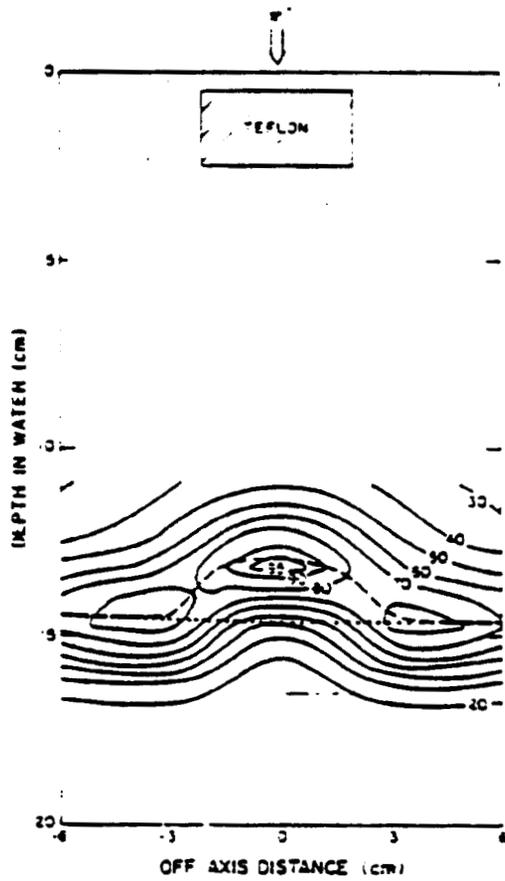


Figure 24. Comparison of open-beam ridge (dotted line) connecting depth-dose peaks for various off-axis distances with ridge (dashed line) under Teflon inhomogeneity

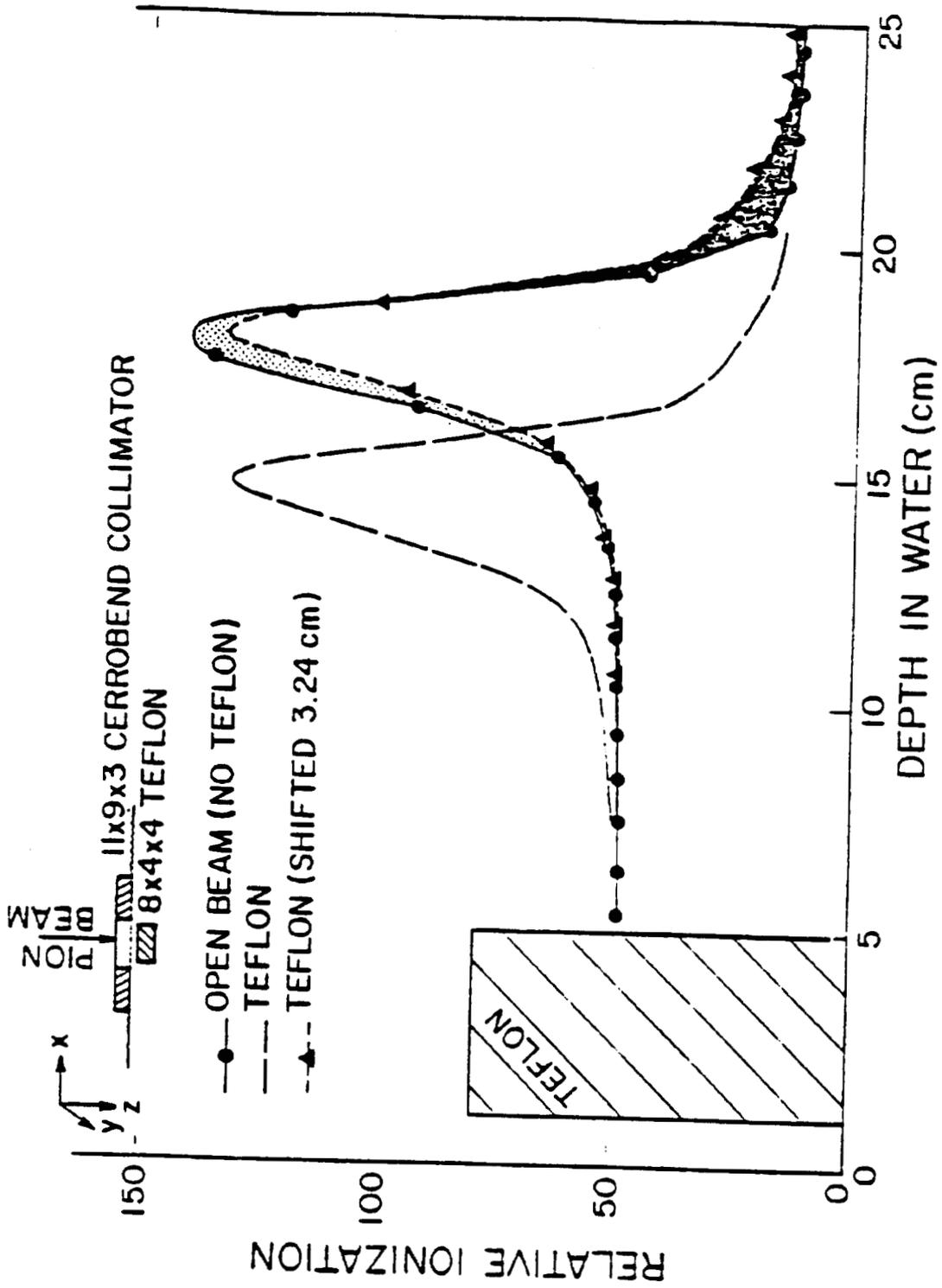


Figure 25. Change in peak dose rate due to transmission through Teflon block

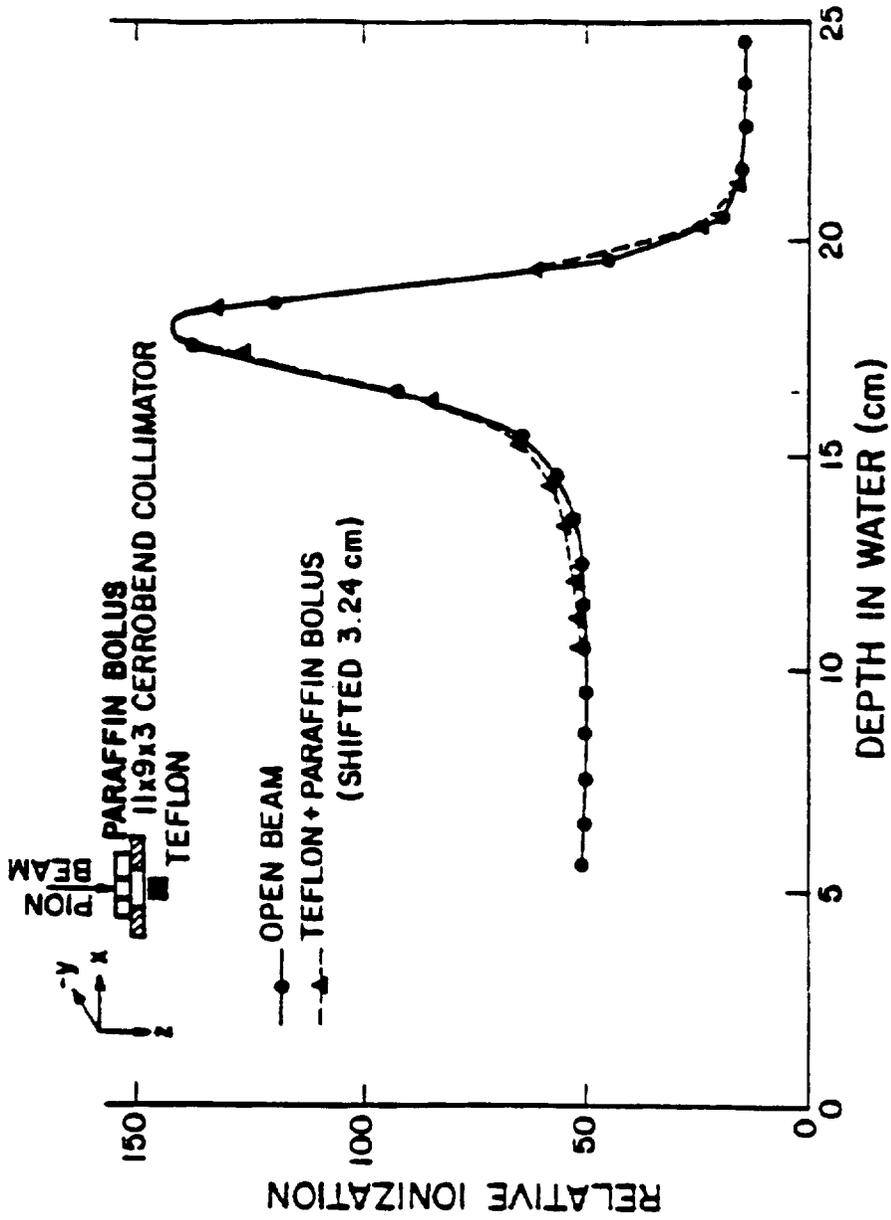


Figure 26. Compensation for Teflon inhomogeneity using parallel beam bolus correction model

(f) Pion absorbed dose determinations. Stopping pions give rise to a variety of secondary charged particles by virtue of their interaction with, and subsequent fragmentaton of, the nuclei of the stopping material. These particles include protons, tritons, deuterons, alpha particles, and heavy ions such as Li and Be. Each of these particle types exhibits broad energy spectra with maximum energies up to approximately 70 MeV.¹¹² In addition, ionization is produced by contaminant muons and electrons, primary pions, and neutrons and gamma rays produced by the star events.

Ionization chambers have become the principal instruments employed for determining the absorbed dose in tissue. Ionization methods require conversion factors that rest on physical interpretation of the energy absorption processes and involve such considerations as secondary charged particle spectra, relative stopping power ratios, the energy required of secondary charged particles to produce ion pairs in various gases, and corrections for the non-tissue equivalence of chamber walls.¹¹³ The precise information required for these interpretations and considerations is not well known for charged particle beams, thereby giving rise to large uncertainties in the specification of the absorbed dose in tissue from pion beams when ionimetry is used. We believe that these uncertainties are on the order of 10 percent.

The major uncertainties arise from our lack of knowledge concerning the pion capture cross-sections for various elements, the energy given to secondary charged particles via pion capture by target nuclei, the energy fluence of secondary charged particles and neutrons, and the energy dependent stopping powers and W values for the secondary particles.¹¹⁴⁻¹¹⁵ Only a large program of experimental and theoretical work will lead to a significant improvement in our knowledge of these factors.

In view of this rather large program of work, and time required to complete it, we decided to check the earlier calculations of the conversion factor for the cylindrical chambers currently in use by direct comparison of the ionization chambers with a calorimeter.

In April of 1979 measurements were performed in the peak of an unmodulated π^- beam and in the peak and plateau of an unmodulated π^+ beam using a thimble chamber and parallel plate chamber of TE (Shonka A-150) plastic walls and TE (methane) gas, a TE plastic calorimeter (Sloan-Kettering Institute neutron calorimeter) and the National Bureau of Standards (NBS) carbon ionization chamber with air gas in conjunction with the NBS carbon calorimeter.

In March 1980, a more extensive set of measurements was performed. These measurements repeated the work done in 1979 and, in addition, data were obtained in the plateau of an unmodulated π^- beam and in the proximal and distal peak of a modulated π^- beam (a 9 cm, flat physical dose spread peak). The 1980 experiments were done using the new charged particle beam TE calorimeter with one measurement also done with the old neutron calorimeter to test the agreement between the two calorimeters (in the plateau of an unmodulated beam). The NBS carbon calorimeter work was not repeated in 1980. The points of measurements are indicated on the pion depth dose curves of Figures 27 and 28.

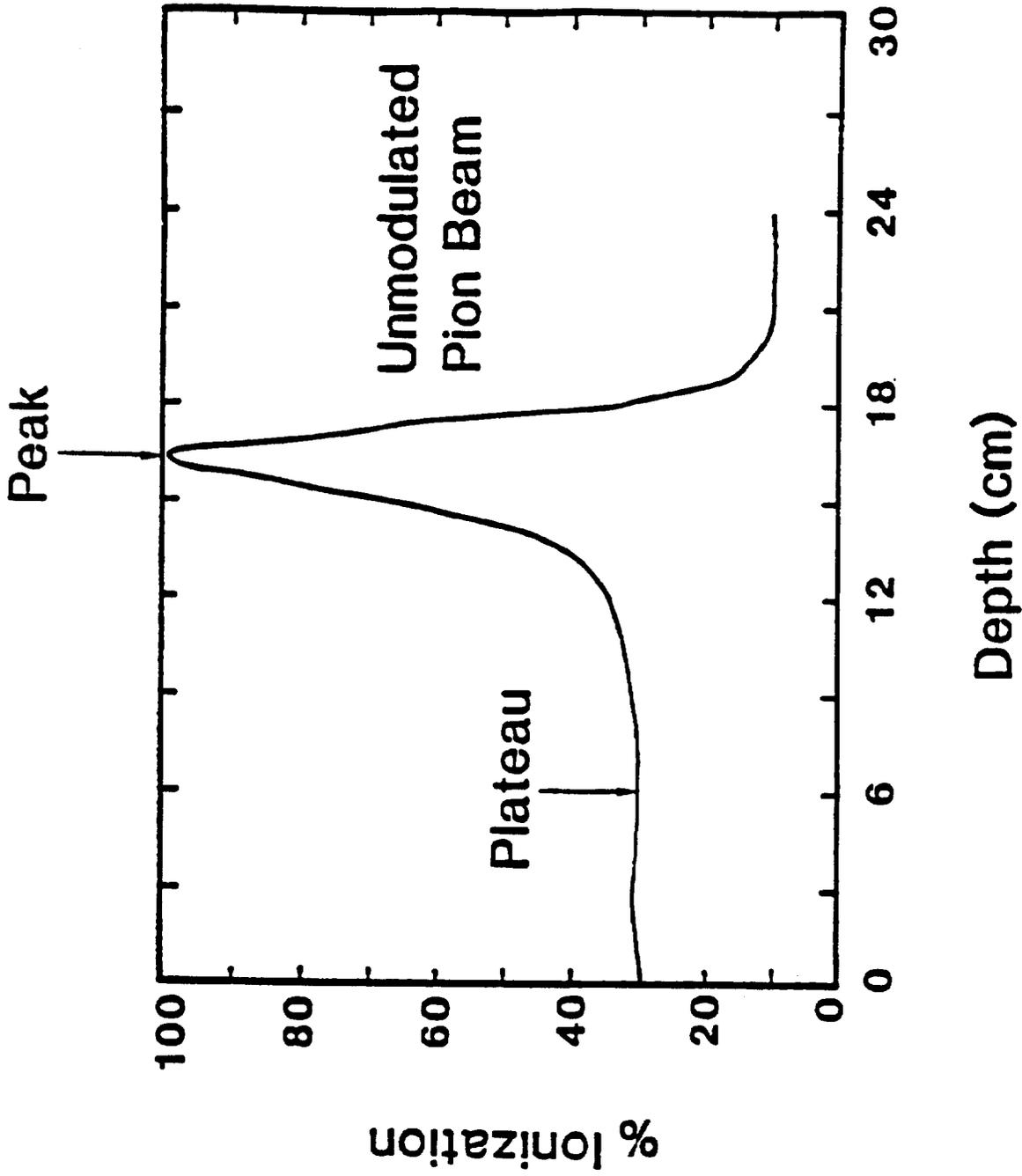


Figure 27. Ionization chamber/calorimeter measurements in an unmodulated pion beam

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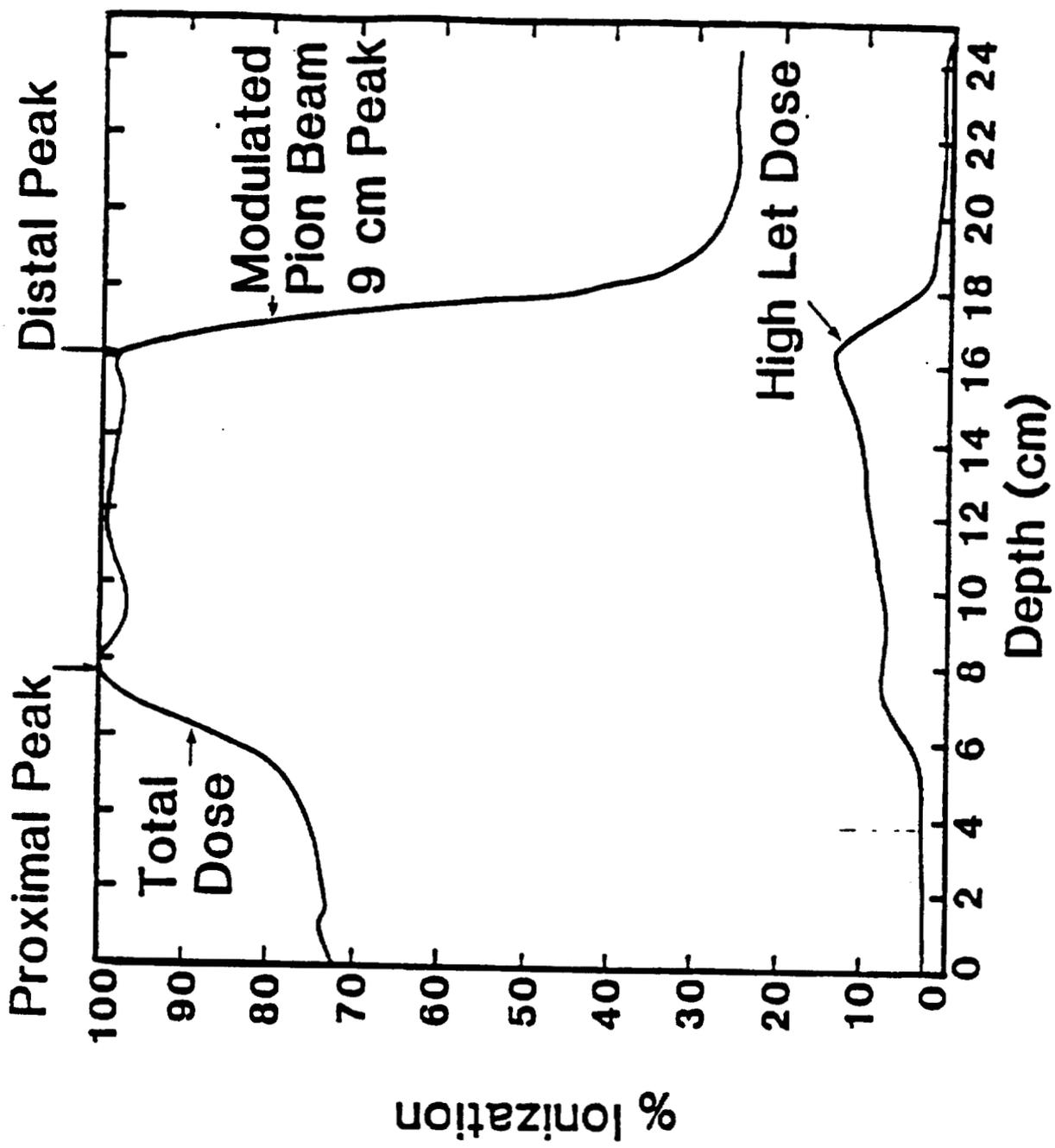


Figure 28. Ionization chamber/calorimeter measurements in a modulated pion beam

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In pion ionization chamber dosimetry the absorbed dose in the chamber wall is determined by the use of the equation

$$D_{w,p} = 100 Q_p \cdot \frac{1}{M_g} \cdot \frac{\bar{W}_p}{e} \cdot (S_{w,g})_p \quad (1)$$

where

- $D_{w,p}$ = absorbed dose in rads in the Shonka A-150 plastic chamber wall
- Q_p = measured ionization charge (Coul)
- M_g = the mass of gas in the cavity (kg)
- \bar{W}_p/e = the average energy required to produce an ion pair in the gas cavity (J/Coul)
- $(S_{w,g})_p$ = the gas-to-wall conversion factor

In practice, \bar{W}_p/e is obtained by averaging over the spectrum of all the charged particles ionizing the gas. A first approximation to $(S_{w,g})_p$ is given by the Bragg-Gray theory and is derived from the stopping power ratio averaged over the charged particle spectrum. The product of these two quantities can be determined from direct intercomparison of the ionization chamber with a calorimeter in the pion beam. This product is given by,

$$\frac{\bar{W}_p}{e} \cdot (S_{w,g})_p = \frac{D_{w,g} \cdot M_g}{100 Q_p} \quad (2)$$

$D_{w,g}$ is determined by the calorimeter directly; Q_p is measured by the ionization chamber and electrometer; M_g is determined by calibration of the ionization chamber on a ^{60}Co beam whose exposure calibration is traceable to NBS.

In this manner we have an experimental determination of the product of two quantities which are difficult to calculate because of the lack of detailed information concerning the charged particle energy fluence of the multiplicity of charged particle types interacting with the cavity gas.

Table 26 gives a summary of the results of the TE-TE experiments. The designation (un) in the position column refers to an unmodulated beam. The differences between the two experiments conducted a year apart, using a different calorimeter and using a different electrometer for the ionization chamber measurements made by the UNM group, are within experimental uncertainty, and no systematic differences are seen in the data. For each measurement, ionization chamber data were taken with both the SKI parallel plate chamber and the UNM thimble chamber replacing the calorimeter core so that the geometry was identical for the calorimeter and ion chamber measurements. The amount of material (TE plastic) between the beam and the center of the calorimeter core, the front face of the parallel plate chamber, and the center of the thimble chamber, was held constant for each measurement. Measurements were made with each ion chamber both immediately before and after each calorimeter run. The uncertainties are random errors in the ion chamber

TABLE 26

SUMMARY (TE-TE)

<u>Particle</u>	<u>Position</u>	$\frac{\bar{W}_p}{e} \cdot (S_{w,g})_p$		
		<u>1979</u>	<u>1980</u>	<u>Mean</u>
π^-	Plateau (um)		29.5±0.6	29.5±0.6
π^-	Peak (um)	29.7±0.5	30.3±0.8	29.9±0.5
π^-	Proximal Peak		30.4±0.7	30.4±0.7
π^-	Distal Peak		30.2±1.0 29.7±0.9	30.0±0.7
π^+	Plateau (um)	29.5±0.4	28.9±0.7 29.1±0.8	29.3±0.3
π^+	Peak (um)	28.3±0.4	28.6±0.9	28.4±0.4

Errors are SD of the mean. Includes random errors only.

readings, the monitor units delivered, and the calorimeter readings. Four sets of ion chamber readings (each chamber before and after calorimetry) were combined with the calorimeter data to calculate $\bar{W}_p/e \cdot (S_{w,g})_p$ from Equation 3.

Table 27 gives the systematic uncertainties in the data. The calorimeter data were corrected for thermal defects (4 percent). The total uncertainty was obtained by adding the random and systematic uncertainties in quadrature.

Table 28 gives the recommended values from these experiments for each particle and position. The π^- peak values from Table 26 (unmodulated peak, proximal and distal modulated peak) cannot, from this experiment, be concluded to be different. The value in Table 28 for π^- peak is therefore, the mean of all the peak data. The uncertainties in Table 28 are total uncertainties.

Table 29 shows a comparison between the values determined from these experiments with the values which have been used for patients since June 1976. Changes in our current statement of absorbed dose in TE plastic cannot be justified on the basis of these data.

Since the gas-to-wall conversion factor, $(S_{w,g})_p$, is expected to be near unity, the values for $\bar{W}_p/e \cdot (S_{w,g})_p$ will be within a few percent of the values for \bar{W}_p/e .

Table 30 gives the results of the measurements for the carbon calorimeter and the carbon-air ionization chamber, along with total uncertainties. One notes that the uncertainties for these measurements with the NBS devices are much smaller than for the TE-TE data.

One interesting point is that the value for π^+ peak in both the TE and carbon data is lower than that for the plateau. Intuitively, one would expect it to be higher. However, the ratio of peak-to-plateau values is 0.969 for TE-TE and 0.967 for carbon-air, leading one to believe that this may not be an anomaly.

In Equation 1, $D_{w,p}$ is the dose in the chamber wall. To obtain the dose in muscle tissue one must use another conversion factor, i.e.,

$$D_{m,p} = (K_{m,w})_p \cdot D_{w,p} \quad (5)$$

where,

- $D_{m,p}$ = absorbed dose in rads in muscle tissue
- $(K_{m,w})_p$ = chamber-wall-to-muscle conversion factor.

To provide an estimate of this conversion factor, we have performed preliminary calculations assuming tissue and TE plastic to be composed of only oxygen and carbon. Utilizing pion capture probabilities and energies given to charged particles for pion capture in carbon and oxygen from two sources (Dutrannois¹¹⁶ and Shortt¹¹⁷), stopping powers for each class of secondary particle, and energy deposited by neutrons, we have obtained the following values for the wall-to-muscle conversion factor:

TABLE 27
UNCERTAINTIES IN MEASUREMENTS

	<u>Systematic (%)</u>
Exposure Calibration	2.0
Conversion Factors	2.7
Ionization Charge	1.0
Corrections (T-P, Saturation)	0.3
Calorimetry	2.5
Total Uncertainty = $\sqrt{R^2 + S^2}$	

TABLE 28
RECOMMENDED VALUES

<u>Particle</u>	<u>Position</u>	$\frac{\bar{W}_p \cdot (S_{w,g})_p}{e}$
π^-	Plateau	29.5 ± 1.4 (4.8%)
π^-	Peak	30.1 ± 1.3 (4.4%)
π^+	Plateau	29.3 ± 1.3 (4.4%)
π^+	Peak	28.4 ± 1.3 (4.5%)

Uncertainties are random and systematic added in quadrature

TABLE 29
 COMPARISON OF MEASUREMENTS AND CALCULATIONS

$$\frac{\bar{W}_p}{e} \cdot (S_{w,g})_p$$

	<u>Measured</u>	<u>Calculated</u>	<u>Ratio (M/C)</u>
Plateau	29.5	29.4	1.003
Peak	30.1	30.3	0.993

Calculated values are those which have been used for patient dosimetry since June 1976.

TABLE 30
SUMMARY (CARBON-AIR)

<u>Particle</u>	<u>Position</u>	$\frac{\bar{W}_p}{e} \cdot (S_{w,g})_p$
π^-	Peak (um)	34.2±0.4 (1.2%)
π^+	Plateau	33.4±0.4 (1.2%)
π^+	Peak	32.3±0.4 (1.1%)

Uncertainties include 1.1% systematic added in quadrature to random errors.

	$(K_{m,w,p})$		
	Smith ¹¹⁸	Dutrannois data ¹¹⁶	Shortt data ¹¹⁷
Plateau	0.98	1.04	0.99
Bragg-peak	0.92	1.02	0.88
Spread peak	0.92	1.03	0.95

It is clear that there are large uncertainties in the value of $(K_{m,w,p})$, the conversion factor used to convert dose in the TE (Shonka A-150) walls of the ionization chamber to dose in muscle tissue. Certainly more refined calculations must be made before better values are obtained. Also, there is no clear choice between the calculated values. The values obtained in this study for $\bar{W}/e \cdot (S_{m,w,p})$ are in excellent agreement with those values currently used in our pion dosimetry.

In view of these considerations, and because our colleagues at TRIUMF and SIN are using the statement of absorbed dose in muscle tissue due to peak pions as we are (numerically the same although their methodology is different), we will not change our dosimetry at this time.

(g) Biological dosimetry. Numerous radiobiological experiments have been conducted to compare the effects of pions and x-rays. Special pion beams have been developed, and dosimetry provided for experiments on monolayer cells; multicellular tumor spheroids; rat colon, spinal cord and mammary gland; and mouse heart, lung, gut, kidney, and implanted tumors of the thigh. Results of these studies are reported under Biology. All of these animal experiments were done with a small area pion beam (5-cm diameter or less) with dose rates as high as 175 rad/min. To accommodate the special anatomical features, custom collimators and/or bolus were fabricated for each experiment. Dosimetry was done using a combination of ion chambers and thermoluminescent detectors. Microdosimetric measurements were also made on this beam to aid in the interpretation of results. Additional experiments were also performed to compare the biological effects of pion beams of different volumes, and to compare π^+ and π^- beams. Extensive dosimetric and microdosimetric measurements were made on these beams as well.

(4) Treatment planning

(a) Previous methods of treatment planning.

Treatment planning for patients with and without the aid of computerized tomographic (CT) scans has made it apparent that adequate treatment plans cannot be developed without the use of CT scan data. CT scans allow a three-dimensional tumor treatment volume to be uniquely prescribed by the radiotherapist and nearby critical structures to be placed in their proper perspective.

A three-dimensional description of the treatment volume from CT scans helps to minimize the dose delivered to normal tissue. Information concerning the longitudinal dimension (parallel to direction of incident beam) of the treatment volume can be obtained only from CT scans. Although x-rays or other diagnostic methods may give the maximum longitudinal thickness of the tumor, the relevant quantity is the effective longitudinal thickness, which is obtained by integrating the linear stopping power of the tumor over the maximum longitudinal thickness. This effective thickness can be obtained from CT data by relating the CT numbers to pion stopping powers.

but not from diagnostic x-rays. Although with static pion radiotherapy the peak dimension in depth must remain the same across the transverse plane of the treatment volume, dynamic pion radiotherapy will permit variation of peak depth-dose deposition. This requires knowledge of the longitudinal thickness of the tumor volume at each point in the transverse plane. Such information can be obtained only from CT scans, even for homogeneous tumor volumes

Probably the most useful information obtained from CT scans is the quantitative description of inhomogeneities. Dose distributions are affected both proximal and distal to inhomogeneities. The distal effect is the change in the pion stopping distribution caused by range changes and multiple scattering arising from tissue inhomogeneities. This phenomenon can be controlled to some extent by use of bolus if a description of the inhomogeneities is available. The proximal effect is the change in dose at tissue-inhomogeneity interfaces caused by variations in the secondary particle emission and density effects. Little can be done to control these phenomena.

In selecting the proper beam tune, peak width, number of portals, direction of portals, collimation, and bolus configuration, the treatment planner must consider several principles regarding static pion beam treatments:

(i) It is advantageous, in cases where critical structures are transversely adjacent to the tumor, to treat with the beam of the least penetration, as the penumbra becomes narrower in the peak region with decreasing pion momentum.

(ii) Beam flatness over relatively large fields can be best accomplished by abutting two smaller fields. This is due to the emittance of pion beams; i.e., the incidence pion flux has a Gaussian type fall-off. Pion fields abut nicely in the transverse dimension because their penumbras are not as sharp as most conventional radiotherapy beams, thereby reducing the probability of hot or cold spots resulting from misalignment.

(iii) The low exit dose of pions allows the beam to be aimed directly at critical organs or structures. Generally, this is not possible with conventional radiation

(iv) Directing the beam through the path of minimal inhomogeneities minimizes the importance of bolus correction.

(v) Overlapping parallel opposed fields tend to flatten both physical and biologically equivalent dose. This is so because not only is the total dose flattened, but also the fractional high-LET component.

(vi) The fixed nature of the pion beam as opposed to the rotational freedom of most megavoltage machines means that the patient must rotate for multiport irradiations. Proper treatment planning, therefore, requires CT scans in each of the rotated positions for assurance of minimal changes in internal anatomy between scanning of the treatment positions.

(vii) Short-term movement of tissues during breathing can occur. This is particularly important in treating small lung lesions. Also, long-term changes resulting from bowel gas or bladder and rectal filling need to be recognized.

(viii) With static beam treatment it is not possible to vary the longitudinal extent of the pion peak to conform to the prescribed tumor volume throughout its transverse extent. Therefore, the radiotherapist must prescribe how the pion peak is to fit in depth around the prescribed treatment volume. In making this decision, sharp gradients (parallel to the incident pion beam) in the borders of the stopping distribution must be considered; these will tend to underdose the distal edge of the tumor volume due to multiple scattering and secondary particle fluxes being greater upon exiting the tumor volume than upon entering.

(ix) The patient's physical condition must be considered. There is usually an optimal set of directions for the pion beam to enter relative to the patient, but because the patient must rotate physically, he must be physically capable of withstanding rotation into those preferred positions for treatment.

The complexity of treatment planning for pions emphasizes the need for close interaction among the radiotherapist, diagnostic radiologist, and medical physicist. Presently, multiport treatments are limited to parallel-opposed and abutted fields. As experience is gained, patient positioning and casting techniques are improved, and CT scans become available at different rotations, then more complicated multiport irradiations will be possible.

When a patient is accepted for pion therapy, the first procedure is to prepare an immobilization cast of the patient which will be used during CT scanning and treatment. Casting and immobilization techniques are discussed in a separate section.

CT scans are usually taken at 0.9-cm intervals throughout the volume of interest. All scans are numbered in reference to a tattoo for each series of scans. Also, a radio-opaque marker provides a method of referencing one scan to another and gives positive identification of the position of the tattoo in the reference CT slice.

After CT scanning the CT slices are called up and displayed on a CT diagnostic console. The physician delineates, by means of a tracking ball, the skin contour, target volume and critical normal structures. These regions of interest (ROI's) are overlaid and stored on the CT data.

The magnetic tape containing CT scan data is read into the bolus design computer file. A particular file (scan) is displayed on a CRT screen, and the target volume is entered with a digitizing pen from a life-size CT image containing the ROI's. Additional input data are the appropriate pion range and range-shifter function. The bolus (Lucite) required to stop the pions at the prescribed target volume boundary is then calculated automatically by the computer programs from examination of the CT data. This calculation assumes that all pion trajectories are parallel and utilizes correlations of relative (to water) pion linear stopping powers

- CALCULATED x PROFILE
- MEASURED x PROFILE
- CALCULATED y PROFILE
- MEASURED y PROFILE

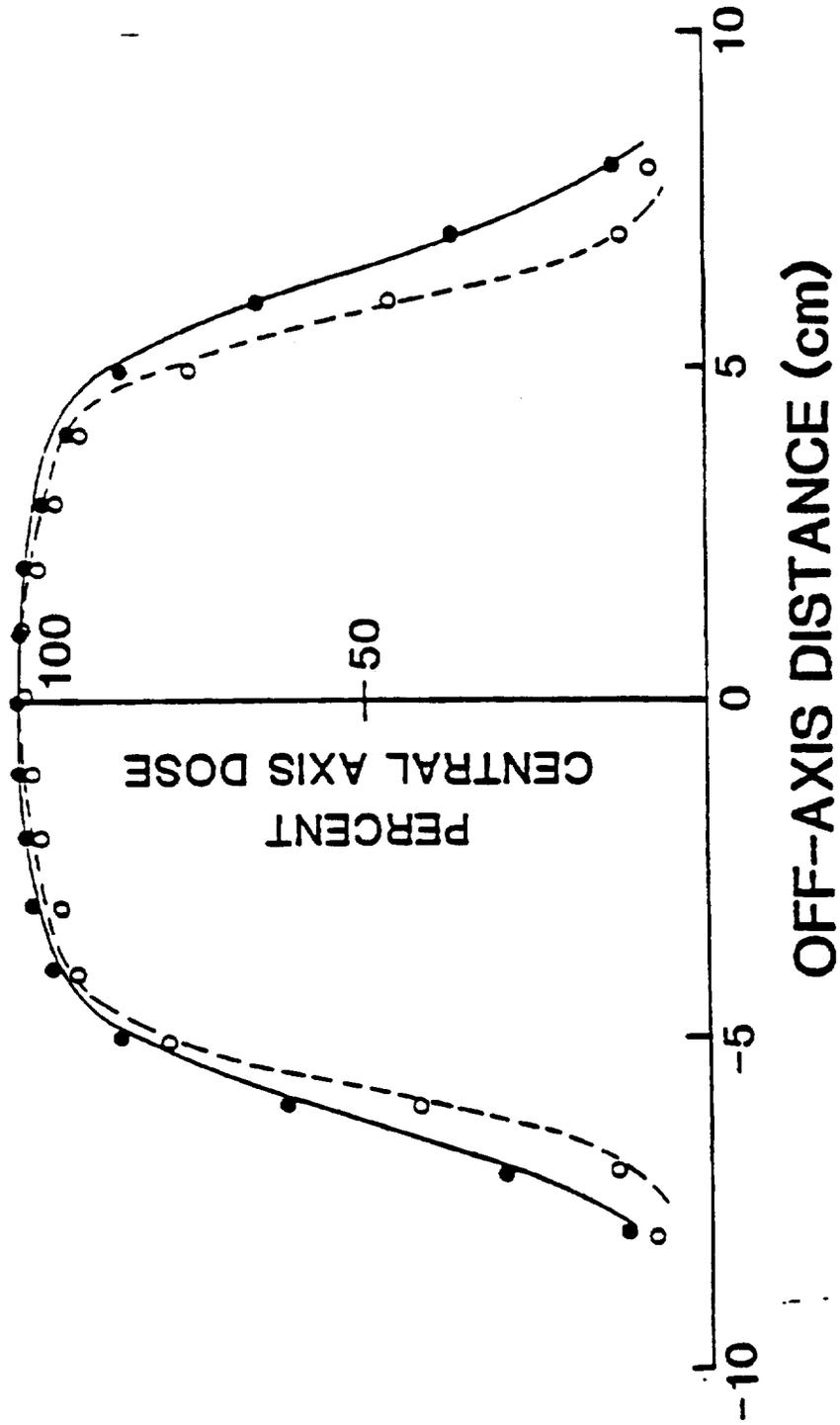
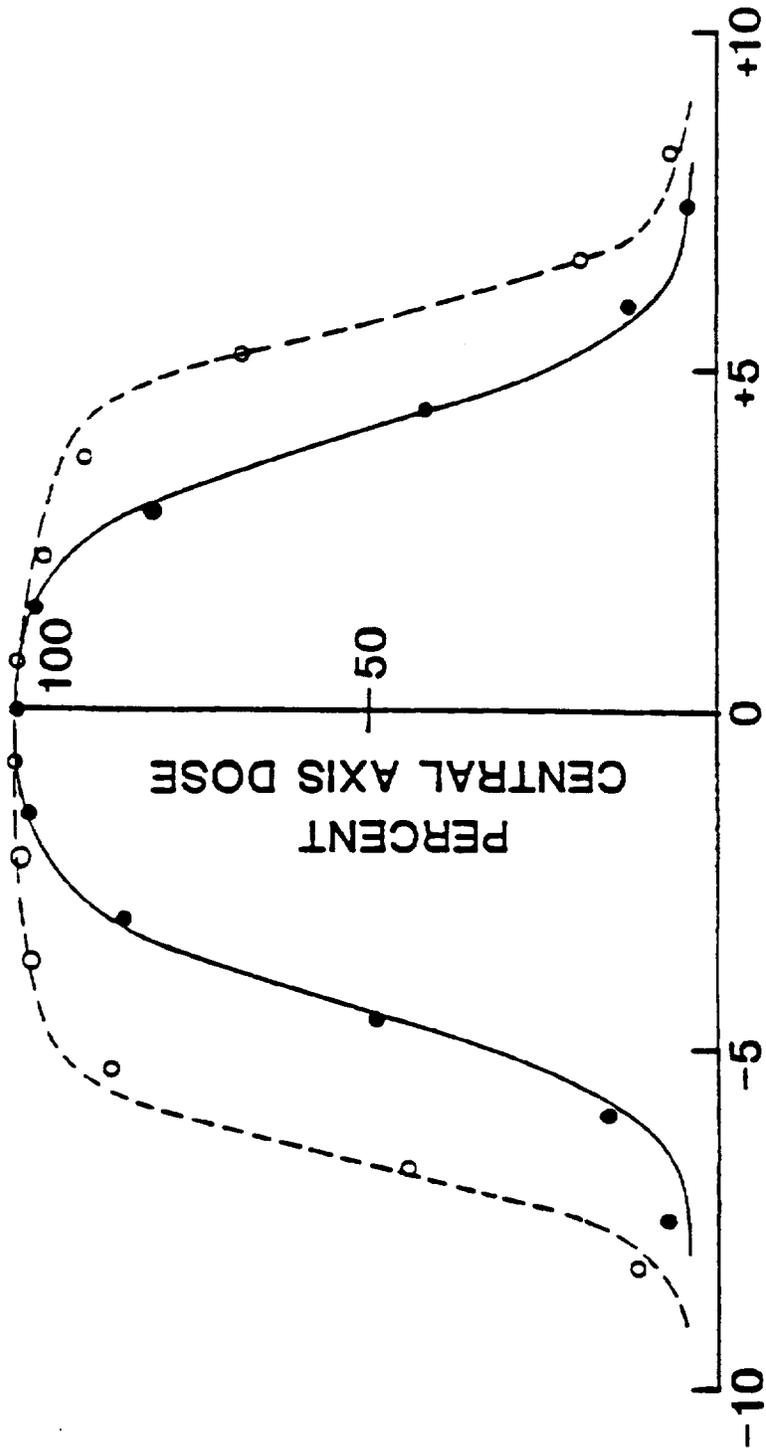


Figure 29. Measured and calculated x, y profiles for 11.6-cm penetration beam

- CALCULATED x PROFILE
- MEASURED x PROFILE
- CALCULATED y PROFILE
- o MEASURED y PROFILE



OFF-AXIS DISTANCE (cm)

Figure 30. Measured and calculated x, y profiles for 16.1-cm penetration ion beam

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- CALCULATED x PROFILE
- MEASURED x PROFILE
- CALCULATED y PROFILE
- o MEASURED y PROFILE

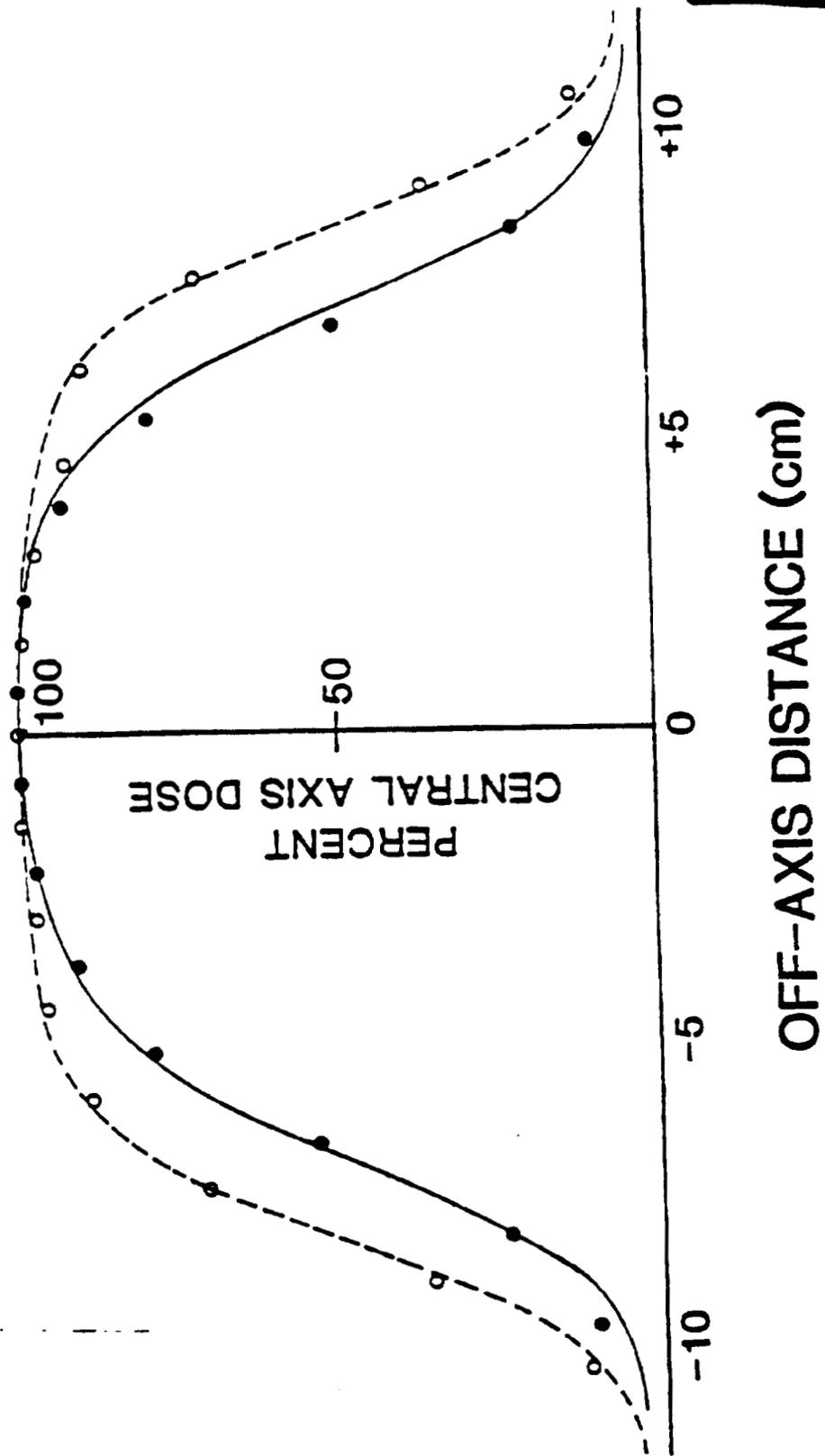


Figure 31. Measured and calculated x, y profiles for 22.9-cm penetration ion beam

Normally, calculations for several slices in the treatment volume are done to evaluate the dose to adjacent critical structures.

In 1982 we will begin treatment planning with the code PIPLAN. This code utilizes a ray-tracing model where actual pion trajectories in the three-dimensional volume represent pencil beams. The program uses beam data measured by multiwire proportional counters for the pion trajectories as well as the measured beam momentum and contamination of muons and electrons. The program includes appropriate physics models for multiple Coulomb scattering and range straggling and models the range modulation of the range-shifter. Patient bolus and isodose distributions will be calculated using direct input of the patient CT data. This mode of treatment planning is discussed in greater detail below.

(b) PIPLAN--Three-dimensional treatment planning

code

(i) Background. A major objective of this project is to demonstrate the practicality of predicting accurate dose distributions for pion beams and to devise treatment plans that will guide the therapist toward maximum understanding of the inherent benefits of pion therapy. From the beginning it was recognized that full three-dimensional (3-D) treatment planning would be needed.

3-D treatment planning is desirable for all radiation modalities, but it is a necessity for pions. Pions have the definite range characteristics of heavy charged particles, but they scatter more. A broad distribution of long- and short-range charged secondaries are produced from in-flight interactions and nuclear disintegration after capture (stars). Stars also produce long- and short-range neutrons. Background components of muons and electrons are present in pion beams. Pion decays produce muons; muon decays produce energetic electrons. Magnetically focused beams generally have a nonanalytic description. Accounting for these and many other physical processes, coupled with clinical observations, appliances, dosimetry, and patient CT data, resulted in the system of programs known collectively as PIPLAN.

When patient CT data became available, software was developed to incorporate it into PIPLAN. Several programs were written to run on the Biomed computer to test decoding schemes and develop calculational and display algorithms. PIPLAN initially was running only on the remote Central Computing Facility (CCF) computers and required new Biomed codes and a well-developed file transfer system to utilize CT data. It soon became evident that the local CT development codes could be more rapidly modified to be useful in planning for patients who were already being treated with pions. This has evolved into a comprehensive method of two-dimensional (2-D) treatment planning.

This method treats 3-D treatment volumes as a succession of adjacent 2-D slices. The system of 2-D programs is capable of accepting seven different formats of CT data, designing bolus, and displaying CT-modified water-dose distributions on life-size CT images. It should be emphasized that this was a significant effort by both the UNM and Los Alamos staff, which resulted in temporary redirection of considerable resources away from direct 3-D development.

Concurrent with this undertaking, a smaller version of PIPLAN, without the calculation module, was installed at Biomed. A file maintenance and transfer system was completed, and PIPLAN at CCF was modified to use CT data. As attention was refocused on achieving more accurate 3-D calculations, several new and unforeseen requirements emerged and were resolved: smoothing of beam-input data, increased statistical accuracy with reduced computer time, fast algorithms for long-range secondaries, a history-dependent multiple-scattering model, inclusion of secondary and tertiary decay products, and increased resolution.

Meanwhile, clinical methods and requirements were changing. Target volumes were expanding, more ports per patient were being used, appliance designs were modified, and new CT capabilities were made available with the installation of the EMI-7070 CT scanner at Biomed. Generally, these required changes in both the 2-D and 3-D codes, but certainly more effort was required to automatically duplicate in PIPLAN the clinical procedures used in the 2-D methods and to keep the total calculation times within reasonable limits.

A notable new feature was the capability of entering target volumes directly on the scanner diagnostic consoles. The increased accuracy and resolution and streamlined procedures were of value both to the 3-D and the 2-D methods. Incorporation of this capability was therefore given a relatively high priority and recently completed

1) Relative aspects of 2-D and 3-D treatment planning. Two-dimensional treatment planning is clinically acceptable in geometries in which the assumptions of parallel beams and negligible inhomogeneity gradients are approximately valid. This has been verified with in vivo dosimetry, PIPLAN, and specialized calculations for static beams which are nearly parallel (50 mrad angular standard-deviation). In particular, in vivo dosimetry has verified 2-D predictions to generally better than 10 percent. This is consistent with PIPLAN calculations which show that the dose in a given CT slice changes by 5-7 percent depending on whether or not adjacent inhomogeneities are included for whole-brain treatment.

For more complicated geometries and other beam designs (fan and spot tunes), the approximations in the 2-D method are not valid. This is easy to appreciate if one considers the half-thickness of a CT-slice (0.45 cm), beam divergence (50 mrad angular standard deviation in each plane), pion multiple scattering (1.5 cm projected standard deviation at depth), the number of 0.1 cm CT pixels which can be averaged radially without significantly affecting CT line-integrals (4 to 5 pixels), and a nominal penetration in the patient (10 cm). The probability of a pion coming to rest within 0.45 cm of the transverse point of entry into the patient is then only about 2.4 percent for static beams. For fan beams, the probability is only about 1 percent. Thus it is essential to have a full 3-D calculation to combine the effects of inhomogeneities, the beam phase-space, and the physics of pions.

2) External appliances. External clinical appliances are modeled in distinctly different ways in 2-D and 3-D calculations. In 2-D models, the effects of external devices are parameterized for a variety of geometries and then used with phantom measurements and calculations. In 3-D, external appliances are simply treated as large inhomogeneities,

but with added consideration of the non-tissue-like secondaries produced in them. The 3-D method offers the advantage of being everywhere equally reliable, independent of geometry. The 2-D method is reliable only to the extent of the quality of parameterization.

3) Effective dose. To the extent that the dose components and their associated RBE's are known, both the 2-D and the 3-D methods can predict effective dose from total dose. 2-D methods use biological and clinical data and dosimetry measurements with various detectors to arrive at parameters and factors that relate total dose to clinical results. The primary parameter in this approach is linear energy transfer (LET). Three-dimensional methods rely on the same input, but can determine the dose components in more detail, with greater resolution, and in new geometries. They also offer the opportunity to define effective dose on an LET continuum, rather than within discrete LET ranges.

(ii) Two-dimensional treatment planning development

1) CT scanner. Following the installation of the EMI scanner, three different EMI software releases were incorporated into the treatment planning programs. Each release affected six programs used exclusively for 2-D planning and one program for merging single CT slices into a 3-D volume in the PIPLAN casefile. Principal changes among these releases pertained to the number of bits used for each pixel value, the ability to recover CT data from overlaid images, the methods of discriminating among regions of interest (ROI) overlays, and extraneous overlay data.

In addition to adapting Biomed software to new EMI software releases, the capabilities available with these releases were evaluated in terms of contractual commitments, Biomed requirements, and documentation.

2) Regions of interest. The CT scanner consoles and software provide for up to six regions of interest (ROI's) to be overlaid on a CT image. Four new programs were completed to incorporate ROI's directly into both the 2-D and 3-D treatment planning programs. The advantages and methods of using ROI's for treatment planning are discussed in detail under 3-D treatment planning development.

3) Dual computer system. Production 2-D treatment planning is done almost exclusively on the Biomed PDP-11/45 computer, while channel control and patient treatments are done exclusively with the PDP-11/70. Because Biomed has two computers operating with the same DEC operating system (RSX-11D), and because the accelerator schedule required a concentrated patient accession rate, it was considered essential to duplicate the treatment-planning capability on both computers. This provides a back-up production capability and an optional load-leveling between machines prior to the beginning of treatment when treatment-planning demands are high and channel demands are low.

This capability was achieved and has been exercised regularly, both for planning production and development. The main efforts were to make the software independent of different peripheral devices on different machines. Additionally, transfer directories, explicit

documentation of releases and versions, and semi-automatic file transfer of latest releases and versions were implemented.

4) Dual digitizing pens. A second sonic-digitizer was implemented. This digitizer and an associated terminal are interfaced to either the PDP-11/45 or the PDP-11/70 by a switch. The interface specifications are different on the different computers and the digitizing-pen software and dependent programs were modified to automatically determine which machine is being used and to obtain pen-data through the appropriate interface.

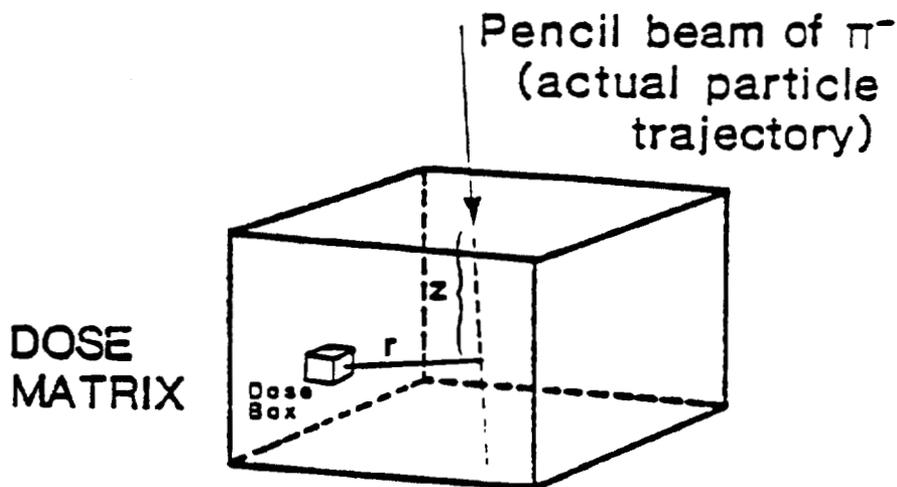
(iii) Three-dimensional treatment planning development

1) Three-dimensional methods. PIPLAN calculates a dose distribution by summing the contributions of individual pencil beams as they pass through various parts of the anatomy (determined by CT scans) and clinical appliances. The dose distribution for a pencil beam is predetermined analytically in water as the sum of its separate components, including the effects of in-flight interactions and straggling. This dose is distributed in depth as a function of water-equivalent range along the trajectory, and radially as a function of multiple Coulomb scattering (which is both geometry and energy dependent). Distributing this dose entails accumulating at each point of interest the relative amount of dose at that point from each pencil beam. This procedure is represented in Figure 32.

Because the treatment beams contain spatially nonuniform ratios of pions, muons, and electrons, and because each particle type has a distinctly different dose distribution, separate calculations are required for each particle type. To model an actual beam, then, requires an accurate phase-space representation of pencil beams. PIPLAN uses individually measured trajectories for each beam tune, with the spatial coordinates, angles, momentum, and particle type identified. Figure 33 shows a comparison of a PIPLAN calculation and measurement using this procedure

The statistical accuracy of this method is determined by the particle fluence in the calculation and the radial range of effect of each pencil beam, as obtained from multiple scattering, and is given by $(4\pi\sigma^2\phi)^{-3}$, where σ is the standard deviation radially and ϕ is the particle fluence. Near the entrance region where σ is small, ϕ must be large and the calculation is limited by computer resources. Three solutions have been implemented, and collectively have reduced the time required for a calculation statistically accurate to 3 percent by a factor of 15. The first was to simply use an arbitrary minimum σ in the entrance region to effectively smooth the transverse dose distributions. Another was to select a subset of the measured trajectories that have essentially no statistical uncertainty in the fluence distribution but still maintain the complex phase-space correlations of a real beam tune. (See 2, Smoothing). Another method of reducing calculation time was through code optimization, taking advantage of different physical interactions responsible for dose (see 3, Neutrons)

2) Smoothing. A complicated problem in pion treatment planning is the representation of the input beams of pions, muons, and electrons. One solution is to use measured particle trajectories and momenta to represent the characteristics of the pencil beams that deliver



$$D_{\pi}(z) = N_{\pi}(z) \left(\frac{dE}{dz} \right)_{\pi}, \quad D_{\mu}, D_e \text{ ionizing collisions}$$

$$D_S(z) = \left| \frac{dN_{\pi}(z)}{dz} \right| \left\{ E_{\text{local}} + E_{\text{long range}} \right\} \text{ star charged products}$$

$$D_T(z,r) = (D_{\pi, \mu, e} + D_S) D_{ms}(z,r) + D_{\text{neutron}}$$

$$D_{ms}(z,r) = \frac{1}{2\pi\sigma_{ms}^2(z)} e^{-r^2/2\sigma_{ms}^2(z)}$$

Figure 32. PIPLAN ray-tracing model

TUNE 16C (MINIMUM RANGE - SHIFTER THICKNESS)

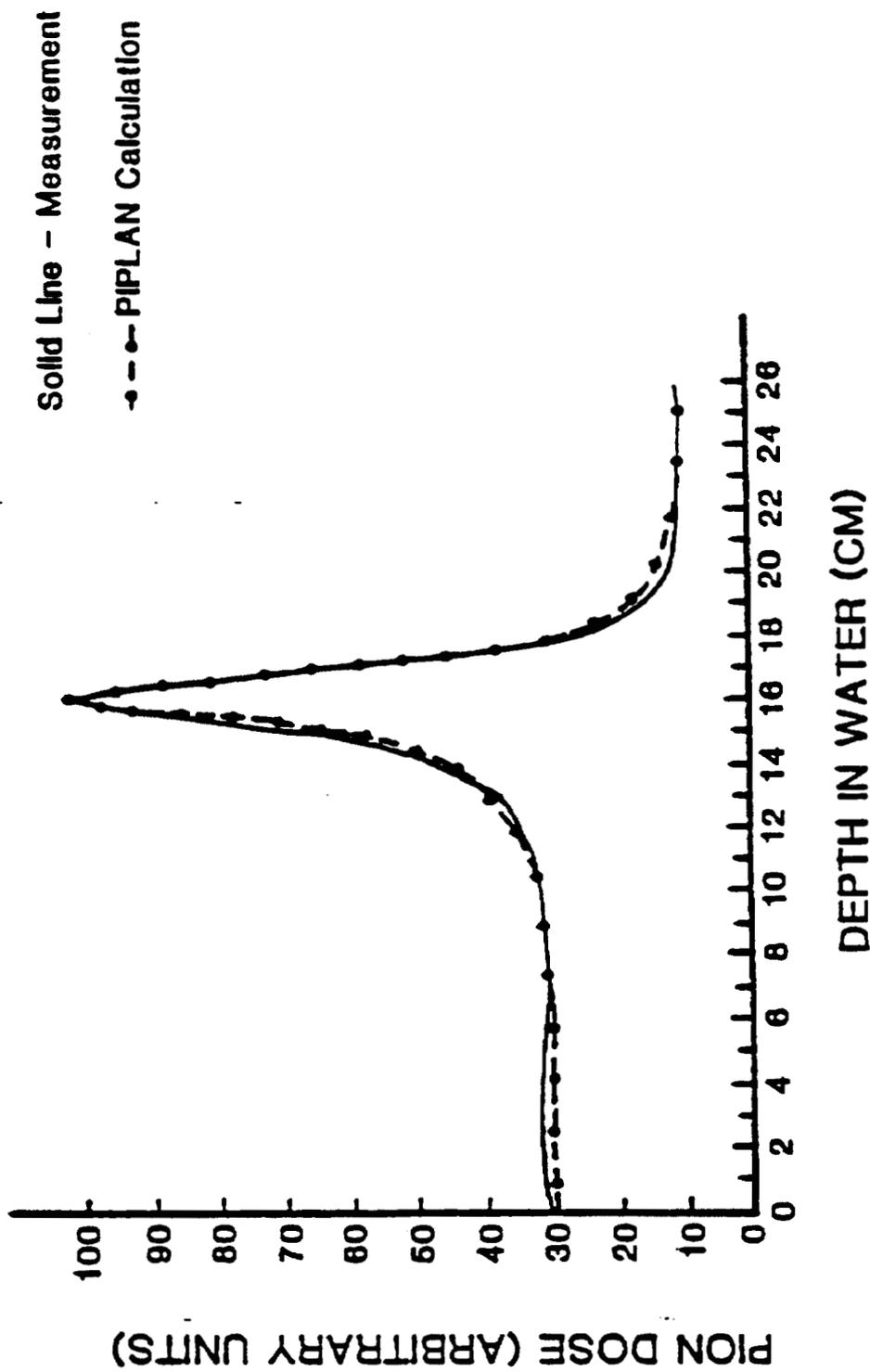


Figure 33. Comparison of measured depth dose of Tune 16C with PIPLAN calculation

dose in PIPLAN. Each pencil beam contains an analytic description of the dose deposited by a small bundle of monoenergetic particles. There is no statistical uncertainty in the dose deposited by a single pencil beam. However, there is statistical uncertainty in the distribution of pencil beams coming from the particle measuring process. The principal effect is unacceptable variation in the isodose contours in the plane (x-y) perpendicular to the beam.

However, it is still desirable to utilize the measured trajectories as the source of the PIPLAN pencil beams. In the five-dimensional space there are important correlations for each particle: x with its angle ϕ , y with its angle θ , x with momentum δ , and ϕ with δ . Rather than approximate these complex distributions, we have reduced the fluctuations in particle fluence by a smoothing process. For each tune, a two-dimensional dose measurement is made in the x-y plane for the uncollimated beam in air. Particles are then selected from the measured tune tape which reproduce the air dose distribution. The procedure works by filling dose bins and rejecting particles that cause the measured air dose to be exceeded. When this same subset of particles, typically 25,000, is run in PIPLAN, the measured air dose is reproduced, as shown in Figure 34. Thus, the air dose measurement becomes the primary beam information in the x-y plane. Multiwire counter efficiency defects and other biases are eliminated from this subset of the chamber data.

Some statistical fluctuations occur in the separate distributions of π , μ , and e . As the different particle dose depositions change with depth, statistical effects reappear. It may be possible to measure with high statistical accuracy the distributions of pions in air with a solid-state detector. Smoothing to the total air dose and to the pion flux distribution simultaneously could improve the situation. Also, the angles in the beam disturb the smooth dose properties at depths other than the one at which the smooth particle subset was obtained. However, a very large gain in contour smoothness has been observed at all depths using the prepared particle subset. Several different smoothing procedures have been used, and work is in progress.

3) Neutrons. An improved neutron model was developed and installed in PIPLAN which accumulates neutron dose due to in-flight interactions in the plateau as well as in the peak region. In addition, the model achieves significant reductions in computing times.

For a given pencil beam of pions, the range of secondary star neutrons is sufficiently large so that a great deal of computer time is required to distribute this dose component. Although the contribution may be small at a given point from the star, each point will accumulate a significant dose from many stars.

The neutron dose distribution from star neutrons was decomposed into short- and long-range components. The short-range distribution is modeled as a Gaussian with $\sigma = 1.4$ cm, which is about the same as that from multiple scattering, and is included with other short-range pion dose components. The long-range neutron dose falls off approximately as the cube of the radius (i.e., less fast than a Gaussian) and has a $1/e$ value at about four times the distance of the short-range neutron dose.

MEASURED AND CALCULATED AIR SCAN - TUNE 16C

Moseley, Robert D., Jr., M.D.

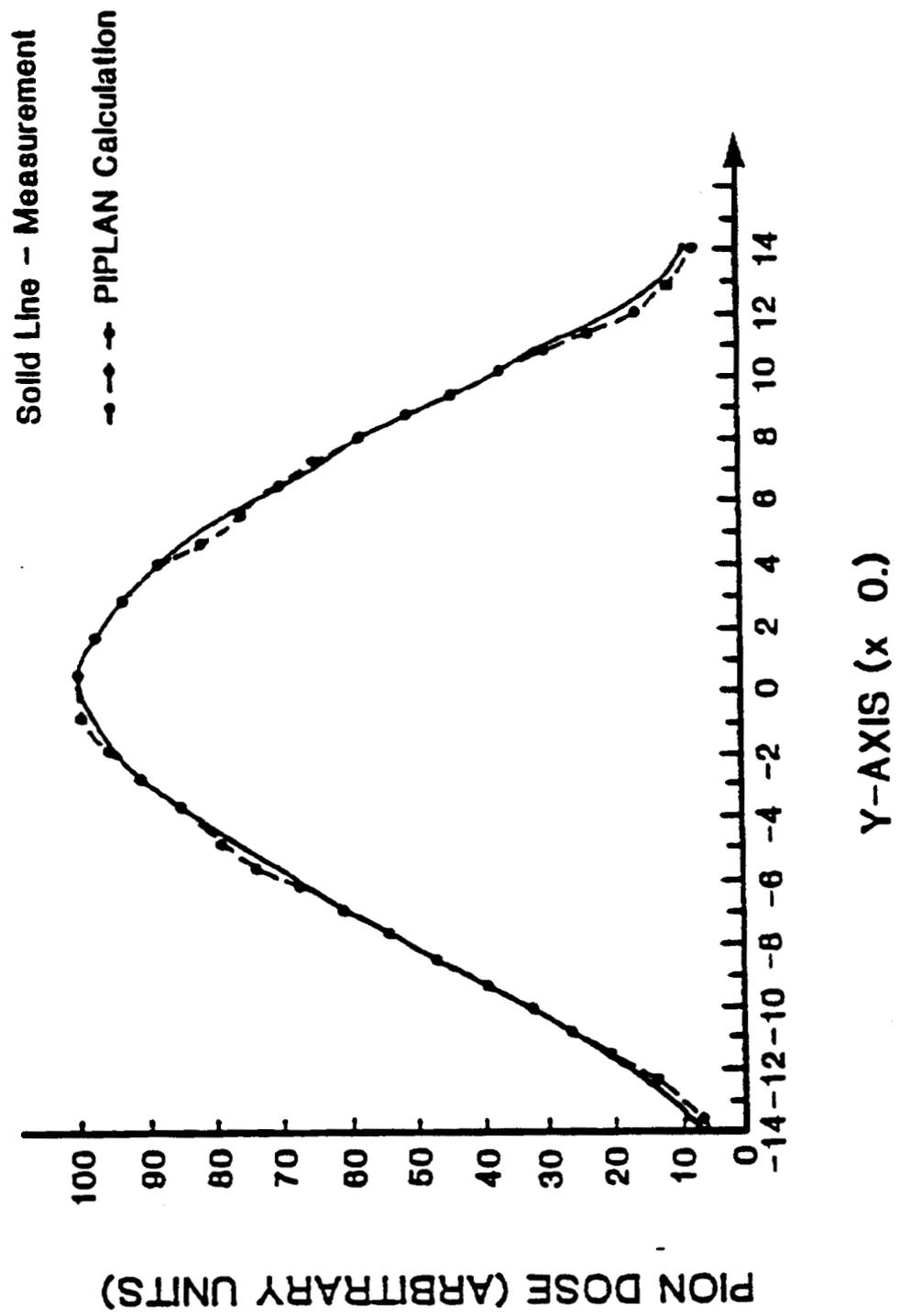


Figure 34. Comparison between measured air scan and PIPLAN calculation using smoothed beam tape (Tune 16C)
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Therefore, to achieve the same statistical accuracy for long-range neutrons as for all the short-range components, only 1/16 of the total neutron fluence is needed for this component. In the calculations, then, long-range neutron dose is accumulated for only 1 out of 15 pion pencil beams, and this dose is multiplied by 15 to keep the total dose correct. For the other 14 pion pencil beams, dose accumulation occurs only at a relatively small number of points in the immediate vicinity of the measured trajectory.

4) Multiple scattering. Most models of charged-particle multiple-scattering relate beam spreading only to residual range or energy and neglect geometrical propagation distances as physical density varies. A new, independent multiple-scattering model was developed and installed to more accurately predict beam spreading through tissue inhomogeneities and air gaps between the range-shifter, collimator, and bolus. This model also resolves the difference between actual range and projected range. Figure 35 compares calculated beam width with experiment.

5) Range modulation. The nearly monoenergetic pion beams used for clinical treatment result in a peak dose spread only about 3 cm in depth, FWHM. This is too small for most treatments. A mechanical device is placed in the beam that varies the amount of degrader the beam must pass through before entering the patient, which yields a spread-out stopping distribution in depth. PIPLAN then must obtain a high-confidence result throughout the spread peak region with fewer stopping pions per unit volume or increase the number of rays to be calculated. For example, if 25,000 rays produce an acceptable answer for an unmodulated beam, about 75,000 rays and three times as much calculation time are required for a 10-cm spread peak.

If one neglects multiple scattering, the pencil beam library dose distribution can be folded with the range-modulation function to yield a composite library depth-dose distribution. This library can then be used to describe the distribution for each ray as if it experienced the full range-modulation function. The number of rays required for a given statistical accuracy is then independent of the modulation function.

However, multiple scattering is a serious problem in modeling pions, especially in clinical situations where inhomogeneities, appliances, and large air gaps between appliances are common. The problem is compounded when using folded library distributions, since the multiple scattering at a given depth in the patient is, to first order, given by the sum of Gaussian radial distributions, where the addends are weighted by the range-modulation function. The resultant pencil beam width due to multiple scattering is no longer conveniently analytic, and the time required to individually keep track of each Gaussian at each point in depth for each ray and directly calculate the width at that point essentially offsets the time gained by folding (even if computer memory was not a limitation).

It has been found, for several typical range modulation functions, beam momenta, and clinical geometries, that the radial spread of a pencil beam at various depths in a phantom can be reasonably approximated (to within about 3 percent in relative probability amplitude) with either a Gaussian or an exponential function. Since normalization is required, only one variable is then required to describe the composite

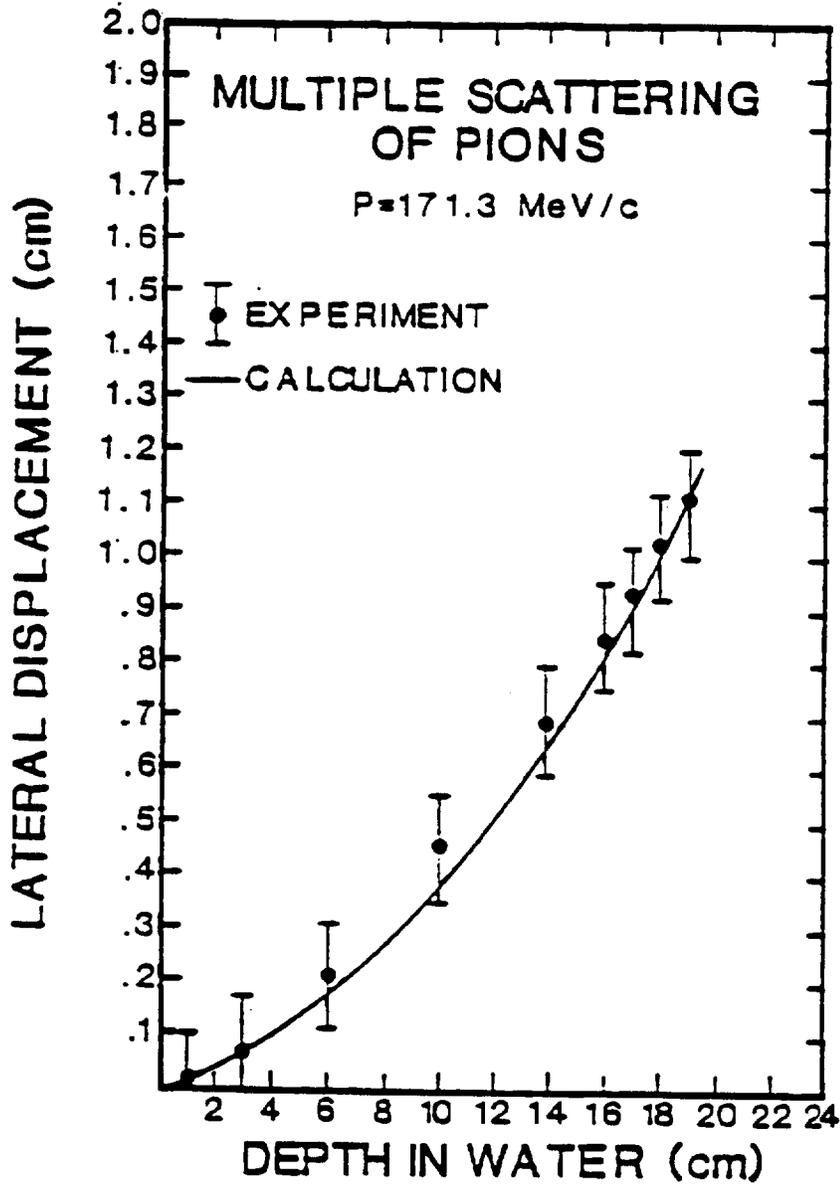


Figure 35. Comparison of experiment with PIPLAN history-dependent multiple scattering model

radial distribution at each depth for a given modulation-function, beam momentum, and geometry. Since modulation functions are designed for each momentum and since the geometry for a given momentum is dominated by a collimator thickness and opening (air gaps), a one-dimensional table of distribution parameters can be precalculated and saved for each modulation function.

The net effect of the procedure is to maintain a constant statistical uncertainty and calculation time for all modulation functions and spread-peak widths. However, the precision of the final dose distribution is less near the edges of a treatment field. This loss of precision is due to the approximation involved, which is predictable and acceptable, and because of second-order effects from inhomogeneities and small changes in geometry across the treatment field, which are not predictable but are probably acceptable, and which need further study. Figures 36 and 37 show comparisons between PIPLAN calculations and measurements for two range-shifter functions.

6) External appliances. Typically, all primary and some secondary muons pass through the clinical collimators while pions stop near the distal surface and are captured by high-Z elements. More neutrons are produced from these captures than captures in tissue, but with a different energy spectrum. The collimator and neutron-dose models were upgraded to account for these effects with several adjustable parameters. Additionally, the relatively large air gaps between the collimator and bolus are taken into account with neutron propagation without attenuation.

The collimator is automatically designed in the same manner as the manual, 2-D method, including adjustable margins and thicknesses. Cerrobend stopping powers are automatically adjusted to yield the desired effective-thickness from the finite number of collimator cells in the PIPLAN density-matrix. Life-size collimator templates, with calculated areas of interest, are produced on hardcopy output for collimator fabrication.

Depending on the channel tune, up to one-third of the particles in the beam can enter the body of the range-shifter through the top cover or through the bellows. The pion component will stop, giving long-range neutrons that contribute dose in the treatment field. The muon component will either be degraded in energy or will stop in the range-shifter, producing long-range electron dose in either case. These components are difficult to calculate, considering the complex geometry of the range-shifter. The patient collimator does not limit these dose components, as they fall well outside its diameter.

The objective was to provide additional internal shielding for the range-shifter that would minimize patient dose resulting from the particles stopping in it. It was found that a metal ring at the top of the range-shifter reduces the dose under it to nearly zero. A brass ring was installed near the top of the bellows. It serves to stop the pions or at least to stop pions higher inside the range-shifter. The on-axis plateau dose is reduced by only about 3 percent; the main change is in the extreme off-axis regions. PIPLAN now models the range-shifter with upper and lower apertures which act as ideal collimators.

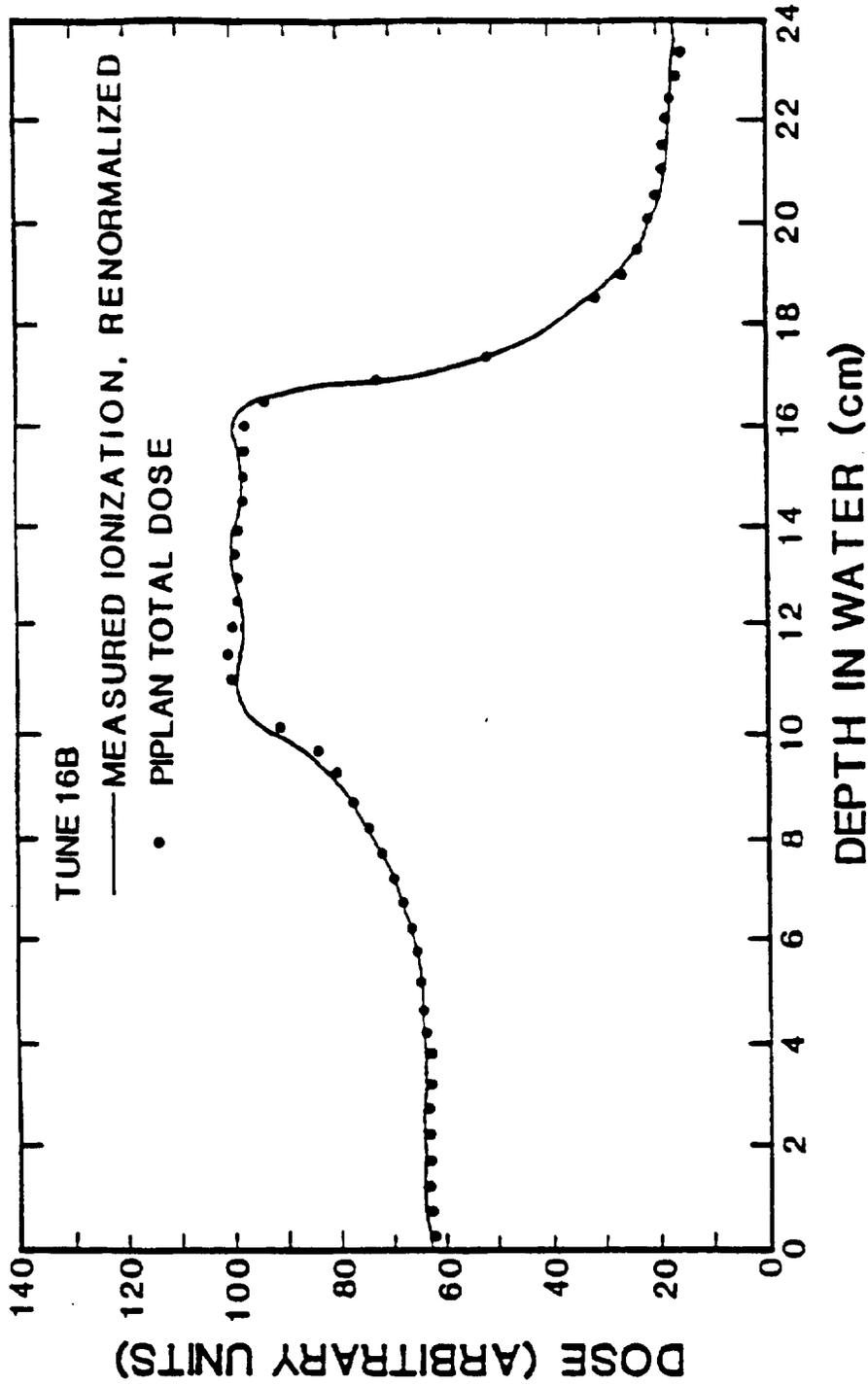


Figure 36. Comparison of measured depth dose of modulated Tune 16B with PIPLAN calculation

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TUNE 12B (RANGE - SHIFTER RS08G12B)

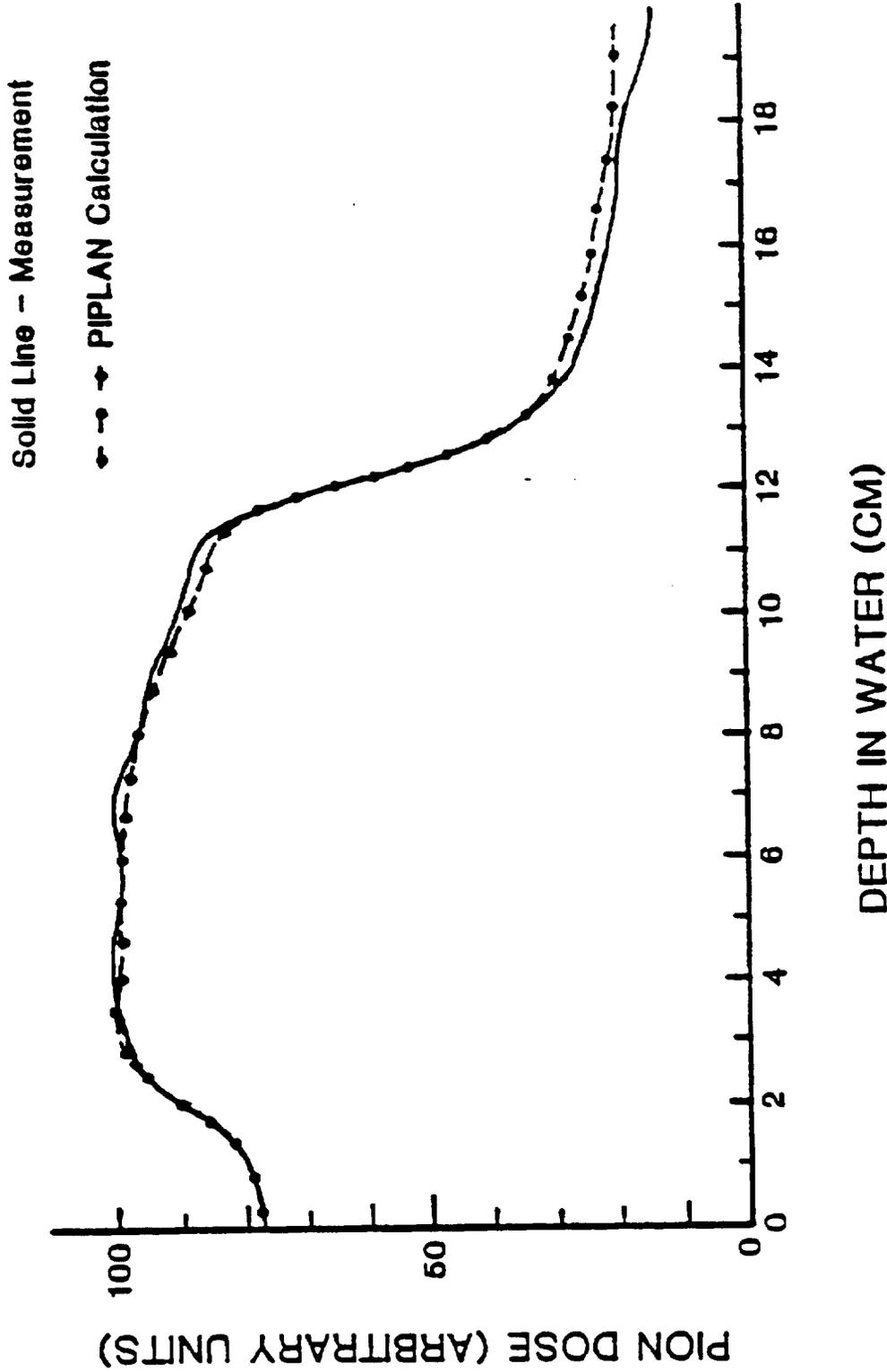


Figure 37. Comparison of measured depth dose of modulated Tune 12B with PIPLAN calculation

Bolus is designed with a parallel beam assumption using CT data and six different modes of alignment of modulated beam with the target volume. All clinical methods used in 2-D bolus design have been implemented, except with much better resolution. Life-size bolus templates are produced on hardcopy output for bolus fabrication.

7) Increased resolution. A significant advance was made which improved the spatial resolution from about 5 to 10 mm on a cubic edge to a 2 mm resolution that is now typically possible. This was accomplished by utilizing the "Large-Core-Memory" (LCM) of the CDC-7600, where all PIPLAN calculations are done. Expansion of the code into LCM resulted in a somewhat longer calculation time, up to about 25 percent, but which was considered to be a necessary step for the spatial resolutions required. A net decrease in calculation time was achieved when the new range-modulation model, described elsewhere, was installed.

8) VAX. A new version of PIPLAN corresponding to that on the Biomed PDP-11/45 was installed on the LAMPF VAX computer. The calculational section of the CCF version was added to the VAX code, and a benchmark calculation for a pencil beam completed. Practical calculation times and reduced costs were demonstrated.

9) Contour processing. PIPLAN does all its calculations in three dimensions. Contours, however, are entered on a series of parallel planes. Volumes are then effectively created by connecting the vertices of a contour on one plane with the corresponding-contour vertices on an adjacent plane. Critical to this procedure is that both contours have the same right/left orientation, the same relative starting point, and essentially uniform spacing of vertices around the contours. These characteristics are automatically satisfied for regions of interest (ROI's) transcribed from CT data tapes. Note that contrary to other surface generating methods, it is not required that the number of vertices be the same from plane to plane.

For manually entered contours, such as with the digitizing pen, these requirements are not obvious to the user. Right/left orientation is automatically reversed if necessary. The relative starting points are monitored and the user alerted if substantial deviations occur. A new feature of PIPLAN is the automatic smoothing of contours to achieve smooth three-dimensional surfaces. A window is placed around each contour point as it is entered. Points too close together are rejected, and points are automatically embedded when input points are too far apart. A major use of this capability has been to change the number of points for a contour after they have been entered to maximize resolution without exceeding memory limitations. Ultimately, memory limitations do affect contour resolution, since about 20 to 30 planes of contours must be accommodated in 6000 computer words.

Another major feature was completed whereby intersecting contours on a given plane are resolved and automatically edited to remove ambiguous areas or densities. Since ambiguities are removed from each plane, volumes are, in principle, also without ambiguities. This principle is violated only for nearly touching surfaces with too few defining vertices.

10) Integrated CT radiography. A new computer code was written to reconstruct the same kind of image as digital x-ray radiography from integrated CT images. ROI's on the individual CT images are superimposed on the "integrated CT radiography" (ICTR) images, but without the distortion that normally results from a point x-ray source. The processing is done on the Biomed computers, with an EMI CT tape as input. A new tape in EMI format is generated with reconstructed images for input to the CT scanner, where all the diagnostic imaging capabilities already exist.

In pion treatment planning, the target volume is given on the CT image and is used for designing bolus and collimators and for beam-tune selection. When planning is completed, x-ray simulation is used for confirmation. At this stage, ICTR with target volume ROI's will play an important role in verifying the anatomical structure and target volume.

11) Decoding CT scanner regions of interest. The automatic methods and algorithms have been developed and implemented to transcribe CT-scanner ROI's to vector contours in treatment-planning programs. Physicians enter ROI's for target volumes and critical sites directly on CT images using a track-ball. Such ROI's have the resolution of the image, and the CT data can be displayed with optimum diagnostic contrast settings. With automatic surface detection and direct use of CT data for inhomogeneities, only the prescription ROI is required, but with provision for four other critical-site ROI's per CT slice if desired.

Advantages to the physician include using the same equipment used for diagnosis, prescribing treatment on diagnostic-quality images, and the ability to prescribe concurrently with diagnosis. The advantages for treatment planning are automatic entry of contours, high accuracy transcription of prescriptions, less duplicated hardware, and greater use of existing programs.

ROI's are obtained by searching the ROI overlay bit-map, which is part of the CT image file, for the most exterior, contiguous pixels. The resulting pixels define one ROI. For single ROI images, the locations of the ROI pixels are converted to x, y coordinates to define vector contours. Vector contours generally do not need the very high resolution obtained from contiguous-pixel ROI's. A vertex-reducing algorithm eliminates points that are too close together. For multiple-ROI images, the successive ROI's are obtained by subtracting the previous ROI from the current overlay bit-map and reapplying the exterior searching algorithm. Small leftover ROI's resulting from double-backs or shaky-hand input are neglected. Figure 38 shows a PIPLAN plot of contours obtained from decoding CT ROI's with 8 mm minimum spacing between vertices.

12) Surface detection from CT. If the patient surface, which is required for treatment planning, is not entered as an ROI on the CT scanner, it can be detected automatically from the CT image at the same time that the image data and other ROI's are being transferred from the CT tape to the patient casefile. With the use of CT data directly in treatment planning, only the surface and target volume contours are required. By detecting the patient surface automatically, the required input and the preparation time are reduced by more than a factor of two. Accuracy is also increased.

C

PIPLAN-11.0 CASE [REDACTED] 13-APR-81 18:15:02

SHEET- 13
5080/6000 USED; BIG SHEET=11 WITH 254; EXPECT 5594
DISPLACE- 0 0 (CURSOR)
ROTATE- 0 0 (PHI, THETA, PSI) DEG FRONT
SCALE- -4
ORIGIN OF SHEET

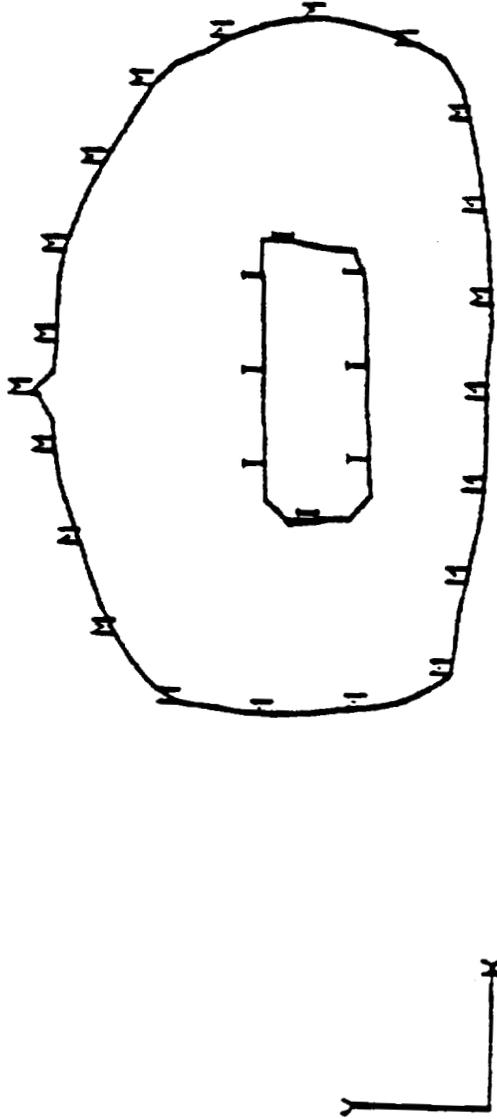


Figure 38. PIPLAN anatomy contour derived from CT regions of interest

Figure 19 is an example of a surface contour obtained from CT data. After averaging and smoothing the image data, a threshold is applied reducing the image to one of lands, lakes, and islands. Using an algorithm similar to that for ROI decoding, shores are established. The merit of the procedure is that inland lakes and islands are neglected. The largest shore perimeter is then used as the surface ROI. The procedure to reduce the number of points in the ROI when transcribing to vector contours is the same as for physician-defined ROI's.

12) Dose distributions on CT console.

A new display capability was developed which superimposes pion dose distributions on patient CT data on the CRT of the EMI 7070 scanner. The advantage of this display method is to be able to present the results of treatment planning to the radiotherapist in a most graphic way and take full advantage of the scanner graphics software.

The data are transferred by magnetic tape to the scanner from the PDP-11/(45, 70) computer used for treatment planning. Duplicating the complex EMI tape format is accomplished by simply replacing the image and ROI data in a copy of any EMI output tape. The limitation of this method is that only preconceived and saved images are available to the physician at the CT console.

14) Supporting libraries. Two sup-

porting libraries were completed: a beam-tune library and a range-shifter-function library. These allow a single parameter to select each of these input files for a given calculation. Supporting maintenance programs were also completed for the beam-tune library, to readily add new tunes and to update tune parameters in header records. The range-shifter library is essentially a collection of the Biomed files used for range-shifter control and is created and maintained with standard text-editors on the various computer systems.

15) Secondary electron dose. A new

model was installed in PIPLAN to account for the dose deposited by electrons from muon decay in the patient. About 15 percent of the input beam particles are primary muons originating from the channel target, and about 20 percent of the input particles are secondary muons from pion decays in the last half of the channel. An average of about 35 MeV is deposited by such electrons, with an average range of about 20 cm. The dose model is obtained by folding the decay-electron energy distribution with depth-dose curves for mono-energetic, parallel electron beams and a geometrical factor for an isotropic, point source. The long-range nature of this dose component allows an accumulation method similar to that for neutrons from pion stars with good calculational efficiency.

16) Secondary muon dose. A new model

was installed in PIPLAN to account for the dose deposited by muons from pion decay both in the beam channel and in the patient. About 20 percent of the input beam particles are secondary decay muons, but not all of them can be identified since they may have the same time-of-flight as primary pions. Thus, in addition to secondary muons defined in the beam-input file, a percentage of incident pions are treated as secondary muons. Each secondary muon is assigned a normalized stopping distribution which represents the distribution

one would obtain if all such muons could be individually identified. The dose distribution from this stopping distribution is then used for each incident secondary muon. For the approximately 3 percent of the pions which decay in the patient, the muon stopping distribution and the surviving-pion distributions are appropriately modified.

17) Casefile upgrade. At Biomed, all treatment-planning data for a given patient are collected into a single "casefile." Different types of data are assigned to different subfiles within the casefile. PIPLAN at Biomed has full editing capabilities for data in the casefile, i.e., fetch, purge, file-update, memory-update, and preserve. The casefile is exported at Biomed to magnetic tape and imported at CCF for calculations. The tape also serves as the archival medium.

At CCF, preserve and memory-update capabilities were added to the pre-existing fetch command. This was a prerequisite for archiving dose distributions and transmitting them back to Biomed for import and interactive port-weighting and graphics output. This was a difficult and time-consuming effort, given the CCF operating system and file structures.

18) CT data resolution. PIPLAN determines the effective or water-equivalent range at various depths in a patient through the conversion of CT data to pion stopping powers. Since PIPLAN does a full three-dimensional calculation, a large bulk of CT data must be available during the calculation. Rapid access requires that these data be in the computer memory, which in turn requires a certain amount of spatial averaging to keep the size within fixed limits. The fetching and averaging of these data for each port may take up to 20 percent of the total processing time. In addition, collecting and transporting the CT data from one computer to another takes a substantial amount of elapsed time.

A study was completed of three anatomical sites (brain, lung, and abdomen) which provides practical guidelines as to how the bulk of CT data can be reduced without affecting the accuracy of PIPLAN or other calculations where the main quantity of interest is a line integral through CT data. In particular, it has been concluded that line integrals to typical depths of interest are insensitive to pixel sizes 4 mm or smaller on an edge. This provides a reduction by a factor of 16 in number of CT values from the usual 1 mm by 1 mm resolution. In addition, it was determined that for integrals of this type the full resolution of diagnostic CT data was not required. The CT scanner values could be reduced to 8-bit accuracy (about 1/10th original resolution), and two such values could be packed into one computer word. This can provide an additional factor of two reduction in the transmission time for CT data.

19) CT data in pion calculations. In conjunction with including CT data in dose calculations, an empirical model was incorporated to relate the scanner x-ray data to pion stopping powers for human lung, fat, muscle, and soft and hard bone. The model is based on experimental measurements of CT numbers and pion ranges in analogs for the above tissues. To obtain dose from energy deposition and to account for multiple scattering in nonhomogeneous tissues, physical-density and radiation-length models were also included. In regions where CT data do not apply, look-up tables are used.

20) CCF system changes. During the past three years, considerable effort has been expended in keeping up with system changes initiated by the CCF. To date, these have included two major changes in the operating system and many changes in system libraries. Changes in the operating system generally required a significant reprogramming effort, especially in input/output operations. Changes in system libraries almost always caused PIPLAN to exceed memory resources and required new overlay structures and associated reprogramming. One forced but welcome reprogramming effort was related to the Common Graphics System (CGS). PIPLAN is now fully compatible with the latest CCF graphics capabilities.

21) PIPLAN status. PIPLAN is capable of performing, in one 3-D calculation, all the capabilities of the 2-D programs and the associated manual treatment-planning operations. This applies for both static and dynamic treatments and includes automatic appliance design, range-shifter function selection, patient orientation, positive pion beams, and effective dose. Extensive experimental comparisons will be made for verification, especially for dynamic treatment.

(c) CT scanner. The EMI 7070 scanner was installed in February 1980, and patient scanning began in March. During the period March 1980 to March 1981, the scanner software and hardware were updated several times. In March 1981, the machine was accepted after having passed all acceptance tests.

(5) Treatment delivery and verification

(a) Patient immobilization, alignment, and transfer systems. These systems have undergone several changes during the past three years; however, the basic approach has remained the same. The two basic concepts that we have followed are:

(i) The patient must maintain the same position, and this position must be easily reproducible during CT scanning, simulation of the treatment, set-up for treatment, and treatment; and

(ii) Patients must be set up outside the treatment room so that beam time will not be wasted.

The basic components of the immobilization system are orthopedic casting materials and vacuum bags. For treatments of the brain and the head and neck, the patient lies in, and is supported by, a cast extending to below the shoulders. The head cast is supported by polyethylene blocks that maintain a level position (the patient lies on his side for these treatments because the pion beam is vertical). The rest of the body is immobilized by a vacuum bag. A mold made from perforated aquaplast is then placed over the head and attached to the polyethylene base of the cast, thus immobilizing the patient. The perforations allow the patient to see and breathe and minimize perspiration by the patient. For treatments of the chest, trunk, and pelvis, the patient lies prone or supine on the treatment table and is immobilized and supported by vacuum bags.

New laser alignment systems have been installed in the CT scanner room, simulator room, set-up area and treatment room. These alignment systems provide for precise reproduction of patient positioning in every area. A vertical laser projects coordinate axes onto the patient surface which are oriented to tattoos. These tattoos serve as reference marks for alignment of the patient, bolus and collimator to the pion channel. Two side lasers in each patient area project horizontal lines onto the patient which enable rotational and height positioning.

During the past year the mechanism for supporting and aligning the patient bolus has been completely redesigned. The new system has more degrees of freedom allowing more flexibility in aligning the bolus to the patient and ensures greater stability in maintaining precise alignment.

New treatment tables have been installed on the two treatment modules, and an identical table has been installed in the simulator room. These new tables provide a rigid support for patients and eliminate the old fiberglass tubs that previously supported patients. This has greatly reduced the difficulty for patients in getting into and out of the treatment apparatus and provides access to the sides of patients for alignment with-side lasers.

(b) Dynamic treatment. Until recently the pion treatments were done exclusively with static multiport (parallel-opposed) techniques using large, essentially parallel, beams for the irradiation of large deep-seated tumors. While such treatments may in some cases provide dose distributions superior to those of conventional modalities, they are still less than optimum regarding the sparing of surrounding normal tissues. Two problems are inherent in shaping the dose distribution of individual portals to fit the target volume:

- (i) Beam uniformity in the plane perpendicular to the incident beam, and
- (ii) Beam shaping in a plane parallel to the incident beam.

The beam transport characteristics of the biomedical channel cause the broad beam profiles to be approximately Gaussian so that it is not possible to have a uniform incident pion flux over the transverse dimensions of the beam. This limitation normally results in a 20 percent dose variation over the target volume. Range modulation of the beam spreads the peak in the dimension parallel to the incident beam direction. This modulation must be sufficient for the dose peak to cover the target volume at its maximum thickness, thereby exposing healthy tissue at other off-axis positions where the target volume has less thickness. In particular, the static method of treatment represents an underexploitation of the beam shaping properties of pions. Figure 40 demonstrates the nature of the problem with static treatments. The central figure represents a treatment plan for the largest extent of a target volume. The pion peak is modulated to cover the target volume for this CT slice, but since one is constrained, for static treatments, to use the same range modulation throughout the target volume, when the target volume becomes smaller excess normal tissue is exposed to peak pions. Also note that within a particular CT slice that one cannot change the modulation function to account for changes in target volume dimensions.

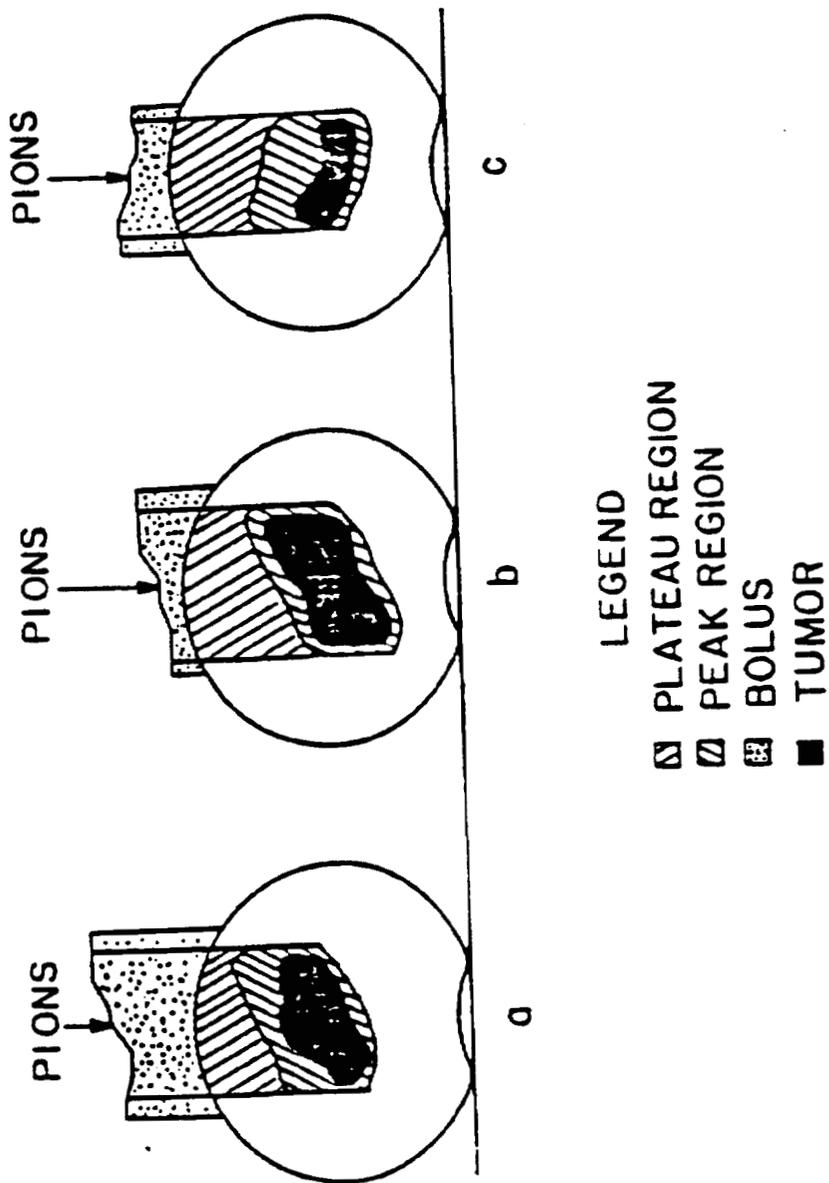


Figure 40. Excess normal tissue exposure with a static pion beam in depth

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We have developed a method for delivering pion doses to deep-seated tumors that provides more normal tissue dose sparing and better field flatness than does the simple static method, where a collimated broad beam covers the entire treatment volume. We have designated this system the "dynamic treatment mode." Implementation of this method of treatment has required the development of special beam tunes in the pion transport channel, new treatment hardware, and a special computer-microprocessor-based control system. In addition, methods of treatment planning and dosimetry have been modified to accommodate this new treatment mode.

Two modes of dynamic treatment have been proposed, one using a "fan" beam and another using a "spot" beam. The dynamic "fan" mode one-dimensionally scans the patient across a highly focused beam, which is narrow in the y-dimension and broad in the x-dimension. The ability to vary the range modulation as the patient is scanned along y allows beam shaping of the peak dose in the y-z plane, but not in the x-z plane. In addition, the ability to control the weighting of each scanning position permits the dose profile in the y scanning dimension to have improved uniformity. The dynamic "spot" mode two-dimensionally scans the patient across a beam moderately focused and narrow in both x- and y-dimensions. The ability to vary the range modulation as the patient is scanned results in complete removal of constraints on the width of the dose peak in the z-dimension at each x-y position. Also, the dose profiles in both x and y will have improved uniformity with proper weighting of the scan positions.

The dynamic "fan" treatment mode has already been implemented. The dynamic "spot" treatment mode is actually an extension of the fan mode whereby the treatment is accomplished by scanning the patient in two dimensions beneath the spot beam instead of scanning in one dimension under the fan beam.

Dynamic treatment is a system consisting of special pion beam tunes (settings of the currents in the pion transport magnets), a computer-microprocessor-controlled hardware system that includes a scanning patient treatment couch, a dynamic pion beam range-shifter, and a pion beam monitor chamber. The system and the coordinate system used are shown in Figure 41. The pion beam, incident along the z-axis, has a stopping distribution that is small in both z and y, but large in x and is approximately cylindrical in shape.

The patient is moved in steps in the y-direction (i.e., across the narrow transverse axis of the beam). As the patient is stepped across the beam, the range-shifter modulates the pion beam so that the resulting depth dose distribution conforms to the maximum thickness of the treatment volume at each step. In this way, the depth dose distribution of the beam can be made broad in regions where the tumor is very thick, but smaller where the tumor is narrow, adding beam shaping capability not possible with static treatments.

The patient is scanned across the beam in steps of 1 cm, and the amount of time spent at each step is varied, to produce a uniform dose equivalent in all portions of the target volume.

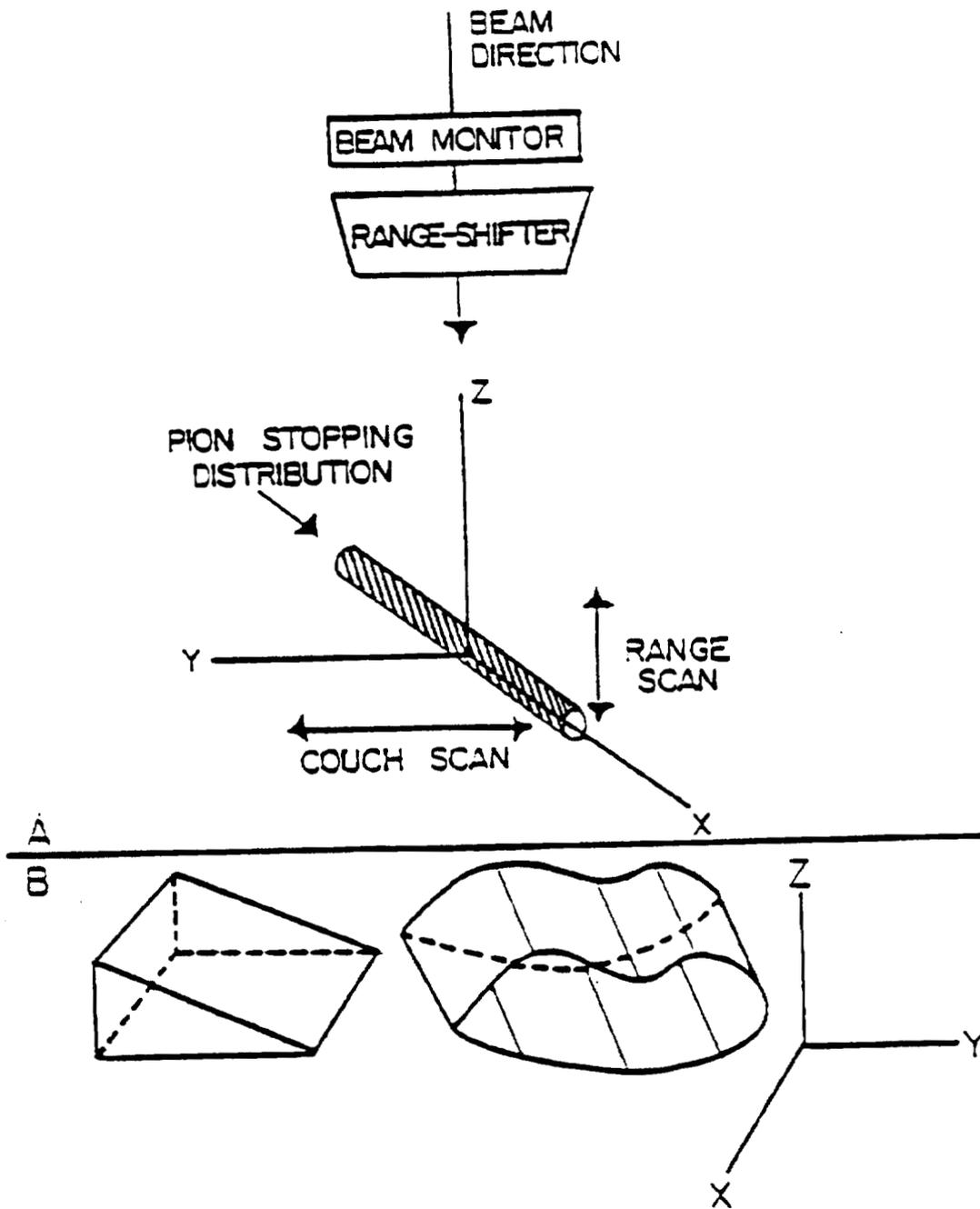


Figure 41. Normal tissue sparing in three dimensions with dynamic fan mode

The width of the pion beam in the x-dimension can be controlled by the beam transport magnets and is selected from a catalog of tunes to be no larger than necessary to completely cover the desired treatment volume. At present, x-dimensions up to 13 cm at the 85 percent dose level are possible. A collimator placed between the range-shifter and the patient shapes the beam in the x-dimension.

The y-dimension of the beam is typically about 3.5 cm FWHM, and the scanning function is selected to encompass the maximum tumor extent in the y-dimension by making the desired number of steps in the y-dimension. Collimation is not necessary in the y-dimension due to inherent sharpness of the beam. Through the use of suitable scanning functions, tumors as large as 18 cm x 75 cm x 14 cm (x, y, z) thick can be treated without having to resort to abutting fields. Figure 41 also shows some sample treatment volumes to which such a beam can be accurately shaped.

The hardware for this system (i.e., the pion beam monitor chamber, the patient treatment couch, and the dynamic range-shifter) are interfaced to a PDP 11/70 control computer through a PDP 11/03 microprocessor. A parallel plate ionization chamber 40 cm in diameter located at the channel exit records the total incident pion flux, thus serving as the pion dose monitor. Based on the output of this chamber, plus a predetermined treatment table stored in memory, the computer-microprocessor system controls and coordinates the movement of the couch and the range-shifter.

Couch motion in five dimensions (three translations and two rotations) is possible. It is achieved by means of D.C. servo motors, whose speed is dependent on a voltage signal generated by the 11/03 microprocessor. Range-shifter thickness is set by an independent controller interfaced to a hydraulically activated servo valve. The range-shifter controller, in turn, is activated by a 12-bit digital word generated by the microprocessor. Both the couch and the range-shifter are equipped with redundant sets of shaft encoders and resistor pots to enable the control computer to verify system response.

To implement a patient treatment, one must calculate the treatment file to be stored in computer memory. This consists of a series of desired range-modulation functions versus couch position, plus the amount of time (monitor chamber counts) to stay at each position. These parameters must be determined in treatment planning from the designated treatment volume and patient geometry.

These parameters are stored on a disk in the PDP 11/70 computer. Before treatment, the 11/70 transfers these data to the memory of the 11/03. Treatment is initiated by manually setting up the patient, along with a collimator and bolus on the treatment couch. The computer then moves the couch to the first step in the treatment table and initiates the first range-modulation function. The pion beam is turned on, and irradiation begins. The computer monitors the integral dose from the monitor chamber and, at the appropriate dose values, moves the couch and simultaneously alters the range-shifter functions. At the completion of treatment, the beam is automatically turned off. The 11/70 periodically reads the shaft encoders on both the couch and the range-shifter to ensure that the treatment is proceeding as planned. All commands to the couch and range-shifter, however, are issued by

the 11/03. This prevents overloading of the main computer, which is also used for numerous other purposes.

The dosimetry and treatment planning for dynamic treatments are complicated by the nature of the focused beam which has a waist, in water, at 95 cm distance from the last channel quadrupole. In practice, the center of the target volume is placed at this waist. As the Bragg peak is swept through the target volume during treatment the penetration and shape of the pion beam will vary. We have found that the penetration varies approximately 5 mm as the Bragg peak is caused to stop from 5 cm before the waist to 5 cm after the waist. Also, the peak-to-plateau ratio of the beam changes somewhat. To account for these changes, a complete file of depth dose curves, covering the maximum dimensions of the target volume, must be generated. This is accomplished by direct measurement of the isodose dose curves in the y-z plane with the beam stopping in water at 90, 95, and 100 cm, then calculating the distributions at other positions by decrement line analysis. After the y-z distributions are obtained, they are integrated in y, resulting in a depth dose distribution which would be obtained by adding the individual beams together laterally in a step-wise fashion, i.e., this process simulates the effect of scanning the beam in the y-dimension and measuring the "effective" central-axis depth-dose curve. Figure 42 shows a typical result of this procedure. The curve denoted by squares is the depth-dose curve measured by a single static beam, while the depth-dose curve denoted by circles is the result of the calculation that simulates the scanning geometry. This entire process is repeated for measurements of the high-LET component of the beam using a thin silicon detector and a Rossi type proportional counter. Figure 43 shows an example of the completed process--an integrated depth-dose curve for both the total dose and high-LET dose. Such curves are generated for the pion beam stopping at any depth on either side of the waist of the focused beam. These curves then serve as a catalog for designing range-modulation functions which spread out the region of stopping pions. For example, if the desired spread peak is 10 cm, the Bragg peak will be modulated to stop in the region 90 to 100 cm. At each step of the range-shifter the range modulation design program will use a depth-dose curve appropriate for that position. The results of this procedure are indicated in Figure 44, which shows a 9-cm range-modulated depth-dose curve that has a physical dose shaped to produce a uniform dose equivalent curve. Also shown is the high-LET dose. The dose equivalent curve is calculated from a model which calculates the RBE at each point on the curve. The model has been confirmed by biological experiments. Range-modulation functions are designed for spread peaks ranging in size from 3 to 14 cm at 1-cm intervals. Figure 45 shows a typical y-z dose distribution for a 7-cm spread peak. Such a distribution is measured or calculated for each spread peak. Finally, distributions of this type are used to calculate the total dose and dose equivalent distributions for the entire dynamic treatment. In the treatment design the appropriate y-z distribution is chosen for each step of the treatment and weights are assigned for each step which result in a uniform dose equivalent (at the 90 percent level) over the entire treatment volume. The weight of each step is adjusted for changes in RBE for peaks spread to different dimensions, taking into account the difference in both the neutron and charged particle components of the high-LET dose.

Table 31 shows the treatment table for a typical dynamic treatment. This treatment required 12 steps at 1-cm intervals. The spread peaks ranged in size from 6 to 10 cm. Also given are the dose weights for each step and the monitor units required to deliver the prescribed

CENTRAL AXIS AND INTEGRATED DEPTH DOSE CURVES

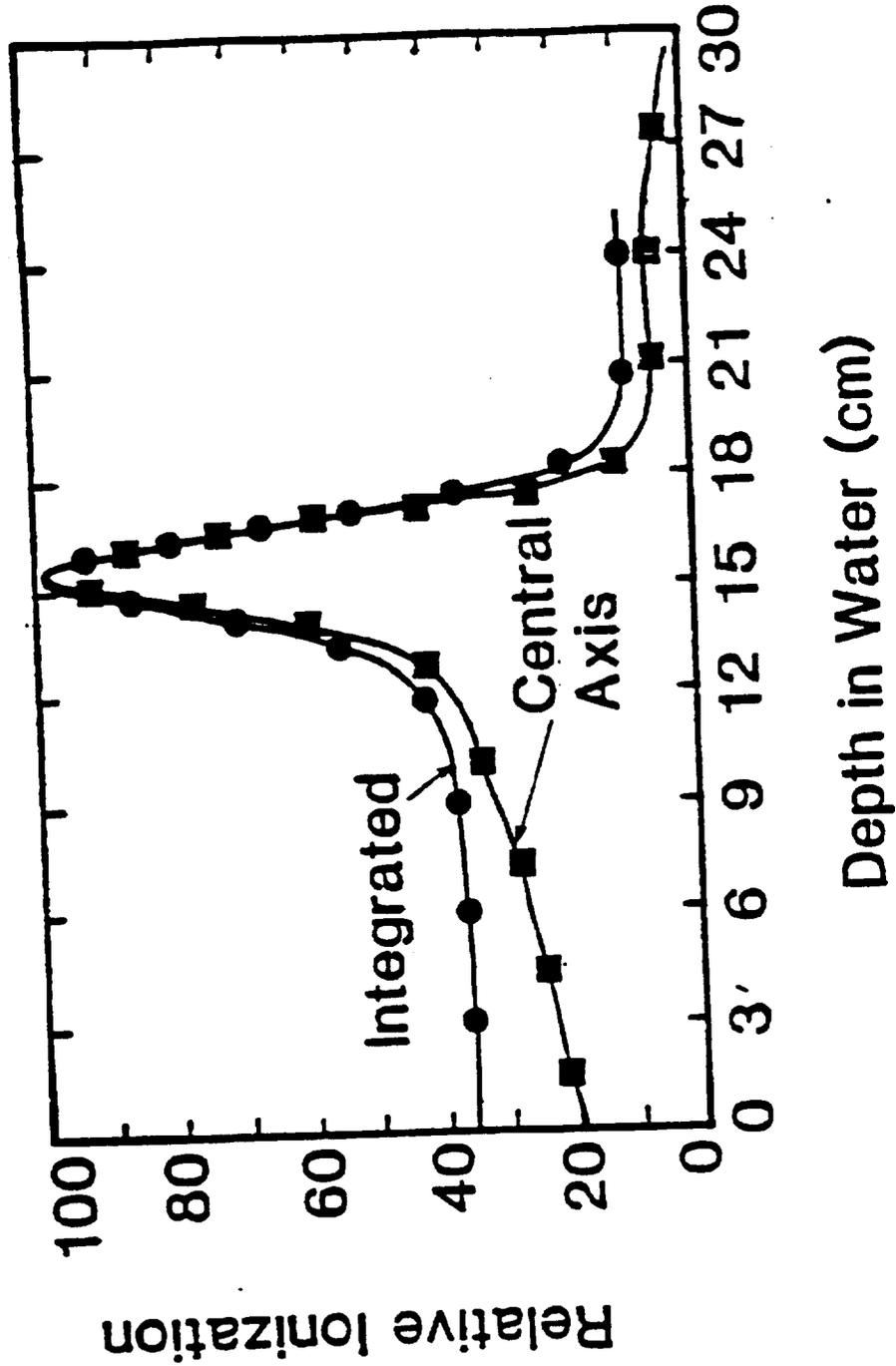


Figure 42. Central axis dose distribution from measurement and calculation for dynamic fan beam

UNRANGE-SHIFTED AVERAGE, INTEGRATED DEPTH-DOSE CURVES

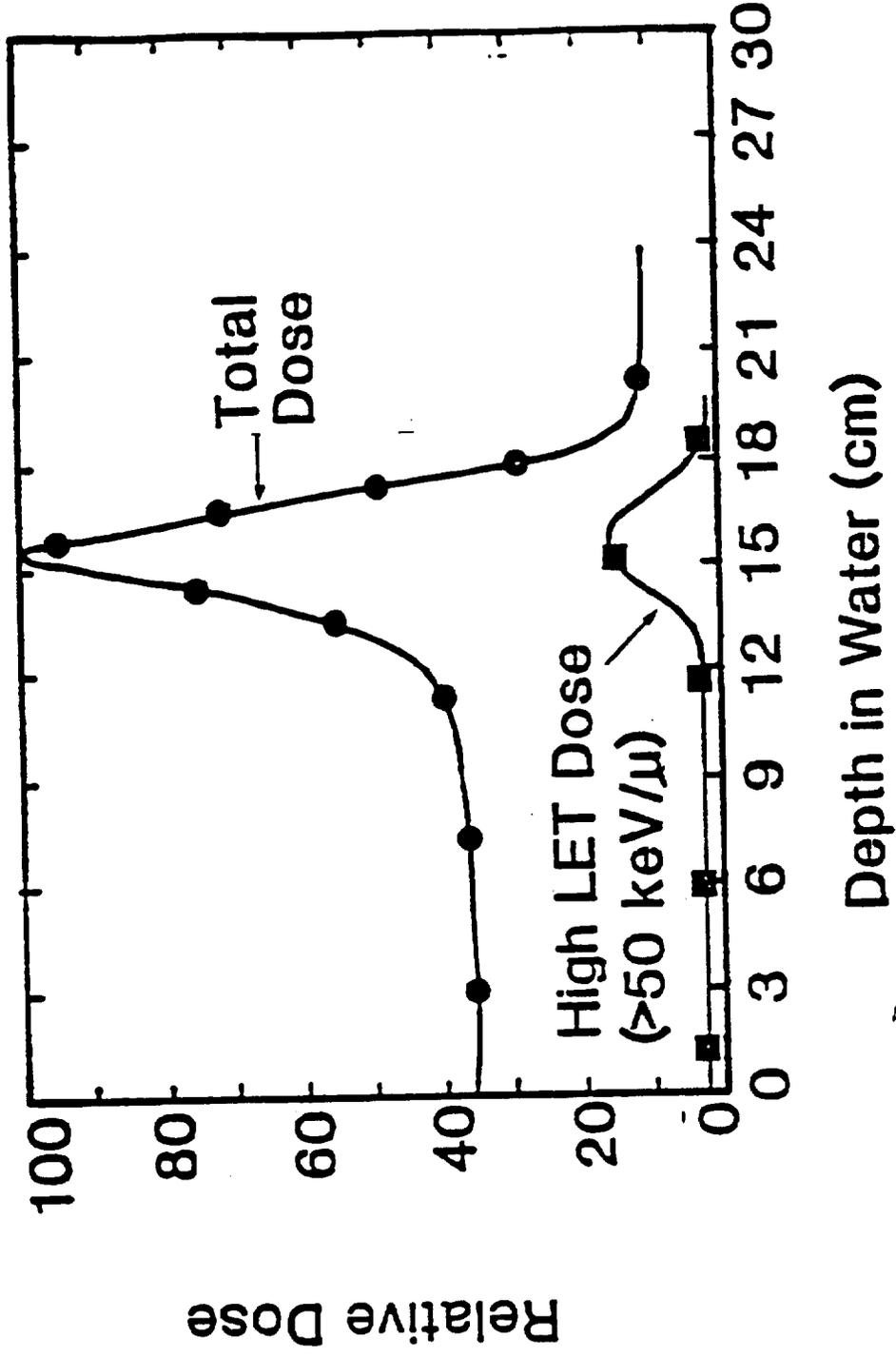
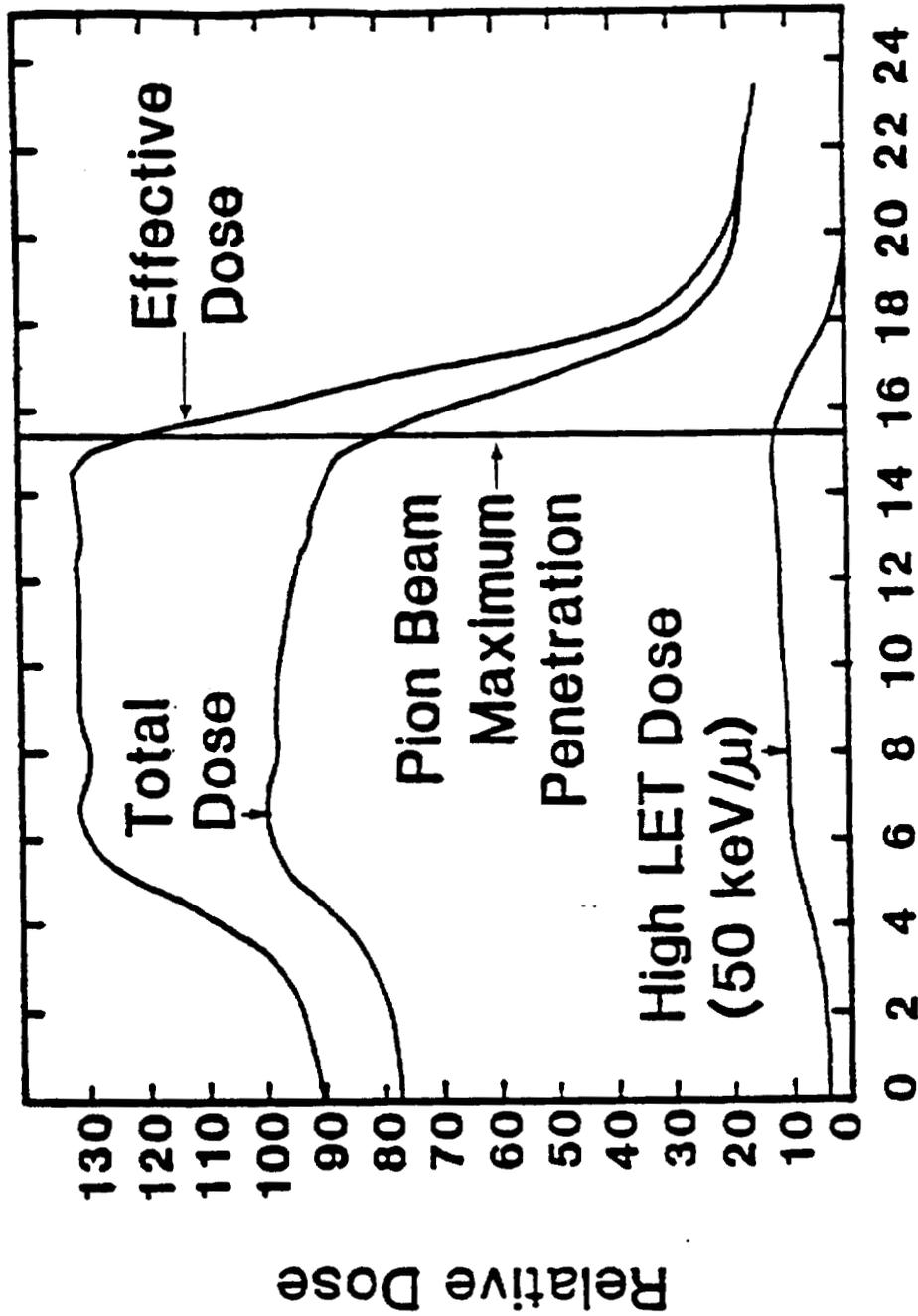


Figure 43. High-LET dose distribution from measurement and calculation for dynamic fan beam

CALCULATED 9 CM RANGE - SHIFTED PEAKS



Depth in Water (cm)

Figure 44. Composite depth-dose calculation for modulated dynamic fan beam

TYPICAL FAN BEAM 7-CM RANGE MODULATED

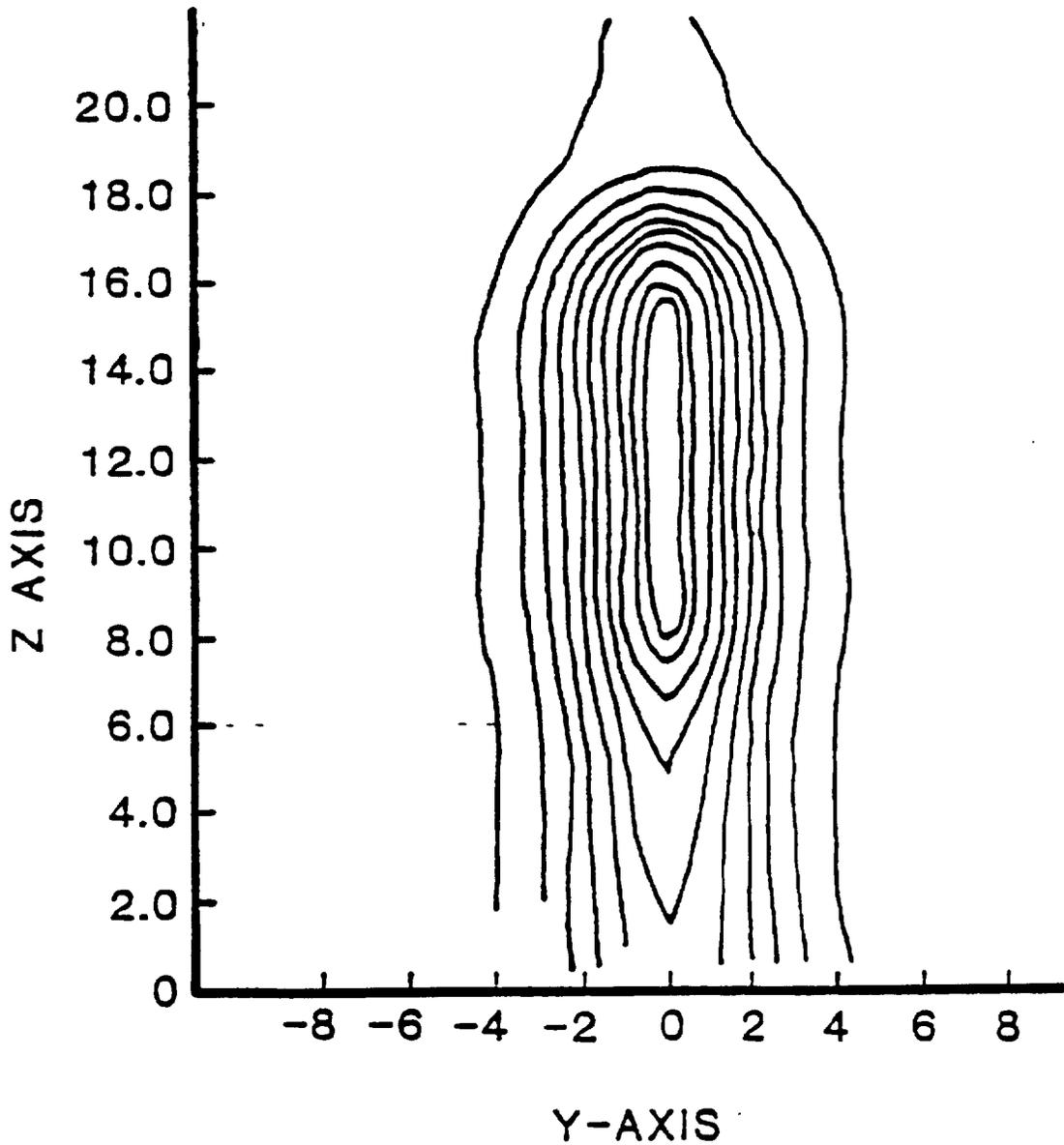


Figure 45. Typical y-z distribution for dynamic fan beam

TABLE 31

DYNAMIC TREATMENT PLAN
RIGHT LATERAL BEAM CONE-DOWN

<u>Step #</u>	<u>Couch Position</u>	<u>Modulation Function</u>	<u>Dose Weight</u>	<u>Monitor Units</u>
1	+5.5	06	0.1871	362
2	+4.5	07	0.0323	66
3	+3.5	08	0.0645	140
4	+2.5	09	0.0774	173
5	+1.5	10	0.0645	149
6	+0.5	10	0.0710	164
7	-0.5	10	0.0710	164
8	-1.5	10	0.0645	149
9	-2.5	9	0.0710	159
10	-3.5	8	0.0645	140
11	-4.5	7	0.0322	66
12	-5.5	7	0.2000	407
			$\Sigma = 1.0000$	$\Sigma = 2139$

Patient head in -y direction

Step #1 is most superior slice

dose for this treatment. Figure 46 shows the resultant physical dose distribution for this treatment. The patient anatomy has been transformed into water-equivalent thickness for the purpose of treatment planning by integrating over the CT numbers and calculating water-equivalent depth from skin surface to the proximal and distal edge of the target volume on each CT slice. Once the appropriate depth of penetration and range-modulation function has been determined for each step from this water-equivalent calculation, the bolus calculation is performed by use of the actual patient CT data. The dose-equivalent distribution is shown in Figure 47. The 90 percent isodose line circumscribes the target volume. These calculations are verified by actual measurements with TLD and ion chambers in a water phantom using the patient collimator and bolus and simulating the entire dynamic treatment. The measurements have thus far always confirmed the treatment plan to be accurate to within 5 percent.

It is planned to implement dynamic "spot" scanning in which the patient is scanned in two dimensions, thus allowing for beam shaping in three dimensions. Table 32 shows a summary of some of the properties of the static and dynamic modes of treatment. In the final analysis we plan to have available all three types of treatment. Patients will be treated by whatever mode best suits the needs of that particular treatment.

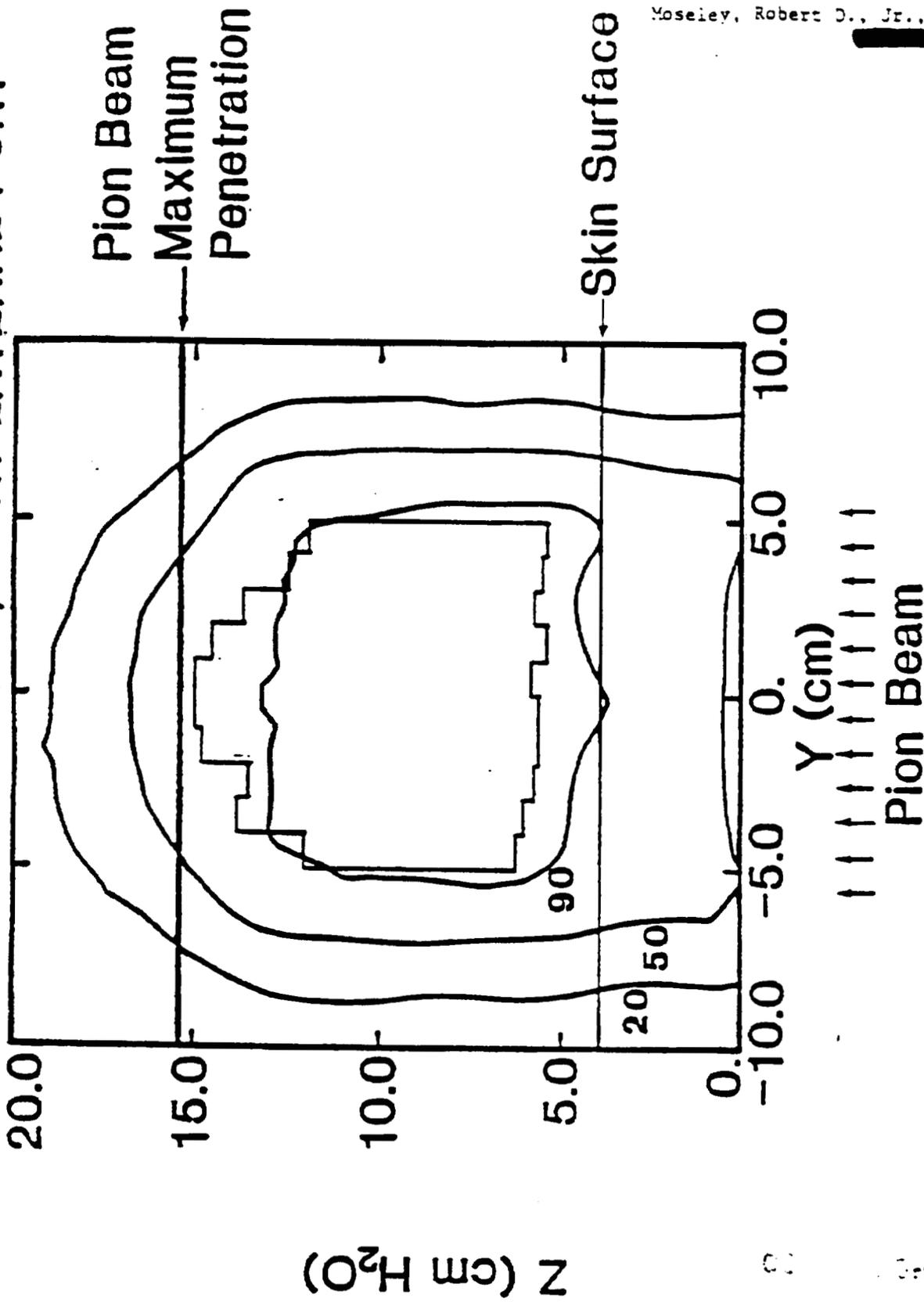
(c) In vivo dosimetry. In vivo measurements are routinely taken on pion therapy patients. Measurements taken on all patients with a small-volume ionization chamber include skin dose at the center of the treatment field and at the edges of the target volume projected to the skin surface. For whole brain irradiations, measurements are taken on both eyes during treatment with right and left lateral fields. Whenever possible, measurements are also taken at various places in the nasal and oral cavities of head and neck patients. Measurements are made in the rectum of patients receiving pelvic irradiations. On occasion, thermoluminescent dosimeters are also used to measure the total dose, and aluminum pellets are used to measure the high-LET dose.

The method of aluminum activation to ^{24}Na has been shown feasible as a high-LET, in vivo dosimeter for clinical pion beams. A 3" x 3" ϕ NaI (Tl) well detector measures the ^{24}Na activity following exposure by windowing the 2.75 MeV photopeak. Calculations of the ^{24}Na activity agree well with experiment if one assumes a production ratio of $0.075 \text{ }^{24}\text{Na}/\text{stopped } \pi$ in aluminum, and an in-flight cross-section of 26 mb. The activity is produced primarily by stopping pions, although 15-25 percent of the activity is the result of neutrons. Thus, the induced activation is a good measure of high-LET dose. By comparison of high-LET dose with that measured by a 7.6 μ silicon detector and a Rossi chamber, the amount of high-LET dose per activation is found to be $1.35 \times 10^6 \text{ rad}/(^{24}\text{Na}/\text{gm Al})$. A clinical set-up has been installed.

Figure 48 shows a comparison of the high-LET dose measured with a silicon detector and with aluminum activation. Figure 49 shows the result of measurements taken in the rectum of a patient during treatment. These measurements are compared with the high-LET dose as anticipated from treatment planning.

The thermoluminescent (TL) sensitivity of LiF (TLD-100, TLD-600, TLD-700) and $\text{Li}_2\text{B}_4\text{O}_7$ (TLD-800) has been measured as a function of depth and off-axis position in a therapeutic negative pion beam to evaluate the usefulness of those materials in pion radiotherapy. TLD-100.

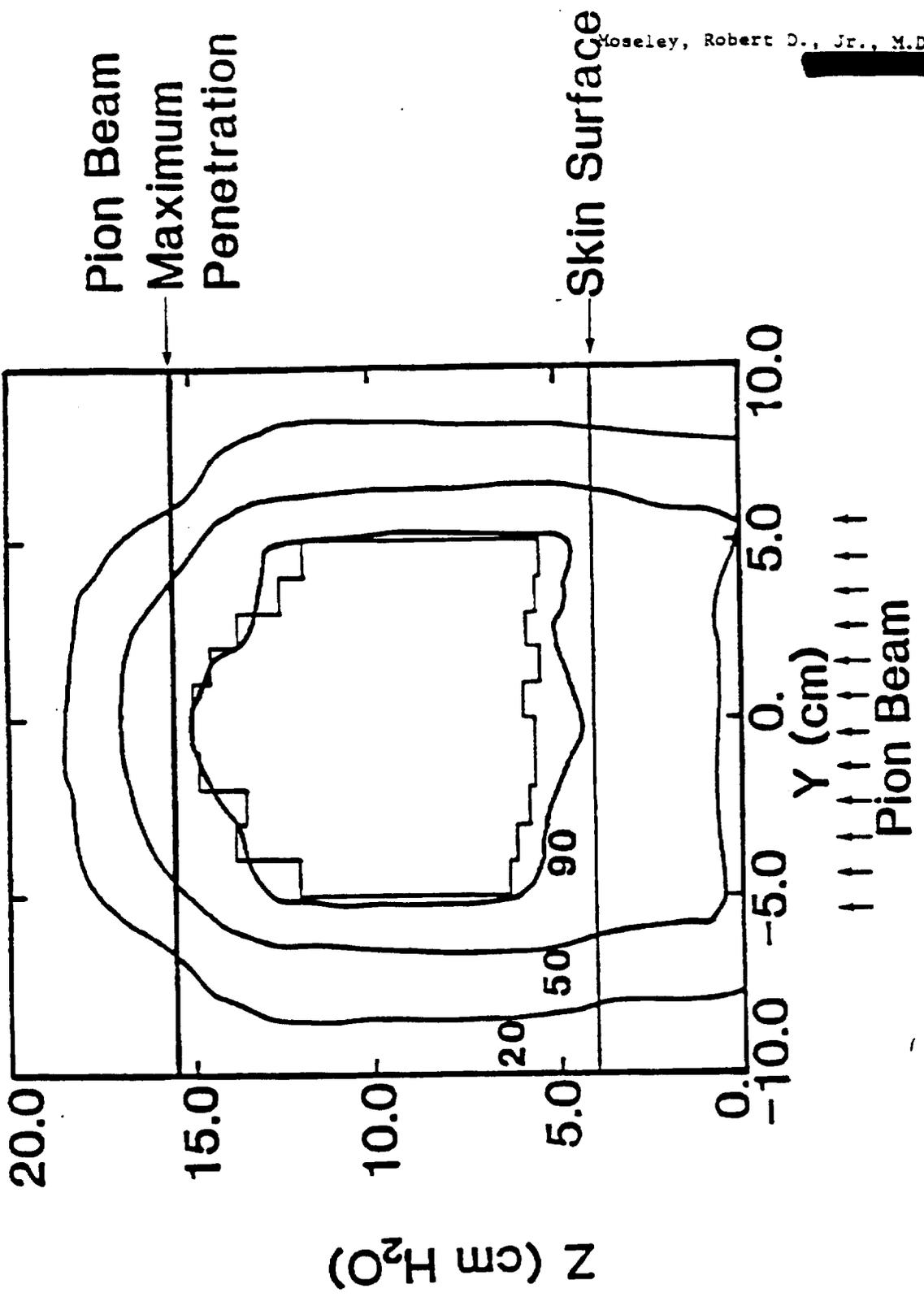
PHYSICAL DOSE DISTRIBUTION, RIGHT LATERAL PC..T



Moseley, Robert D., Jr., M.D.

Figure 46. Physical dose distribution for dynamic fan beam treatment

EFFECTIVE DOSE DISTRIBUTION, RIGHT LATERAL PORT



Moseley, Robert D., Jr., M.D.

Figure 47. Effective dose distribution for dynamic fan beam treatment

TABLE 32

SUMMARY OF STATIC VERSUS DYNAMIC TREATMENT PROPERTIES

<u>Property</u>	<u>Static Mode</u>	<u>Dynamic Mode</u>	
	<u>Broad Beam</u>	<u>Fan Beam</u>	<u>Spot Beam</u>
Uniformity in x	Fair	Fair	Good
Uniformity in y	Fair	Excellent	Good
Collimation and beam edges	Fair	Fair	Fair
Dose rate	Good	Good	Good
Y-z dose shaping	None	Excellent	Good
X-z dose shaping	None	None	Good
Difficulty in treatment planning	Excellent	Moderate	Most difficult

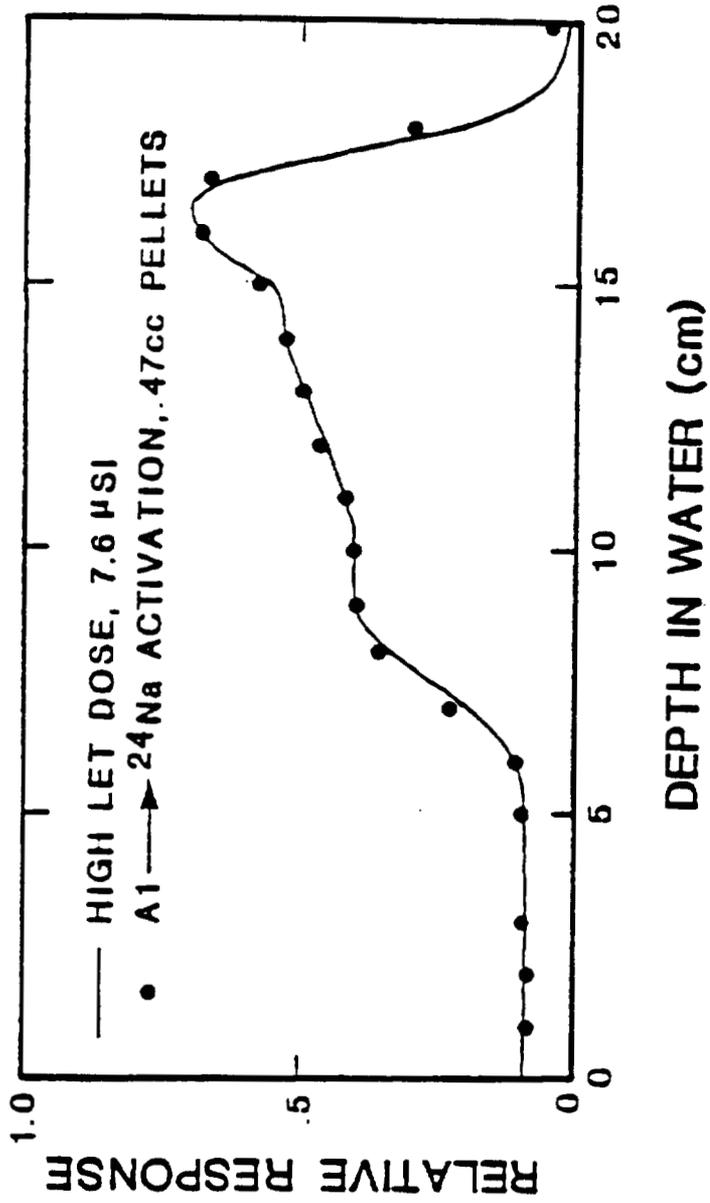


Figure 48. Comparison of high-LET dose measured with silicon detector and with aluminum activation

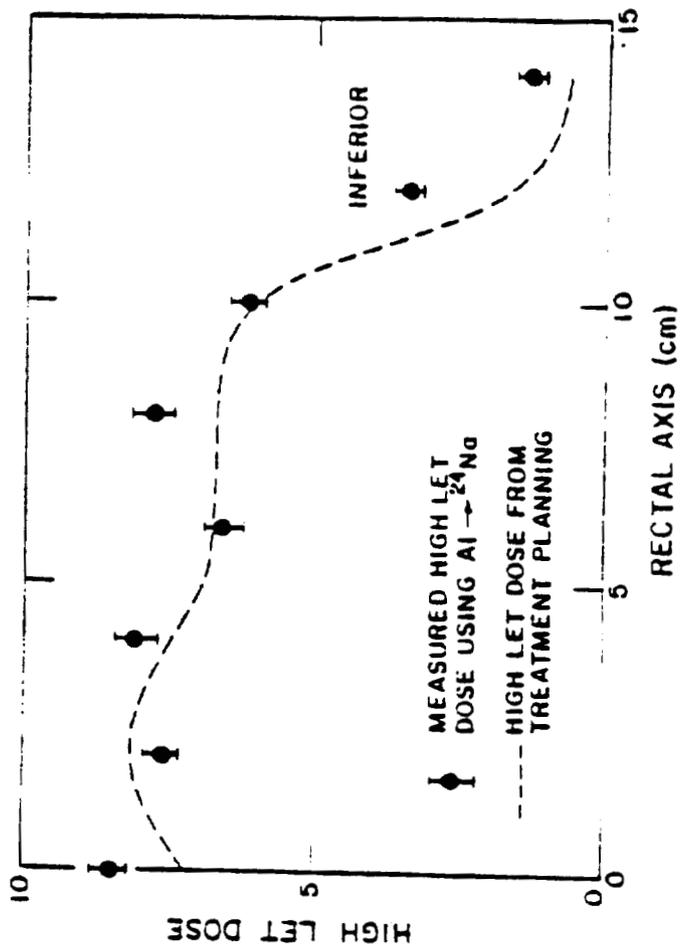


Figure 49. Measured versus calculated high-LET dose in rectum of patient

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TLD-600, and TLD-800 have been shown to be of little use in in vivo dosimetry because of grossly changing neutron Kerma with depth. The neutron source comes primarily from pion absorption in the lead-alloy collimator. The 200°C TLD-700 response agrees well with the depth-dose spectra, except for small changes due to the varying LET distributions. This variation can be partially accounted for by incorporating the known LET response of LiF. The 260°C peak of TLD-700 has been found to be approximately four times more sensitive than the 200°C peak to a high-LET dose. Using a simple model of the LET responses, the measured 200°C and 260°C peaks predict total dose within ± 4 percent and high-LET dose within ± 50 percent; therefore, indicating TLD-700 to be a good in vivo dosimeter for total dose but only an indicator of high-LET dose.

Table 33 gives the results of a typical set of in vivo measurements on patients (other than skin dose) using an ionization chamber. The low and high readings for rectum measurements reflect the variations in rectal filling and difficulty in localizing the in vivo dosimeter.

Thermoluminescent dosimetry (TLD) is also used extensively to verify treatment plans, especially for dynamic treatment, in a water phantom under conditions that simulate actual patient treatment. Because a large number of dosimeters are exposed at one time, the required read-out time is considerable. For greater efficiency, the read-out system has been automated.

A system was designed to automate the operation and data collection from a TLD reader system. The system was composed of a Harshaw 2000A and a Harshaw 2000B integrating pico-ammeter. In addition, a Hewlett-Packard two-channel chart recorder was sometimes used by manual control. A CAMAC serial highway driver controlled by a Kinetic Systems 3992 serial highway driver and a remote CAMAC crate controlled by a Kinetic Systems 3952 serial crate controller have been added. The CAMAC serial highway allows control and data transfer to the PDP 11/70 computer. To collect data, a Kinetic Systems 3520 12-bit analog-to-digital converter (ADC) is used. Use of this module required the construction of a CAMAC compatible amplifier to bring the Harshaw outputs up to the levels required by the ADC. In addition, a Kinetic Systems 3087 output register is used to control on/off functions such as starting and stopping the chart recorder and the TLD reader.

Use of the system outlined above is coordinated through a relatively simple Fortran program. The program first initializes the serial highway and then prompts the operator for the requisite parameters for operation of the system, i.e.: (i) time intervals between readings, (ii) total time required, (iii) temperature range desired, (iv) total number of samples to be read, (v) whether the chart recorder is required, and (vi) information to identify the sample and the source of its exposure.

With computer prompting, the operator's responsibility is reduced to supplying samples and responding to further prompts. The system can thus be used with a minimum of effort and training.

Digitized data are output to an array in the program. When a sample is finished, the array is written to a disk data file for permanent storage.

TABLE 33
IN VIVO DOSIMETRY RESULTS

<u>Patient #</u>	<u>Site</u>	<u>Calculated Dose</u> <u>rads</u>	<u>Measured Dose</u> <u>rads</u>	<u>Calculated/</u> <u>Measured</u>
[REDACTED]	Oral Cavity	112.6	107.9	1.04
	Rectum	54.0	64.3	0.84
	Rectum	60.9	63.0	0.97
	Rectum	63.4	68.8	0.92
	Rectum	58.9	57.8	1.02
	Rectum	62.7	53.7	1.17
	Rectum	57.3	57.7	0.99
	Rectum	56.7	60.1	0.94
	Rectum	59.8	63.8	0.94
	Rectum	57.6	60.0	0.96
	Rectum	61.4	63.7	0.96
	Oral Cavity	129.1	140.0	0.92
	Rectum	62.1	61.3	1.01
	Rectum	60.8	58.4	1.04
	Oral Cavity	93.9	94.0	1.00

A protocol for zero adjustment of the system is still under development. The overhead in the environment has thus far allowed repeatable timings in the range of 0.5 sec for 90 sec readings. In the range of 0.1 sec overhead in the system distorts time by a small but respectable factor. This project will soon be expanded to include a system to read LYO luminescence detectors and then a series of sodium iodide crystals in the pion therapy treatment room.

(d) Positron visualization of stopping pion distribution. The method of positron emission tomography for visualizing the stopping distribution in patients irradiated by negative pi mesons is under investigation. Three methods of visualization have been shown feasible for monitoring stopping pions: (i) pi mesic x-rays using an Anger camera; (ii) prompt high energy gamma rays being viewed by spark chambers or multiwire proportional counters; and (iii) positron-emitting radionuclides being viewed by conventional positron cameras. We have chosen to study the positron method, as (i) and (ii) must be done during patient irradiation which leads to high background problems. It will also be easier to extract a quantitative 3-D reconstruction using current technology of positron tomography.

Prior to the recommendation of clinical use of this method a set of problems was specified for study. These included (i) the correlation of positron activity with stopping pions, (ii) the effects of biological diffusion of positron emitting isotopes from the production site, (iii) the development of an experimental positron imaging system, (iv) the evaluation of the system using animals, and (v) the clinical evaluation of the system on patients.

The first problem has been extensively studied by Mausner *et al.*¹¹⁹ by irradiating solid disk phantoms of tissue equivalent and other materials. Their data give positron isotope activation as a function of depth for a narrow momentum-spread pion beam. They quote the absolute numbers of positron emitters as .0154 ¹¹C/stopped π^- and .0071 ¹³N/stopped π^- for tissue equivalent materials. For the tissue equivalent material, one can range-modulate their narrow beam results using a typical 8-cm spread patient depth-dose curve function. In Figure 50 the result of range-modulating their data is compared with the stopping distribution as measured by Dicello and Zaider. The positron activity is greater than the stopping pion distribution in the proximal peak because of in-flight interactions leading to ¹¹C activation.

The effect of biological diffusion, in which activated nuclei are transported away from the irradiation site, has been evaluated. For positron emission tomography to be feasible, this diffusion rate must have a half-life greater than both the counting period and physical half-life of the radionuclides, so that this diffusion will not grossly affect the image and the data acquisition rate. The biological half-life of the activation has been measured within irradiated tumors of the rectum, pancreas, lung wall, and head and neck.

The resulting decay curves for the four anatomical sites, rectum, pancreas, lung wall, and head and neck are plotted relative to the roast phantom in Figure 51. The mean life, τ_d , obtained from fitting the data and the resulting chi square/degree of freedom for each case show the abdominal cases to have the most rapid diffusion with half-lives of

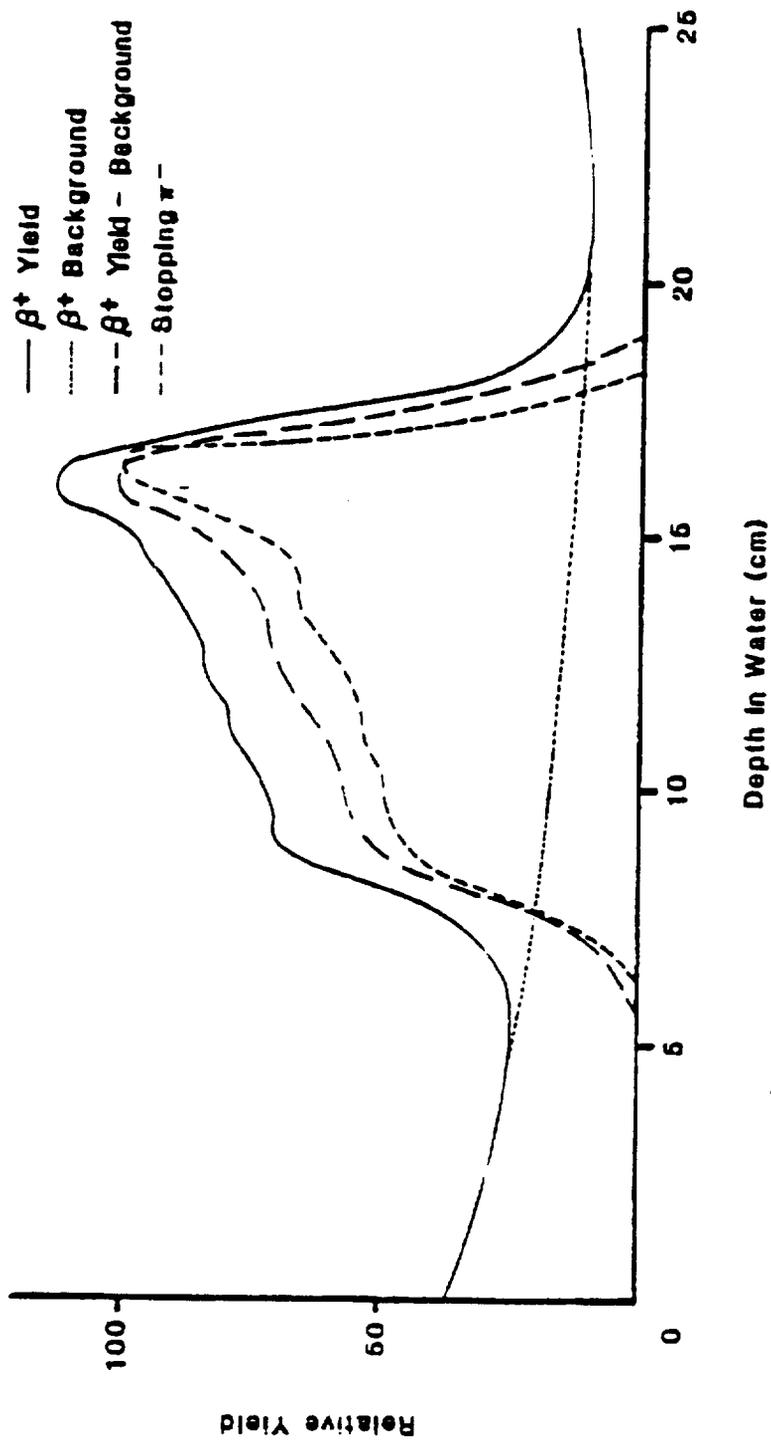


Figure 50. Range modulation of positron emission data versus measured stopping distribution

β^+ Activity in ν^- Irradiated Volume

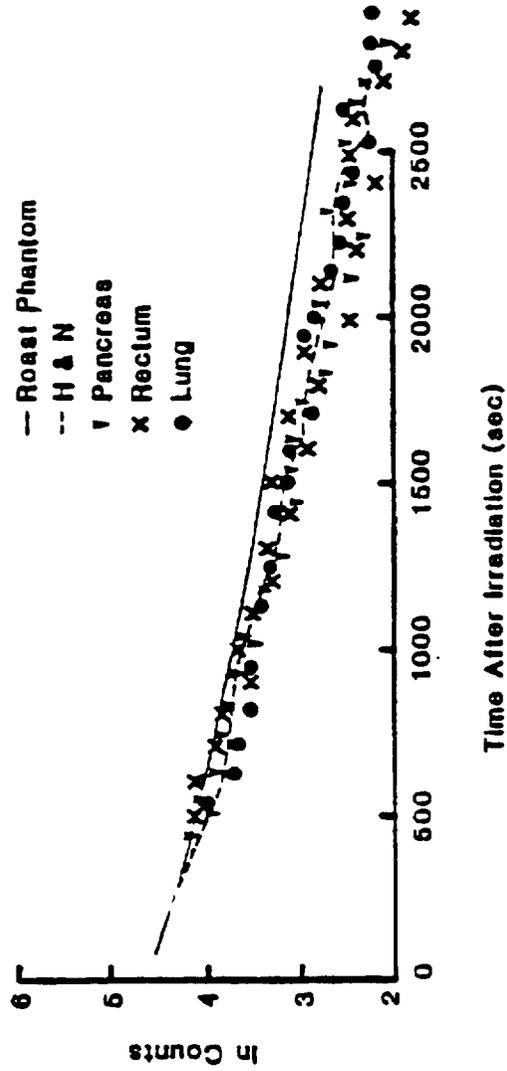


Figure 51. Decay curves for four anatomical sites relative to phantom decay curve

approximately 40 min, while the head and neck and lung wall have half-lives of approximately 60 and 80 minutes, respectively.

The validity of assuming that all radionuclides have the same diffusion rates has been checked by fitting the data in two time intervals: $t \rightarrow t \pm 1350$ sec and $t \rightarrow t \pm 900$ sec to $t \pm 1890$ sec. The results from such fits agreed within statistical uncertainty for each anatomical site except for the lung wall, in which case the first interval yielded a 112 ± 39 min half-life compared to 38 ± 10 min for the second interval. Such results imply that perhaps the ^{11}C has a shorter biological half-life than the ^{13}N in the lung wall.

The preceding results indicate that for these specific cases the biological half-life of the activated β^+ emitting radionuclides depends upon the anatomical site, varying from 38 to 79 minutes for the sites measured. The abdominal tumors had greater diffusion rates than the tumors in the other sites. This result agrees with the expectation that increased vascularity should increase diffusion.

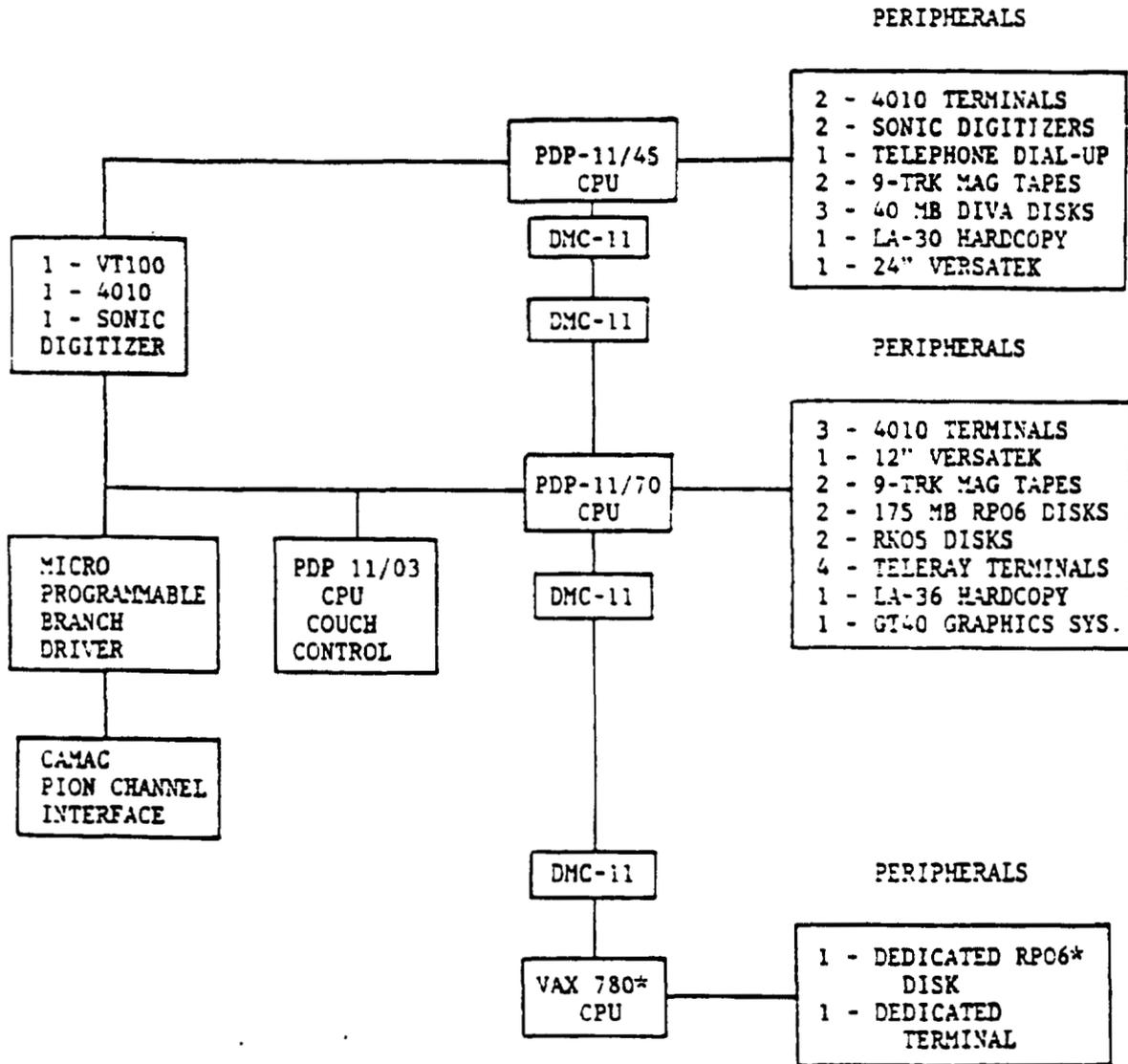
The longevity of the biological half-lives should not cause significant reduction in count rates during the 15-minute counting intervals planned for patient tomograms. On the other hand, the results suggest that solid tumors may have a biological half-life different from that of surrounding healthy tissue. If this difference is large, some problems might arise in interpreting positron tomograms, as the data will represent some time-averaged strength depending on the biological half-life.

Preliminary measurements with a positron detection system on patients with lesions of the pancreas, rectum, head and neck, and lung indicate that diffusion rates of activity from these sites should not be a limiting factor in measurements. Three NaI crystals have been purchased and will be used to test the feasibility of a low-cost one-dimensional Anger camera for positron detection. Hardware tests for determination of detector configuration to provide for optimal resolution are in progress, as is software development for the data acquisition system.

(6) Systems operation, development, and maintenance

(a) Channel control systems. The pion delivery system includes a pion production target which needs to withstand very high power density and an 11-magnet channel for collecting, momentum-analyzing, and shaping the pion beam. The channel contains two slit systems, a movable wedge system for tailoring momentum distributions, and multiwire proportional chambers for determining the five-dimensional phase space of the pions, muons, and electrons contained in each of the numerous beams used to treat patients. At the channel exit there is a large ion chamber beam monitor and a programmable range-shifter. A computerized control system is used for control, monitoring, and data acquisition (where appropriate) of all channel hardware, and also for treatment couch motion in dynamic scan treatments. The configuration of the control system is shown in Figure 52.

A new air-operated channel beam plug has been designed, fabricated, and installed in the channel. This plug improves the reliability of the channel and reduces patient turnaround time.



*Not owned by pion project - made accessible by LAMPF Group MP 1 as a resource.

Figure 52. Biomedical facility computer system configuration

(b) Computer systems. The channel control computer was upgraded from a PDP-11/45 to a PDP-11/70 with associated improvement in mass storage devices. The PDP-11/45 has been dedicated to treatment planning. Both systems were interconnected with a DECNET communications link and operate under an RSX-11D operating system.

CAMAC parallel highway line drivers have been purchased to improve the CAMAC system reliability; these will be installed in the near future. An operator channel interlock alarm panel has been completed and is being installed.

A Digital Equipment Corporation graphics subsystem (GT-40) with a PDP-11/04 processor was attached to the PDP-11/70 treatment computer. This device will allow faster graphics to be utilized and will be useful in visual presentation of CT scanner data to treatment planners and physicians.

The RSX-11D operating system was modified to improve CPU utilization by the addition of background priorities for calculational programs which would otherwise place too heavy a load on the machine to co-exist with patient treatment procedures. The functioning of the operating system was improved by enabling programs to better interact with one another, and some operating system restrictions were removed to allow computer users to accomplish their work more effectively without the need of operations personnel. Operating system errors were isolated and remedied as necessary. The system has been replicated to run on both the 11/45 and 11/70 computers, an arrangement that is most satisfactory to computer users. Special software was written to allow operation of the CAMAC microprogrammable branch driver (a 17-bit device) through the 11/70 computer (which requires 22 bits for proper utilization). The control computer and the treatment-planning machine have been interconnected with the DECNET communications package allowing great versatility in machine usage.

The channel control software has been improved to keep pace with changes in the hardware and daily operational procedures. The set-point monitoring software was redesigned to use streamlined data-acquisition methods which reduced the steady-state system overhead. Software upgrading has included reconfiguration of patient treatment codes for more efficient operation, acquisition of a more efficient file backup system for on-line backups, purchase and installation of DECNET for interprocessor communications, automation of the target-scanning procedure, and development of codes for dynamically scanning the patient under the pion beam.

Treatment planning and dosimetry support included the creation of machine-language input/output routines to optimize the execution of treatment planning, resolve incompatibilities between the programs of various authors, ameliorate problem trouble-shooting, and provide general programming assistance. The preparation for dynamically scanned treatments has included development of an operating and communication system for the 11/03 microprocessor that will control the treatment room equipment.

The DECNET hardware lines between the treatment-planning and control computers were upgraded from DL-11 to DMC-11 communications devices. This has increased the communication speed between machines ten-fold. The treatment planning PDP-11/45 received a third 40-megabyte Trident disc transport which allows two treatment plans to be

executed simultaneously. One additional sonic digitizer and its associated Tektronix terminal were added to the treatment-planning PDP-11/45. They were made hardware-switchable to the PDP-11/70 control computer. This has produced treatment planning backup capability for peak production periods and for the case of catastrophic failure of the PDP-11/45 treatment planning computer.

(c) Treatment systems. A new improved range-shifter (for either backup or routine use) has been fabricated and is currently under test. Mechanical redesign of the Philips treatment couch feedback encoders has vastly improved couch reliability during dynamic treatments. Gray scale encoder linkages for the Philips treatment table have been redesigned for increased mechanical resolution and reliability during dynamic patient treatments.

(d) Patient data base system. DATATRIEVE, a product of the Digital Equipment Corporation, has been selected as the data base system for analysis of clinical data based on operating cost, advantages in ease of use, statistical capabilities, compatibility with current operating systems and accessibility.

DATATRIEVE utilizes an English-like command language combined with interactive data input to make an easily used data base system for those whose expertise does not normally include computers, i.e., physicians and other health care workers. Commands such as FIND, SORT, SELECT and PRINT combined with Boolean expressions exemplified by GREATER-THAN or NOT-EQUAL produce record selection expressions such as:

FIND ALL PATIENTS WITH AGE GREATER-THAN 50

The data base has been established on a Digital Equipment VAX computer, utilizing eight different forms for initial observation, follow-up reports, and so forth. The data base currently includes 3.1 million bits of information on 173 patients.

Experience in setting up and using the data base has been excellent with no major problems encountered. While the initial work was performed with DATATRIEVE Version 1.1, Version 2.0 with enhanced features has been installed, and the data base has been converted to this latest version.

iii. Publications

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3. Specific Aims

a. Beam development and characterization

- i. Continue to improve the reproducibility of the various therapy beams.
- ii. Streamline the dosimetry data acquisition for channel tuning and development studies.
- iii. Develop a therapeutically useful spot beam and investigate collimation techniques for dynamic treatments.
- iv. Explore the possibility of using a larger transverse fraction of the pion beam to obtain higher dose rates.
- v. Improve the uniformity of beam quality in the x-dimension.
- vi. Develop a technique for smoothing the low-momentum beam tapes.
- vii. Ascertain the usefulness of current cycling for channel quadrupole magnets.
- viii. Evaluate the long-range neutrons and electrons from muon decay.
- ix. Develop positive pion beams for possible use for large field irradiation.

b. Dosimetry

- i. Complete all clinical dosimetry to include characterization of physical and high-LET dose distributions for all beam configurations.

- ii. Refine biology models for pion beams to include RBE's for various normal tissues and various fractionation schemes.
- iii. Develop methods to accurately calculate beam profiles, depth-dose distributions and planar isodose distributions for all pion therapy beams, and develop methods for accurately calculating the output (calibration) of any beam configuration.
- iv. Develop more accurate dose conversion factors for ionization chambers; study the effects of chamber size and geometry.
- v. Complete comprehensive studies of whole-body neutron dose.
- vi. Perform studies of various collimator materials to minimize secondary neutron effects.
- vii. Continue CT and pion beam studies (calculations and measurements) with various tissue substitutes to obtain a better understanding of pion interactions in various materials.

c. Treatment planning

- i. Improve clinical utility of the PIPLAN three-dimensional computerized planning code by:

- (1) Upgrading biologically effective dose models for PIPLAN.
- (2) Implementing full dose optimization for multi-port treatments.
- (3) Performing comparisons of treatment plans for static treatment and dynamic treatment using both the "fan" and "spot" beams.
- (4) Enhancing graphics output for three-dimensional clarity and ease of interpretation by the physician and treatment planning physicist.

- ii. Improve accuracy of PIPLAN by:

- (1) Defining and incorporating the second muon phase-space into incident beams; upgrading muon/electron distribution models.
- (2) Resolving differences between monitor chamber and beam measuring systems to allow absolute dose calculations.
- (3) Including neutron LET distributions as a function of distance from source for effective dose calculations.
- (4) Upgrading multiple scattering models for treatment appliances and rapidly changing tissue gradients.

- iii. Improve efficiency of PIPLAN by:

- (1) Conversion to a VAX computer.
- (2) Incorporating code enhancements for increased speed, interactive operation, and addition of new modules.

d. Treatment delivery and verification

- i. Fully implement dynamic treatment using fan tunes.
- ii. Develop capability to perform dynamic treatment using "spot" tunes.
- iii. Continue refinement of in vivo dosimetry techniques.
- iv. Continue study of visualization of stopping pions by means of positron emission imaging.

e. Systems operation, development, and maintenance

i. Channel control systems

- (1) Continue preventive maintenance and repair of all channel and control system hardware.
- (2) Provide system support during patient treatment.
- (3) Design a new target controller with redundant position checks for improved target scanning capability.
- (4) Build a special-purpose scanner for channel diagnostics.
- (5) Improve diagnostics for magnet current drifts.
- (6) Improve magnet control codes to allow more rapid tune changes.

ii. Computer systems

- (1) Expand the serial highway of the CAMAC system, and provide CAMAC system diagnostics.
- (2) Implement PDP-11/03 range-shifter control for static treatment.
- (3) Redesign the dosimetry scanning system using an intelligent CAMAC crate.
- (4) Provide hardware and software conversions to shift three-dimensional treatment planning to an in-house VAX computer (to be purchased with funds provided by the U.S. Department of Energy to LAMPF).
- (5) Upgrade the Biomedical Facility computer operating systems.

iii. Treatment delivery systems

- (1) Complete assembly and installation of a new, improved range-shifter (with a five-fold increase in modulation frequency).
- (2) Implement techniques for automatic fabrication of patient boluses.
- (3) Improve dynamic treatment hardware and software to provide capability of treating all appropriate patients by the dynamic scanning method.
- (4) Continue to refine patient immobilization, alignment, CT, treatment planning, and treatment delivery system to maximize patient through-put.

4. Methods of Procedure

a. Beam tuning and channel development

i. Improvement of therapy beam reproducibility. Beam reproducibility continues to be a problem despite the large effort expended to solve it. The major remaining factor causing lack of beam reproducibility is believed to be variation in vertical proton beam position from one LAMPF run cycle to the next. Each new run cycle brings a new production target, and any variation in construction or assembly becomes an uncertainty in absolute calibration of the target scan information. These position errors are magnified at the channel output by a factor of up to six. The normal proton beamline diagnostics can locate the proton beam to 1 or 2 mm, but this is not sufficiently accurate to guarantee reproducible pion beam output position.

There is evidence that some variation in pion beam position remains even after careful monitoring with the target scans during the run cycle. A considerable amount of clinical dosimetry time is spent adjusting for these beam shifts, both at the beginning of a run cycle and during the cycle. A program has been started to track down conclusively the source of these shifts or to at least to develop the capability to rapidly make adjustments for shifts.

The plan is to build a scanner that will perform rapid x-scans with minimal setup time. A prealigned ion chamber and scanner attachment arm will offer error-free automatic alignment. Bend-plane x-scans will be made as often as needed to correlate with target scans or other channel data. Comparisons will be made with the routine dosimetry checks. Solution of this problem would improve treatments and free considerable beam time for other projects.

ii. Streamlining dosimetry data acquisition for channel tuning and development studies. A large fraction of the beam tuning/channel development work involves dosimetry rather than multiwire chambers. Only a limited amount of low intensity beam time is available for chamber work. Also, certain problems are becoming so specific that multiwire data are not as immediately interpretable as dose in water. The measurements do not require the same precision as the routine clinical dosimetry, and as a result, a much faster single chamber dosimetry method is desirable to accomplish the beam tuning/channel development goals. A program for this work is evolving, with the following specific goals:

(1) Improved range-shifter cycle time. Dosimetry collection with the range-shifter generally requires a full cycle (10 sec) per data point. The re-engineered backup range-shifter is not yet functioning satisfactorily, and the range-shifter now in use is not designed for high speed. We propose to implement some new ideas in the mechanical design of the backup device and thereby gain a factor of 5 or 10 in speed. Also, the present range-shifter function uses coarse steps and consequently undergoes large accelerations. A function with very small steps produced under microprocessor control or generated from a more ambitious computer-controlled function generator is needed to achieve the higher speeds. Presently the range-shifter runs on a time base that is independent of fluctuations in proton beam current. Control of the shifter function based on monitor chamber signals might produce better data and would eliminate repeating data points when the proton beam current is fluctuating.

(2) Larger ion chambers. We wish to build or purchase ion chambers with volumes 10 to 100 times greater than those of the thimble chambers now in use. The material need not be TE plastic. For example, a chamber designed for scans in the x-z plane could be rather long in the y-direction without producing any adverse effect on the data for the static beam tunes. Such a chamber would be used for beam reproducibility studies.

Another use of a long ion chamber is in the evaluation of the dozens of possible fan tunes that have been generated by the beam tuning work. The long ion chamber, if sufficiently uniform in response, would integrate dose over the y-dimension or scanning dimension of the fan beam. In this way, an accurate z-representation is obtained without requiring a two-dimensional y-z scan and subsequent integration of the y data. More accurate x-representations of the beam will also be obtained by integrating over the y-dimension.

(3) Current measurements. Performing current measurements rather than charge measurements should be easily possible with the larger ion chambers. For dosimetry scans without the range-shifter, the data are just the current ratio of the ion chamber to the monitor chamber. Both signals can be digitized and the count rates read out.

In many beam tuning experiments, the range-shifter only serves the function of spreading the beam sufficiently in depth to wash out the momentum-position correlation present in most beams. This x-p effect makes it impossible to obtain unrange-shifted bend plane x-scans near the pion peak. A simple wedge can compensate for the change in depth with position and allow meaningful x-scans without the range-shifter. Such wedges have been used for fan beam dosimetry.

iii. Development of a therapeutically useful spot beam and collimation techniques for dynamic treatment. Some tuning effort has been aimed at developing a spot beam. Reduced multiple scattering in the channel has improved the predictive capability of the channel tuning system, and as a result, the measured spot tunes should come closer to the calculated ones. Spot beams will be developed for three momenta; at present, only a 167-MeV/c solution exists. Ideas for a spot beam delivery system to be pursued are:

(1) A simple spot beam collimator would be elliptical in shape, fitting tightly around the base of the Gaussian-shaped particle distribution. It would principally collimate muons from pion decays late in the channel, leaving the purest pion beam possible with this channel.

(2) The transverse fall-off of the spot beam is not sharp enough in some cases, and additional collimation is desired. Improvement is possible by collimation in the y-plane where the beam is more parallel. Collimation is less effective in the x-plane. Use of the conventional collimator below the elliptical one would be possible but would be very awkward and adds too much extra drift space for the pion beam. A simple dynamic collimator design could combine the function of both of the above-mentioned collimators. An elliptical collimator would be translated in both dimensions (x,y). When the patient position is such that the beam is in the center of the field, the ellipse is centered, giving maximum beam transmission. When the patient is scanned to a position where the beam falls near the edge of the field, the ellipse would move to give proper collimation.

(3) Further extension of the dynamic collimator concept uses rotation of the ellipse. By rotation, a different degree of curvature can be applied to a particular edge, depending on the shape of the treatment volume and which edge of the beam is being cut off. A more circular beam spot is needed for such a system. The elliptical contour might then be replaced by a shape containing a larger range of curvatures to accommodate more complex volumes. The patient would be positioned so that the most critical edges would be collimated in the y-plane. Rotation of the patient table can be imagined, but those motions of the table are not fully instrumented at this time. The eccentric motion of the collimator can be reduced to circular motions easily handled by servomotors.

(4) Dynamic treatment implies three-dimensional shaping of the beam. Collimation can be used at any point during the treatment. For example, if the range-shifter function has a large step in its bias to avoid a critical region, collimation along both sides of this interface will improve the sharpness of the edge obtained. Average dose rate is the only limitation as to how much internal shaping is done.

(5) We have never been able to achieve in practice the very desirable close spacing between the collimator and the stopping region needed to obtain the best edges in dose distributions that pions can produce. The maximum height of the bolus is the limiting factor. A higher density fluid in the range-shifter would let more of the bolus function be handled by range-shifter bias and allow the dynamic collimator to come closer to the patient.

(6) Another way to alter total range dynamically is by changing the beam momentum. The dynamic spot beam mode may be well-suited for this possibility. The detailed shape of the beam is less critical for this application than for the broad static beams, and the muon halo variation with energy is not a problem. Beam tuning studies would be needed at many more momenta than usually considered. For example, there are large changes in the tune for different energy static tunes; the magnet settings do not just scale with field. The problems have to do with the wedge degrader altering the "source" of particles entering the beam shaping section. We now have successful experience sweeping the LAMPF power supplies with a 10-sec period. The third bend magnet BM03 has been varied for a study of fan tune x-dimension field flattening. It should not be difficult to sweep all magnets under preprogrammed computer control. The limiting feature is and has always been the added complexity for tuning, dosimetry, and treatment. A 2-sec range-shifter cycle within a 10-sec momentum cycle might provide sufficient coverage. Each of the five range-shifter cycles (or 10 half-cycles) would be different to adjust for energy. Then a single dosimetry data point (or 10 points with MICA) would still take only 10 sec, as it does now. It may be that momentum variation of the channel exceeds our present capabilities. But at least for the spot beam development at the three standard momenta, we will keep in mind a continuous momentum variation. We should consider this "maximum utilization" mode for possible application to future pion therapy facilities.

(7) A complete design exists for a fan beam dynamic collimator. After some experience with dynamic treatment, the need for fabricating the device will be re-evaluated.

iv. Production of higher dose rates. Apart from increasing proton current, several possibilities exist to increase dose rate for selected cases. These include:

- (1) Providing with a single pion field the combined dose distribution of the commonly used broad-field/boost-field combination. It may be that the typical Gaussian shape of the smaller, high-dose-rate fields is a natural shape for some subset of the cases. The beam edges would still be collimated in the present fashion.
- (2) Developing beams with different x- and y-dimensions to match custom treatment volumes.
- (3) Utilizing alternate tunes for the channel entrance triplet to produce a modest pion increase (~20 percent) at the expense of slightly reduced momentum regulation.
- (4) Removing the wedge degrader (which sharpens the depth-dose distribution) and utilization of the full momentum spread, modified only by the momentum slits.

v. Improvement of x-dimension beam uniformity. The fan tune polarity configurations are also being investigated for use in static tunes with an objective of reducing the wide $e-\mu-\pi$ spatial separations at the end of the channel. Improved results have been obtained at some expense in field uniformity. These solutions are, therefore, more useful for smaller fields.

vi. Smoothing of low-momentum beam tapes. The smoothing of beam tapes (see Treatment Planning) is still under development. Results are not satisfactory for the low momentum cases due to significant contamination.

vii. Examination of current cycling. We have always cycled the quadrupoles along with the bending magnets, although there has never been any observed problem if cycling was omitted. Obvious changes are evident in the bending magnet fields, depending on whether they are cycled. Dosimetry is needed to investigate this problem.

viii. Evaluation of long-range neutrons and electrons from muon decay. The large dose enhancement in the plateau with collimated beams currently believed to be neutron dose has been investigated (see Treatment Planning section). No completely satisfactory explanation of the effect has been found, although PIPLAN has a neutron model approximating the effect.

A more general set of experiments has been started to understand the long-range components in the beam, principally neutrons and electrons from muon decay. Plans are to use ordinary dosimeters that do not selectively enhance or suppress neutron dose. Variations in phantom geometry will be used to emphasize different components. In almost every instance, comprehensive calculations are required to go along with the experimental studies. The problem is to find geometries that are easily calculable and that vary the strengths of the many components of the beam.

Control of the long-range collimator component requires the use of pre-collimators to minimize the number of unused pions that reach the final collimator. Many opportunities exist for some precollimation, the most effective probably being inside the upper part of the range-shifter.

Studies of collimator materials are in an advanced stage. Calculations and measurements indicate that iron has desirable characteristics; clinical evaluation is planned.

ix. Development of positive pion beams. The biomedical channel can transport both positive and negative pions. Positive pions are attractive for some treatment situations, such as whole pelvis irradiations. For these treatments the positive pions could be used for the large field and negative pions used to treat the primary tumor bed. An additional advantage of positive pions is that the cross-section for their production is about five times that for negative pions. Therefore, the dose rates are increased accordingly.

Positive pion beams are very much like proton beams, having similar dose distributions and RBE, and could therefore be used in a trial versus negative pions to test the importance of the high-LET component of negative pions. This work requires complete dosimetric characterization of the unmodulated beams, design of range-modulation functions, and dosimetric verification of the final treatment beams. Evaluation of the effect of the electron dose ($\pi \rightarrow \mu \rightarrow e$) can be performed by PIPLAN.

b. Dosimetry

i. Characterization of physical and high-LET dose distributions for all beam configurations. As the catalog of beam tunes, including negative and positive pion beams from broad, "fan," and "spot" beams, is completed, these beams must be completely characterized by extensive measurements of both total and high-LET dose. These measurements are necessary as a standard set of data against which calculations can be compared.

ii. Refinement of biology models. The RBE of the pion beam is partially dependent upon the size of the range-modulation function, specific tissue, fraction size, and overall length of treatment. Development of models for RBE which can be incorporated into dose distribution calculations is proposed. This effort is necessary because the RBE differences for different treatment configurations can vary by at least 20 percent on the basis of the size of the spread peak alone without regard to other considerations. Optimal pion therapy and meaningful clinical trials require that this effort be undertaken. Preliminary work has been performed, including the development of a simple model of RBE based on the high-LET component of the pion therapy beams. This model was used to calculate range-modulation functions predicted to have a uniform biological effect across the spread peak. Measurements with biological systems have shown that, to first order, the model is a reasonable predictor. However, the model is extremely simplistic and does not incorporate other than a standard treatment regimen (4500 rad in 35 fractions).

iii. Calculation of beam profiles, depth-dose distributions, planar isodose distributions and beam calibration. The characteristics of the dose distribution and dose rate for any particular patient treatment depends upon the beam tune, size and shape of the collimator, and size and shape of

the spread peak. At present, dosimetry measurements must be performed for each treatment field to characterize the beam. This demands a considerable amount of manpower and beam time. Development is proposed of both analytical and empirical methods to calculate these effects and thereby predict the beam characteristics for any given configuration.

iv. Development of more accurate dose conversion factors for ionization chambers. The uncertainty in the statement of absorbed dose for pions is on the order of 5-10 percent. Most of this uncertainty is due to the lack of detailed knowledge of pion interactions in various materials used in dosimetry. Especially lacking is information concerning the pion capture cross-section, the cross-sections for charged particle production in various elements, and energy fluence of secondary charged particles. Although there is a scarcity of complete physical data, sufficient data is believed to exist to perform calculations leading to reasonable approximations of the effective W value for gases commonly used in ionization chambers and the gas-to-wall and wall-to-muscle conversion factors.

Computer codes already developed at the University of Washington by Hans Bichsel and associates will be adapted to perform these calculations. The results of the calculations will be tested against matched pairs of cylindrical and spherical, TE plastic and carbon ionization chambers using various gases and also against measurements with TE plastic and carbon calorimeters.

v. Determination of whole body neutron dose. The neutron dose to various body organs such as eye and blood-forming regions will be determined to obtain an estimate of the risk of producing cancers for a typical pion treatment. Neutrons are produced by pion interactions in the channel, range-shifter, collimators, and patient. While the majority of neutrons are produced at low energies there is a tail in the neutron spectra extending beyond 100 MeV.

This study will be accomplished by a combined program of measurements and calculations. Programs have been developed at LANL that can transport neutrons and calculate neutron absorbed dose. These programs can incorporate anthropomorphic geometries for calculating dose to specific organs from the neutron spectra and fluence. The neutron spectra will be measured by activation foil analysis, a well-established technique. A series of experiments will be done to identify sources of neutrons and their strength. A neutron study group at LANL has a neutron spectrometer that can measure neutrons up to 20 MeV in energy, and this group has agreed to participate in some limited experiments.

vi. Evaluation of collimator materials. Collimators are currently made from a low melting point alloy composed of bismuth (50 percent), lead (26.7 percent), tin (13.3 percent) and cadmium (10.0 percent). The collimators are made of sufficient thickness to completely stop pions. Pions stopping in the collimator produce neutrons with a broad energy spectrum with a high energy tail extending above 100 MeV. In general, higher Z materials produce fewer neutrons at the higher energies and more neutrons at the lower energies with the number of neutrons per pion capture increasing with Z. The high energy neutrons have direct implications for dose within the treatment field and for whole body neutron dose.

Investigation of other materials for collimators is proposed, including multilayer collimators with hydrogenous material next to the patient to absorb neutrons. It is important to minimize the neutron body burden (the increased skin dose has not been shown to be a clinical problem) in view of possible late effects, i.e., secondary tumor production. These studies have not been done previously because the preliminary work requires a highly flexible and reusable collimator material and because preliminary calculations predicted a neutron dose outside the treatment volume that is on the order of 1 percent of the tumor dose.

vii. Study of CT and pion effects on various tissue substitutes. A program is in progress to investigate the properties of various tissue substitutes (muscle, lung, fat, brain, hard and soft bone) on the Biomedical Facility CT scanner and on pion therapy beams. The treatment planning programs at LAMPF require a knowledge of the correlation between CT numbers and pion linear stopping powers so that proper compensating bolus can be calculated. The nature of pion interaction, i.e., pion capture cross-sections and production of secondary particles being different for each element, requires that tissue substitutes be matched both in density and chemical composition to human tissue. These tissue substitutes will also be used in geometric and anthropomorphic phantoms to verify treatment planning in simulated patient treatments.

c. Treatment Planning

i. Improvement of PIPLAN clinical utility

(1) Upgrade of biologically effective dose models.

A continuous research effort to assess the effect of pions and incorporate this knowledge into the treatment-planning effective-dose model is a primary goal of this project. PIPLAN combines the physical parameters of dose and LET with clinical and biological observations to obtain effective dose. Presently, the latter are available only for a few fractionation schemes. Empirical models will be developed and included in PIPLAN to predict the results of alternative schemes, in particular the results of multiple cone-down and boost fields. Additionally, the effect of combined pion and conventional treatments will be modeled. Access to pertinent biological and clinical results should allow these capabilities to be rapidly realized.

(2) Implementation of full dose optimization for multiport treatments. PIPLAN currently combines multiport dose distributions for a given treatment plan with predetermined port weighting. This capability will be enhanced to automatically choose the appropriate weights for an optimum effective or total dose distribution from selected ports. Criteria will be specified at critical sites as to whether the dose at the site must have a definite value, a minimum or maximum value, or an allowed range of values. Non-unique solutions will be resolved on the basis of site importance and standard weighted, least-squares techniques. PIPLAN will also be modified to independently save calculated distributions for each port, including both high- and low-LET components for input to the weighting procedure. If the calculations are performed remote from Biomed (LCF or CCF), then the distributions will be transported to Biomed by writing them to the patient casefile and transporting via magnetic tape, by high-speed data links between remote computers and Biomed, or by telephone lines to terminal-cassettes and then to Biomed.

(3) Comparison of static and dynamic ("fan" and "spot" beam) treatment plans. Once the full arsenal of treatment modalities is available, we must perform comparative studies to determine the real advantage of each method and determine the general conditions for which each modality will be useful. In some situations (for example whole brain irradiations), dynamic treatments offer little or no advantage.

(4) Enhancement of graphics output. Complex data can be reasonably viewed in two dimensions in black and white graphics by appropriate shading and selection of different symbols and representations (solid lines, dashes, dots, etc.). However, when viewing data in three dimensions, with CT data, contours, and isodose distributions simultaneously displayed, the viewer is confronted with a complex problem of visually sorting out the information. We believe that it is necessary to provide three-dimensional information to the therapist and treatment planner. This is particularly important in the case of dynamic treatments where the beam is being shaped in three dimensions to the target volume.

(a) Isodose (isoeffect) contour on CT data and anatomical contours. The capability to concurrently display these three types of data already exist in the PIPLAN Biomed version for a Tektronix 4010. The software needs to be interfaced, however, in a comprehensive way to utilize several devices:

(i) Hard-copy film (color or black and white) through the CCF graphics capabilities. Options here include both 35 mm slides and microfiche.

(ii) Various display terminals in addition to the 4010: 1) the GT-40, which is an eight-intensity, vector, refresh CRT, and 2) a raster-scan, diagnostic-quality, color terminal to utilize color and intensity to clarify the output.

(iii) Color printer, in addition to the life-size Versatec printer already on hand.

(b) Contour manipulation with light-pen. The light-pen capabilities of the GT-40 will be utilized in PIPLAN in two significant ways.

(i) Contour modification of anatomy contours and most particularly the target volume contours. Full contour editing capabilities already exist in PIPLAN through the 4010 cross-hair cursor. Light-pen input would be a more convenient and faster means to replan for cone-downs and modified target volumes.

(ii) The addition of separate dose calculations for several ports with optimized weighting should be controlled easily by the operator with the GT-40 light-pen.

(c) Three-dimensional displays. PIPLAN currently can display any two-dimensional plan, with three types of data, in any orientation with a three-dimensional volume. It can also display isometric or perspective three-dimensional images at any orientation. However, on a Tektronix single-intensity, non-refresh CRT, the image is very difficult

to interpret. A raster-scan color terminal is required for useful, interactive three-dimensional images. CCF graphics capabilities are being explored and may provide clinically useful methods of displaying three-dimensional images and data.

(5) Incorporation of other radiation modalities.

PIPLAN is easily modified to incorporate additional radiation modalities, and many existing physics models can be readily adapted to this end. Most of the problems associated with secondary-producing beams and three-dimensional inhomogeneities have already been solved for pions. While the physics of other modalities differ greatly from those of pions, the required techniques of propagating precalculated and weighted distributions are quite similar. Electron and photon three-dimensional models will be implemented for the calculation of dose in a conventional or combined modality radiation treatment plan. Initially, treatment-planning models appropriate for the clinical machines at the CRTC in Albuquerque will be incorporated. With this capability, every patient could be routinely treatment planned for both pion therapy and conventional therapy, utilizing the best features of both. The comparison of isoeffective curves for each kind of treatment would be a valuable aid to the radiotherapist in the treatment planning process. Neutron and heavy-ion beams are not directly part of this project, but three-dimensional treatment planning for such beams is a potential within the PIPLAN framework. The utility of a three-dimensional conventional radiation treatment-planning code to the medical physics community would be a major contribution of this project.

ii. Improvement of PIPLAN accuracy

(1) Definition and incorporation of secondary muon phase-space; upgrade of muon/electron distribution models. Current models in PIPLAN assign an average momentum dose distribution to muons occurring from pion decay in the last half of the channel. The distribution is obtained from all possible secondary muons that can pass through the channel apertures. However, this distribution does not reflect the changing muon momentum distribution across the radiation field. The difficulties of identifying the secondary muon phase space and proposed solutions are discussed elsewhere. To the extent that such muons cannot be uniquely and fully specified on a particle by particle basis, PIPLAN will model the secondary muon phase space with position-dependent momentum distributions.

PIPLAN currently includes isotropic electron dose from muon decays. Electrons from muon decay average about 35 MeV and consequently have a range on the order of 20 cm and deposit about as much energy as the charged star secondaries and half as much as the neutral star secondaries.

Primary muons usually comprise about 7 percent of the beam and secondary muons usually about 20 percent. The secondary muons have a stopping distribution extending from the surface to a few centimeters beyond the primary muons. The wide stopping distribution arises from forward and backward decays of pions in the third quarter of the channel and nearly all decays in the last quarter of the channel. Specific decay directions leave the muon in specific polarization states, which are largely retained as the muon comes to rest and then decays. The electron dose distribution is in turn determined by this polarization and is not isotropic. Polarization models have been completed and, with the availability of definite secondary-muon

momenta, the PIPLAN secondary electron dose model will be upgraded to be sensitive to the initial muon polarization and secondary electron distributions.

(2) Resolution of differences between monitor chamber and beam measuring systems for absolute dose calculations. By design and method, PIPLAN is an energy-conserving model and predicts absolute dose per incident particle given in the beam-input file. Clinical dose is established by an ionization chamber and quoted as dose per primary monitor-chamber unit. If the ionization chamber response in pion beams is known and if the number and type of particles per monitor-chamber unit is known, then calculation and experiment should agree. The former is known to about 10 percent, but the latter is limited by the fact that the phase-space measuring system does not detect all particles passing through the monitor chamber, with the percentage varying with beam tune. Consequently, calculations and measurements are normalized with different factors for each beam. To the extent that undetected particles lead to uncertainties in the beam phase-space and composition, the point of normalization is also somewhat uncertain. It is partly for this reason that from beam to beam, small adjustments (on the order of 5 percent) in some PIPLAN physical parameters are required to fit measurements for different beams. (Note that required parameter adjustment is also attributable to limitations in various physical models.) Absolute dose is a valuable check on the overall calculational accuracy. To predict dose absolutely without parameter adjustment for different beam tunes and geometries assures accuracy in the dose components and thereby in the effective dose. It also serves to define physical parameters within the experimental uncertainties as a check on experimental design and interpretation. The proposed approach to phase-space definition is discussed elsewhere. However, it is not expected that the measured phase space will be sufficient in itself to allow absolute dose calculation without some additional upgrades in PIPLAN or in a preprocessor program to simulate undetected particles in the beam-input file.

(3) Incorporation of neutron LET distributions as a function of distance from source. To accurately model effective dose, it is necessary to account for the changing neutron spectrum as a function of distance from a pion star. PIPLAN currently uses an average neutron LET. This is adequate in the center of large target volumes, but questionable in certain geometries. For example, the effective neutron dose to the spinal cord from a concave target-volume shaped around the spine is much different from that of the physical neutron dose or the effective neutron dose from nearby planar or convex target volumes. The PIPLAN neutron dose model will be upgraded to reflect changing LET as a function of changing neutron spectrum.

(4) Upgrade of multiple scattering models for treatment appliances and rapidly changing tissue gradients. PIPLAN uses a recursive multiple-scattering model which is sensitive to inhomogeneities and large air-gaps associated with clinical appliances. Measured, central-axis, depth-dose curves of modulated and collimated beams show a 10 to 15 percent entrance-dose enhancement relative to calculations. This enhancement varies with collimator opening. Preliminary experiments were unable to resolve the nature of the elevated plateau. Neutrons from pion stars in cerrobend and electrons from muon decay just under the collimator are believed to be the principal causes. As discussed above, the electron dose model needs momentum (and polarization) specification of secondary muons for completion. A new neutron model for cerrobend was added to PIPLAN to elevate the calculated entrance dose. A clinically acceptable total dose calculation is obtained, but the parameter

values appear to be unrealistic. To accurately represent the entrance effective dose, both near collimator edges and on the central axis, with a large probable neutron component, all the components of this entrance dose must be established. This will require further experimental measurements, specialized calculations, and further modification of PIPLAN models

An optional calculational capability will be added to PIPLAN to divide the original trajectory into subtrajectories dependent upon scattering in external appliances and to propagate the weighted subtrajectories through the patient. It is proposed that the same approach be used, as an optional calculational capability, for neutron and electron secondaries arising in the patient, with the inhomogeneities given by CT data (to distinguish normal soft tissue from carbon-rich fat and calcium-rich bone). Normally, this refined calculation and associated increased computer time will not be necessary. However, it could be quite important in the vicinity of critical organs, such as the eyes near sinus cavities or the spinal cord surrounded by bone next to lung.

iii. Improvement of PIPLAN efficiency

(1) Conversion to a VAX computer. The conversion of the CCF version of PIPLAN, where the calculations are currently performed, to a VAX computer has several benefits:

(a) Decreased calculation expense by eliminating the costs associated with the CDC-7600 computers. If the VAX is one of the VAX computers for the Meson Physics Facility, there may be some charge-back to this project, but this would be a much smaller cost than CCF. A VAX at Biomed would eliminate these charges, as well as improve efficiency of data flow, compared to the use of magnetic tapes or intercomputer links to transmit data between computers.

(b) The large, virtual memory available with the VAX operating system (VMS) is of particular benefit to the dose calculation, where fine resolution of the patient anatomy and external appliances is necessary for accuracy.

(c) Again, the large memory allows separate accumulation of stopping distributions and dose components throughout the volume of interest. This is a prerequisite for some of the physics upgrades.

(d) The stable operating system (vendor supported) and large memory of VMS allow development to be concentrated on treatment-planning capabilities, rather than on coping with changing systems and limited memory of CCF.

(e) The extensive graphics capabilities of the CCF will still be available on the VAX. The LANL computer networks and distributed-processor capabilities provide convenient access to microfilm and microfiche output.

(f) Both treatment-control files generated as part of the dose calculation and treatment-delivery files can be transported directly between the Biomed control computer and the VAX with minimum software development.

(2) Incorporation of code enhancements for increased speed, interactive operation, and addition of new modules.

(a) Conversion of interactive programs to run in both batch and interactive modes. This will many times free the operator for other activities, balance computer loads, and enhance flexibility of personnel scheduling.

(b) Conversion of batch programs to run in both interactive and batch modes. For time-sensitive processing, the user can observe the progress of the program and change the course of processing to get the most useful results in the shortest time.

(c) Conversion of other selected programs to run in both batch and interactive mode. PIPLAN routines are currently separated into system-independent and system-dependent libraries. The former are exclusively transportable FORTRAN routines. The latter are exclusively input/output related. Greater efficiency and through-put will be attained by coding system-dependent routines in machine language. A gain in speed by a factor of two has been attained in some areas.

(d) Increased capacity for anatomical contours. PIPLAN currently provides for about 3000 coordinate points (x, y pairs) in up to 30 slices. In some cases this significantly limits contour resolution.

(e) Increased modularity. With PIPLAN's command structure it is extremely easy to add new capabilities, except that computer memory limitations make very large programs impossible, even with extensive overlays. PIPLAN modules are currently being reconfigured so that new programs can be quickly generated with the same ease that new commands were previously added.

d. Treatment delivery and verification

i. Implementation of dynamic treatment with fan tunes.

Dynamic treatments using fan tunes in which patients are scanned one-dimensionally through the narrow region of a beam focused in one dimension provide additional beam shaping (shaping in two dimensions) over that obtained using broad parallel beams (shaping in one dimension), thus gaining increased sparing of normal tissues. This treatment mode will be fully implemented so that it can be routinely used in those cases where it has a clear advantage. Treatment planning comparisons will be performed between static and "fan" dynamic treatments to determine those situations where dynamic treatments are preferred.

ii. Development of dynamic treatment capability with "spot" tunes. Dynamic treatment using "spot" tunes involves scanning a patient in two dimensions under a beam focused in two dimensions and thus allowing for beam shaping in three dimensions. This is believed to be the only method whereby pion therapy can be fully optimized by sparing the maximum amount of normal tissue. This effort requires: (1) fully characterizing spot tunes for three penetrations, (2) developing range-modulation functions for these beams; (3) performing biologic confirmation of the uniformity of the effective dose for the range-modulated spot tunes, (4) performing dosimetric and biological studies in phantoms to confirm absorbed dose and effective dose distributions for simulated treatments, and (5) implementing treatments.

iii. Refinement of in vivo dosimetry techniques. Several systems have been developed at LAMPF for in vivo dosimetry, including intracavitary ionization chambers and TLD for total dose, and aluminum activation and silicon detectors for high-LET dose. The precision and accuracy of these systems will be improved. Systems such as TLD 700 which have potential for use as both low and high-LET dosimeters will be investigated.

iv. Study of visualization of stopping pions by positron emission imaging. Study of visualization of the stopping pion distribution in patients will be continued by means of imaging the positrons emitted by radioactive nuclei produced as a result of pion capture. Patients are taken directly from the treatment room to a counting area where a simple positron camera utilizing four NaI crystals is used to scan the treatment volume. The activity in the treatment volume is anticipated to be approximately 50 mCi. Construction of a positron emission scanner is not proposed, nor will this be a major research effort. This preliminary study is necessary to gather information concerning positron visualization of stopping pions so that future pion facilities can be advised about the necessity for and usefulness of this technique.

e. Systems operation, development and maintenance

i. Channel control systems. A group of engineers, technicians, programmers and computer operators is needed to provide maintenance and repair capability, and ensure the development of hardware and software for improvement of channel reliability, efficiency, and dose characteristics for patient treatments.

Hardware support in the form of repair, maintenance, preventive maintenance, and improvement will be provided for the following:

- (1) Target (TV monitor, controllers, interlocks, etc.)
- (2) Channel magnets (bus bars, water lines, thermal and flow switches, radiation levels, etc.)
- (3) Channel helium (pressure, bubblers, supply)
- (4) Slits and wedges (operational checks, controllers and suppliers, DVM's)
- (5) Multiwire proportional counters (gas delivery systems, cabling, encoders)
- (6) Monitor chamber (gas flow system, chamber integrity).

ii. Computer systems. Current treatment planning with PIPLAN requires the Laboratory Central Computing Facility and a substantial charge is made for computing time. A dedicated VAX at the Biomedical Facility would be more convenient and eventually provide savings exceeding its cost. The exchange of the PDP-11/45 and VAX would require considerable staff support.

It appears to be desirable to change operating systems to a more current DEC-supported operating system which provides for increased data-base capability, more efficient large-code execution, and better system management features. This will be accomplished with assistance from outside software specialists.

CAMAC and control circuitry will be further streamlined to improve module performance.

iii. Treatment delivery systems. Installation and testing of the new range-shifter (mechanical components, hydraulic system, calibration, electronics, and alarms) will be completed.

Dynamic treatment hardware and software currently exist, but improvements can be made in terms of application to routine daily treatment. Upgrading, maintenance, and repair will be performed for the treatment couch system (encoders, controls, interlocks, and mechanical components). A collimator handling system and a motorized laser positioning system will be designed and installed in the treatment set-up area.

Several systems have been designed using various materials for fabricating patient boluses. Currently, boluses are being made from 9 mm thick sections of Lucite by tracing onto the Lucite the bolus outline for each CT slice, then cutting out the bolus on a band saw. The sections are then glued together, referencing each CT slice to a common coordinate axis, to construct the three-dimensional bolus. While this method produces a fairly good product, it is subject to error, is somewhat hazardous, and produces a fine Lucite dust requiring the technician to wear a face mask. Automation of this procedure is proposed through acquisition of a used automatic milling machine operating from paper tape or magnetic tape, or by designing a micro-processor controlled system, whereby a block of Lucite is cut into a three-dimensional bolus.

Limited availability of the pion beam and the segmenting of beam time into cycles make it imperative that all patient work-up and treatment procedures be highly efficient so that a maximum number of patients can be treated. This efficiency, however, must be in keeping with a high standard of quality, precision, and accuracy. This work is, of necessity, an on-going program and by its nature requires that all systems be in a process of evolution. Because of the research nature of the project and our commitment to optimization of pion therapy, no procedure is considered to be perfect, and all are subject to improvement.

A continuing effort to improve casting and immobilization techniques is necessary to fully exploit the three-dimensional dose-shaping capabilities of pions. Methods developed for the pion project will be implemented at the CRTC because high-precision x-ray therapy dictates that casting and immobilization be just as highly developed as for charged particle beams.

6. Anticipated Results

The anticipated results of the total physics effort are:

- a. Development of technology necessary to safely and efficiently deliver pion therapy.
- b. Development of technology, methods, and procedures for treatment planning, patient set-up and treatment, and verification of treatment, so that pion therapy is highly optimized, accurate, and reproducible.

c. Development of dosimetry and RBE models so that the statement of both absorbed and effective dose is accurate and meaningful

d. Development of the complete system of integrated components so that patient through-put is maximized. Concurrent with this, quality control systems will be developed to ensure that quality is not sacrificed for quantity.

7. Significance

Highly optimized pion therapy holds the promise of significant improvement in the local control of certain large tumors without corresponding increases in morbidity.

This project is conducting the necessary investigations to determine whether pions may fulfill their promise and whether they should be added to the armamentarium against cancer.

The success of pion therapy depends, in a large measure, on a highly concentrated and sustained effort in basic physics and technology. If this effort is not performed, pion therapy will not be given the fair trial that it deserves.

8. Facilities Available

The Pion Biomedical Facility has the following facilities (see also Section II):

- a. Pion transport channel (vertical beam).
- b. PDP-11/45 and 11/70 computers and an array of peripheral devices (terminals, CRT displays, printers, microprocessors, CAMAC Modules, etc.).
- c. Electronics shop and medical physics laboratory.
- d. Office facilities for research and administrative staff.
- e. EMI 7070 whole body scanner.
- f. Philips Medio 5500 simulator
- g. GE 300 kVp Maxitron x-ray unit.
- h. Equipment for physics dosimetry, microdosimetry, in vivo dosimetry, visualization, and treatment planning

In addition, the numerous shops, laboratories, and resources of LANL are available to the project.

9. Collaborative Arrangements

Dr. Smith is the principal investigator and chairman of the American Association of Physicists in Medicine (AAPM) Charged Particle Beam Dosimetry Task Group. This task group is composed of physicists from charged particle therapy projects in the United States, Canada, Europe, and Japan. The group is involved in dosimetry intercomparison among the charged particle therapy projects.

Funds have been requested in this proposal to bring experts in calorimetry from the National Bureau of Standards and the University of California/ Los Angeles to Los Alamos to perform measurements on the pion therapy beams. We have worked closely with these individuals, and they have performed preliminary measurements here in the past.

Treatment planning, dosimetry and microdosimetry comparisons with other high-LET projects are pending approval under a separate contract from the NCI.

C. Biology1. Investigators

<u>Name</u>	<u>Title</u>	
Mudundi R. Raju, D. Sc.	Fellow	LANL
A.J. van der Kogel, Ph.D.	Visiting Research Scholar	UNM
N. Tokita, M.D., Ph.D.	Staff Member	LANL
William C. Black, M.D.	Chief, Oncologic Pathology	UNM
Mario Kornfeld, M.D.	Neuropathologist	UNM
Robert E. Anderson, M.D.	Pathologist (Chairman, Pathology Dept. . SOM)	UNM
Scott Jordan, M.D.	Pathologist	UNM
Charles R. Key, M.D., Ph.D.	Pathologist	UNM

2. Introductiona. Objectives. The objectives of this program component are:

i. To provide biological dosimetry using cultured cells to verify whether the range-shifter functions used to spread Bragg peaks are optimal for therapy in producing uniform cell-killing and to measure RBE as a function of peak width.

ii. To measure RBE of pion beams for cell mutagenesis and transformation.

iii. To measure relative biological effectiveness of fractionated doses of pion beams for acute effects (mouse skin, mouse gut) and late effects (rat cervical spinal cord, kidney, and colon and mouse lung and lens).

iv. To estimate carcinogenic potential of pion beams from tumor induction in animals exposed to pions for late effects studies.

v. To study RBE of pions on well differentiated and poorly differentiated rodent tumors in comparison to RBE for normal tissues to determine whether there is a correlation between tumor differentiation and tumor response, and whether such correlation might extend to the clinical situation.

b. Background

Clinical and radiobiological studies using pion beams began simultaneously. However, because of earlier dose rate limitations, only limited data on the radiobiology of clinically relevant beams are available to date.

Previously obtained results in pion radiobiology were interpreted as indicating that small amounts of high-LET radiation can eradicate the large shoulder of the cell survival curve. This conclusion was based on results of studies performed by Yuhas and associates with assays of killing of plated single cells and growth delay of multicellular tumor spheroids (MTS) as outlined in the progress report below. These results indicated that pion irradiation differed from x-irradiation only in a reduction in the shoulder region of the

C.

cell survival curve. The slope of the log portion of the x-ray control and pion curves was identical for multiple cell lines. It was postulated that this effect was due to inhibition of repair of sublethal injury by the high-LET component of the beam, and subsequent data from experiments with growth delay in MTS in which conditioning doses of pions were followed by x-rays were felt to substantiate this. On the basis of such studies, it was hypothesized that a minimal "threshold" amount of high-LET contribution to the total dose would result in such inhibition of sublethal repair of injury caused by the remaining low-LET component of the beam, and that the biological effect of the pion beam, at least in beams of clinically relevant dimensions, was not so much dependent upon the ratio of high-to-low-LET components of individual treatment beams as on the presence of this threshold amount of high-LET dose.¹²⁰ A specific experiment designed to test this hypothesis entailed irradiation of MTS at proximal, middle and distal portions of range-modulated peaks (8, 11, and 14 cm) for a collimated 10 x 10 cm field, with subsequent measurement of growth delay. The results showed no detectable differences in biological effectiveness either within individual modulated peaks or between peaks of varying size.

On the other hand, data presented by Skarsgard¹²¹ based on the gel-tube suspension method as employed at TRIUMF suggested a small but reproducible increase in RBE for clinically relevant field sizes between the proximal and distal portions of the range-modulated peak and an increased RBE for small as compared to large peaks. These data have been reproduced in the data generated in September and October 1980 by Raju and associates at LAMPF and reported below.

The apparent discrepancy in results and interpretation may be related to one or more of several factors. The use of plated cells or MTS by Yuhas and his associates probably does not allow the same degree of precision in determining the biological characteristics of the peak region as does the gel-tube system used by Skarsgard and Raju because the former systems provide many fewer data points and much less structure in the curves. Data presented in the detailed progress report below suggest that re-interpretation and clarification of these results are necessary. In addition, because of dose rate limitations, normal tissue radiobiology was done using a very narrow Bragg peak rather than the widely modulated Bragg peaks used in therapy. Thus, the pion radiobiology program as relevant to the clinical program must be re-evaluated in terms of basic assumptions and appropriate experimental design. This re-evaluation will be based upon application of well documented techniques of assessment of cell survival in cultured cells,^{122,123} acute injury to mouse intestinal mucosa¹²⁴ and foot skin,¹²⁵ and late injury to the spinal cord, kidney, colon, rectum, lens and lung. Systems have also been developed for quantitative histological evaluation of late damage in kidney by Jordan *et al.*^{126,127} and lower intestinal tract by Black *et al.*¹⁴

c. Rationale. The radiation quality of pion beams varies depending upon depth at penetration, field size, and width of the range-modulated Bragg peak. Since these parameters vary widely in different therapeutic applications, it is necessary to define radiobiological characteristics of pion beams used for radiotherapy as a function of beam dimension. Such characterization will be made using cultured cells and assessing acute effects on mouse skin and gut. In addition, late effects on various dose-limiting normal tissues and the effects of a pion beam of 6-cm width on rodent tumors will be assayed.

d. Progress report. The studies performed by Yuhas et al. were reported earlier¹²⁰.

i. In 1980, collaborative efforts were undertaken with Dr. Mudundi Raju, of the Life Sciences Division of Los Alamos National Laboratory, to perform detailed studies of the biological characteristics of the beams used in clinical applications.

(1) In vitro studies

(a) Gel-tube suspension system. The more sensitive gel-tube suspension system, in which single cells suspended in a medium containing gel are irradiated and cell-killing is assayed by colony formation, has recently been employed by Raju et al. (with support primarily from NCI Grant No. 5 R01 CA 17290, Comparative Studies of Heavy Particles in Radiotherapy). The following questions were addressed:

(i) Are the range-shifter functions optimal for therapy in terms of producing uniform cell-killing across the range-modulated peak for various beam tunes?

(ii) Are there differences in RBE among beams of different peak widths of a given beam size?

(iii) Are there differences in RBE among pion beams of different sizes but of a given peak width?

Since the differences in biological effects among various pion beams are not expected to be large and many treatment beams must be studied, the biological system employed should be highly reproducible and capable of giving extensive data for a given experimental period. For that reason the gel system^{122,123} developed by Skarsgard¹²¹ was selected for these studies.

Cultured hamster cells (V79) were suspended in tissue culture medium containing gelatin and kept in plastic tubes. Several tubes were exposed to graded doses of pions by keeping the tubes immersed in a water phantom oriented in the beam direction. After exposure, the gel was pushed out of the tubes and sliced into 3 mm slices; each slice was transferred into a petri dish and viability of cells in each slice was assayed by colony formation.

Figure 53 shows depth dose distribution of a pion beam (Tune 16B) of 14 cm peak width and the corresponding cell survival as a function of depth for doses of 200, 400, and 600 rad at the proximal peak (at a depth of 1.5 cm). The data clearly show that cell-killing across the peak is uniform. The cell survival data were obtained for doses of 100-700 rad in 100-rad steps, and only three doses were shown for clarity. Cell survival as a function of dose at any depth can be obtained from these data, thereby providing extensive information for this beam tune. Figure 54 shows cell survival curves for the Tune 16B, 14-cm peak width, at the proximal, mid, and distal positions of the peak and for 300 kVp x-rays. As one would expect from physical considerations, the distal peak position is more biologically effective than is the proximal peak position.

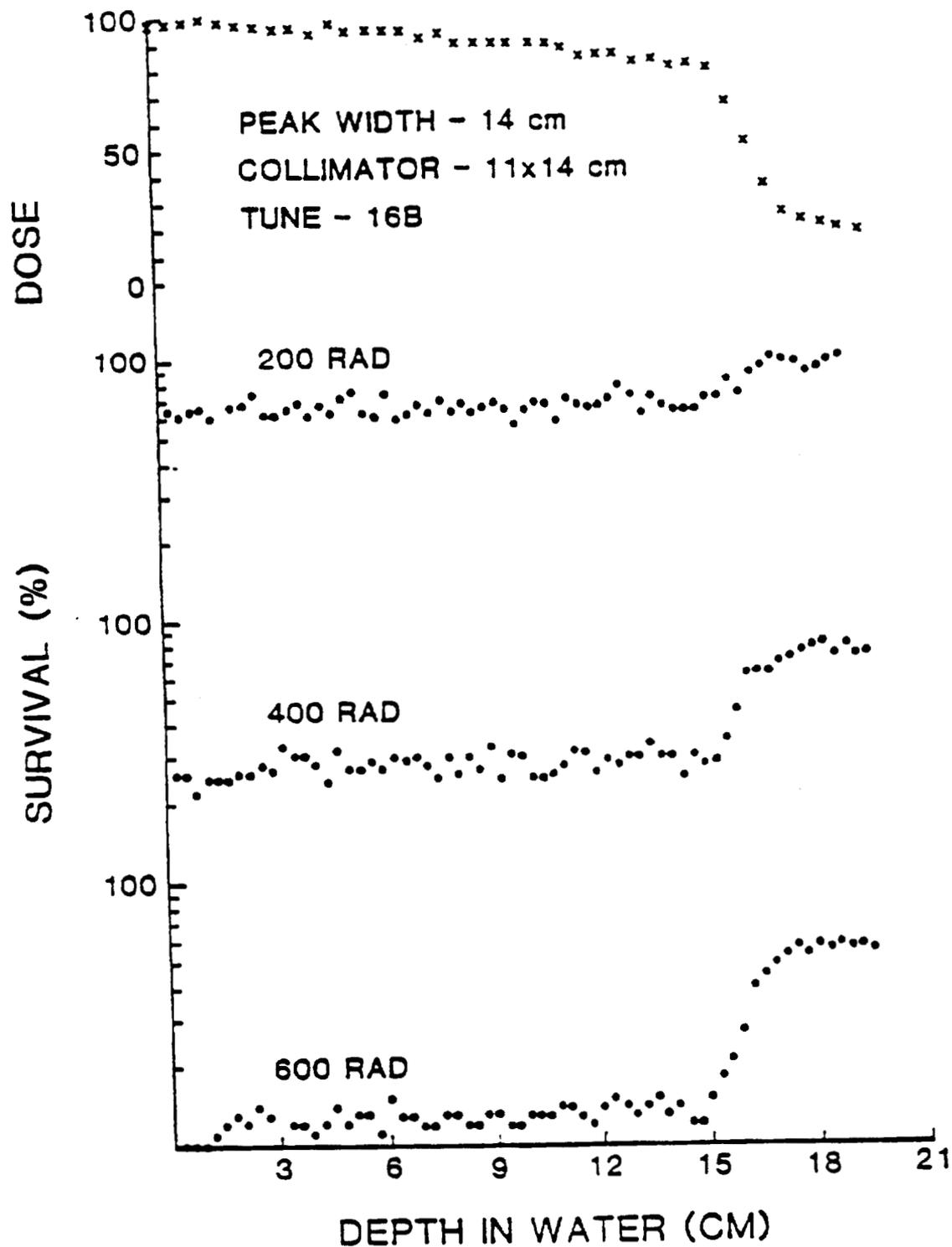


Figure 53. Dose distribution and cell survival as a function of dose and depth, Tune 16B, 14-cm peak

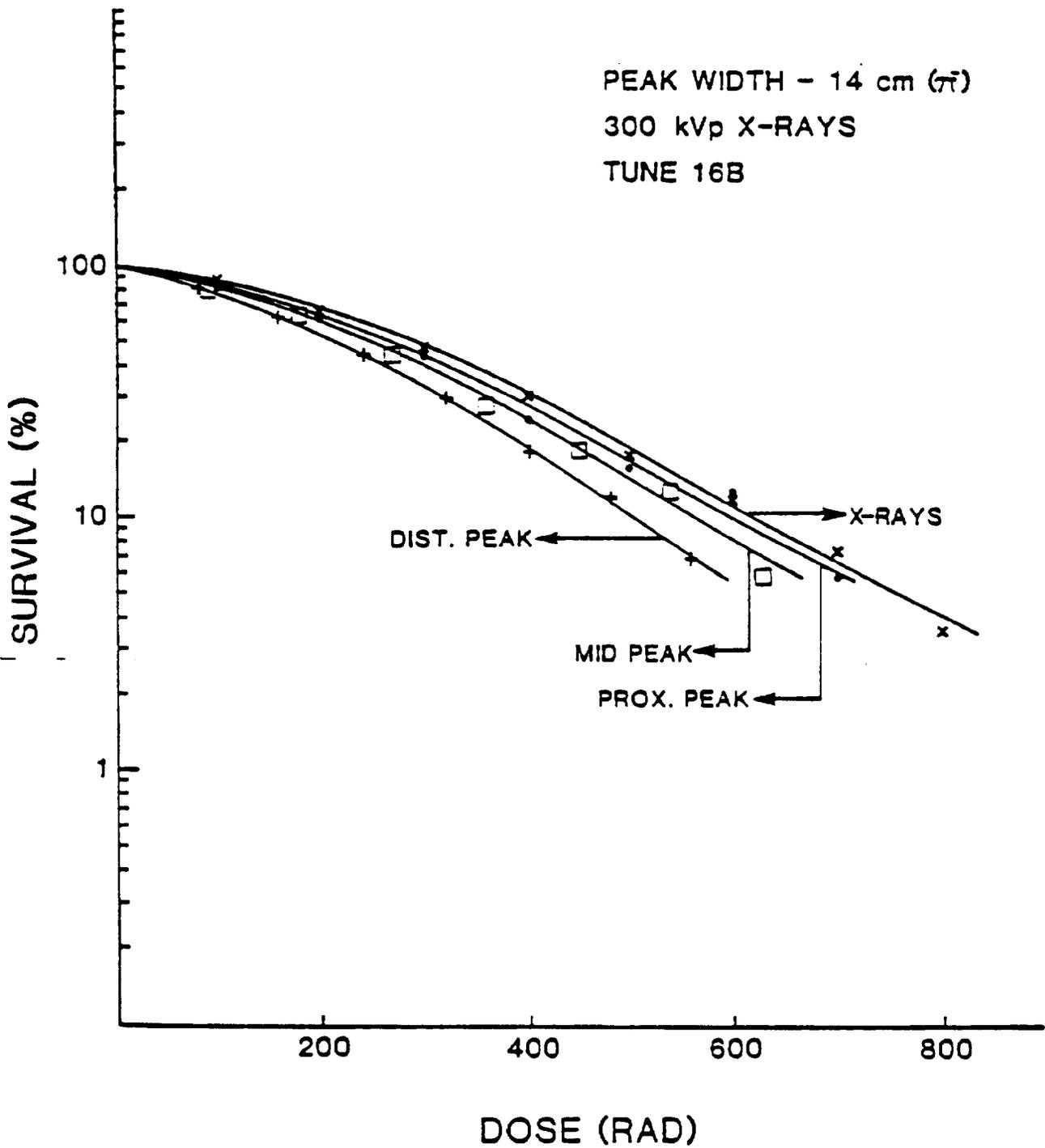


Figure 54. Cell survival curves for proximal, mid, and distal positions of pion beam (Tune 16B, 14-cm peak) versus x-rays

The cell-killing profile at peak center of the 14-cm peak of Tune 16B and the dose distribution of a collimated pion beam (perpendicular to the beam direction) are shown in Figure 55.

Figure 56 shows the data for Tune 16B, 6-cm peak width. These data suggest that the dose at the distal side of the peak needs to be slightly reduced to produce uniform cell killing.

Figure 57 shows the data for Tune 16B, 10-cm peak width, for different size collimators. The symbols (\cdot , $+$) in cell survival data correspond to two separate experiments, and the data show good reproducibility. Also, when a small collimator (7 x 7 cm) is used, the dose contributed by the secondaries produced in the collimator can be clearly seen; this is also reflected in increased cell-killing.

Figures 58, 59, and 60 show cell survival curves for pion beams (Tune 16B) of peak widths 6, 10, and 14 cm at proximal, mid, and distal peak positions, respectively. The data for these curves are derived from cell survival data with depth of penetration shown in Figures 53, 56, and 57. In all these positions of the peak, the effectiveness decreases with increasing peak width.

Figure 61 shows the data for Tune 12B, 10-cm peak width. These data suggest that the dose at the distal end should be slightly increased for obtaining uniform cell-killing.

Figure 62 shows the data for Tune 23B, 10-cm peak width. These data suggest that the dose at the distal end should be slightly decreased for obtaining uniform cell-killing.

The radiation quality of pion beams may depend on beam size, although the peak width is kept the same because of the contribution of neutrons from pion stars. The data shown in Figure 57 do not indicate significant differences in cell-killing with variable collimator size when the peak width is kept the same. Figure 63 shows survival curves utilizing the data of Figure 57, indicating no significant differences between pion beams of sizes 7 x 7 cm and 14 x 17 cm. Preliminary experiments have been done using fractionated doses of pions on the mouse intestinal crypt cell system to see if the biological effects of fractionated pion exposures depend upon beam size when peak width is kept the same. The results show that the large beam is slightly more effective than the small beam.

Cell-killing data for various beam tunes and peak widths have been modeled and programmed in a computerized data base by A.R. Smith and his associates so that the data can be used in the design of range-shifter functions and in treatment planning system modifications.

(2) In vivo studies

(a) Tumor. Mice bearing the MCa-11 mammary tumor were exposed to graded total doses of high-intensity peak pions or x-rays either as single fractions or as three daily fractions. The data are not sufficient to determine whether the single dose curves are parallel, but it is readily apparent that pions are 1.2-1.4 times more effective than x-rays

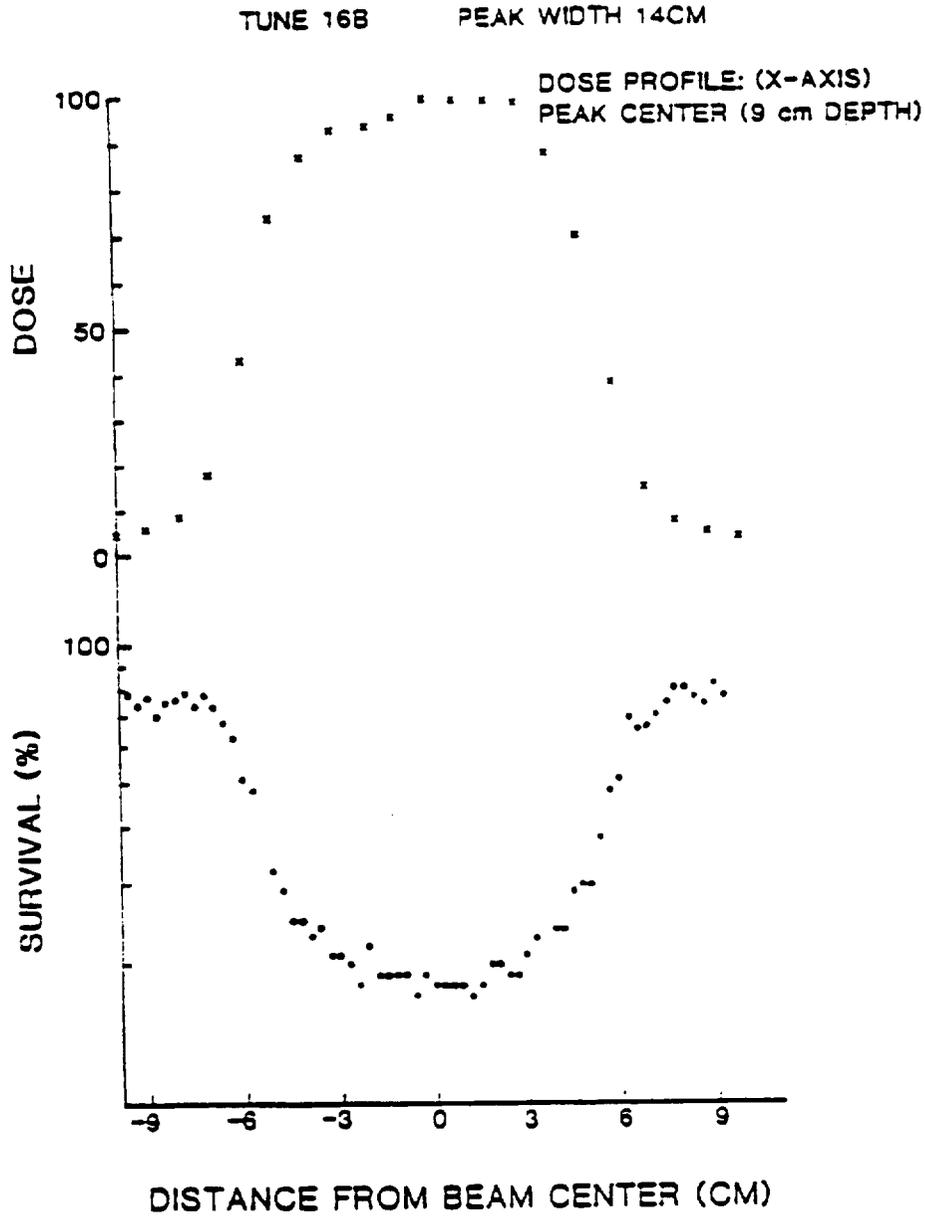


Figure 55. Central-axis dose profile and cell-killing at peak center of collimated pion beam (Tune 16B, 14-cm peak)

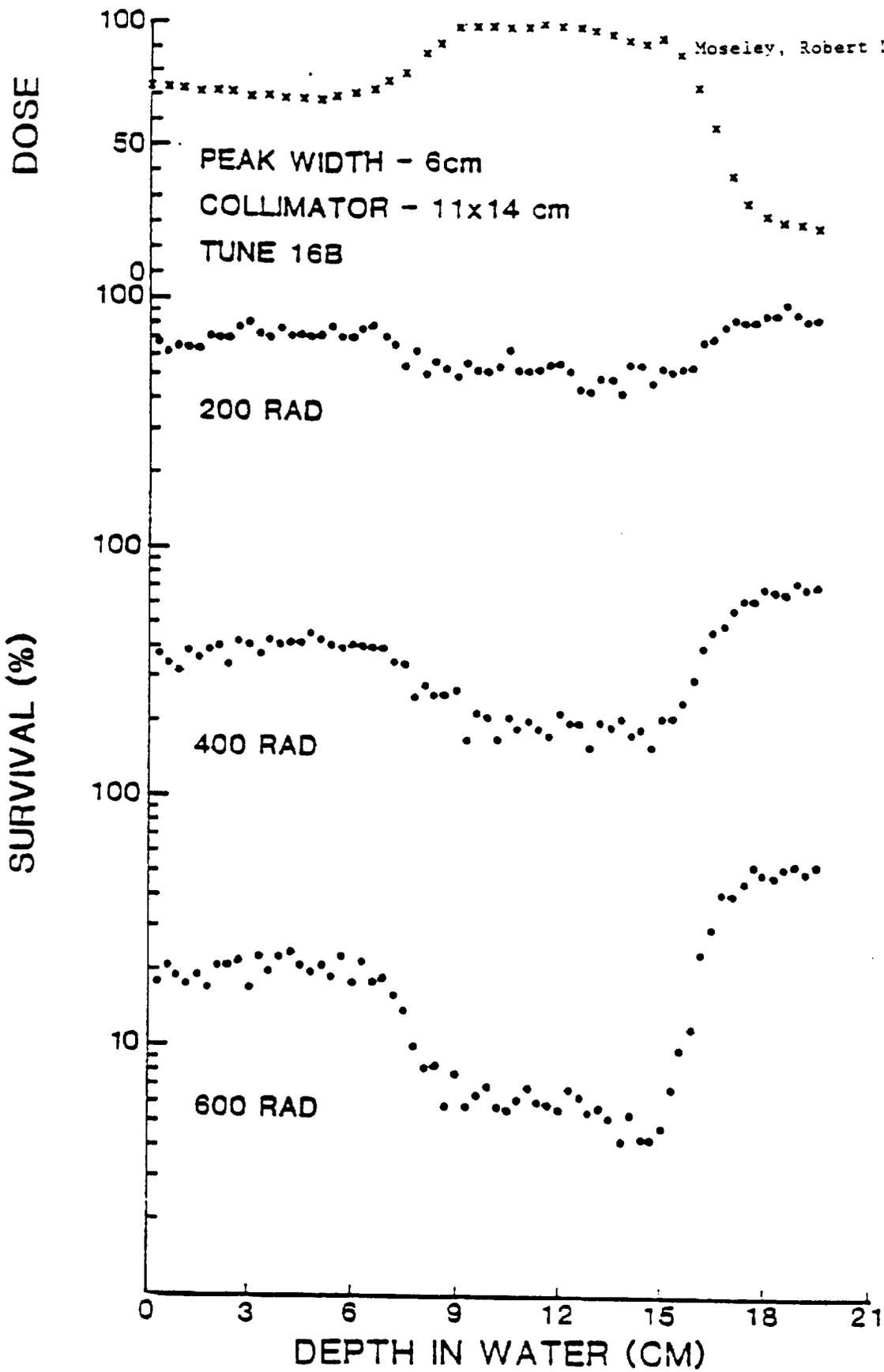


Figure 56. Dose distribution and cell survival as a function of dose and depth, Tune 16B, 6-cm peak

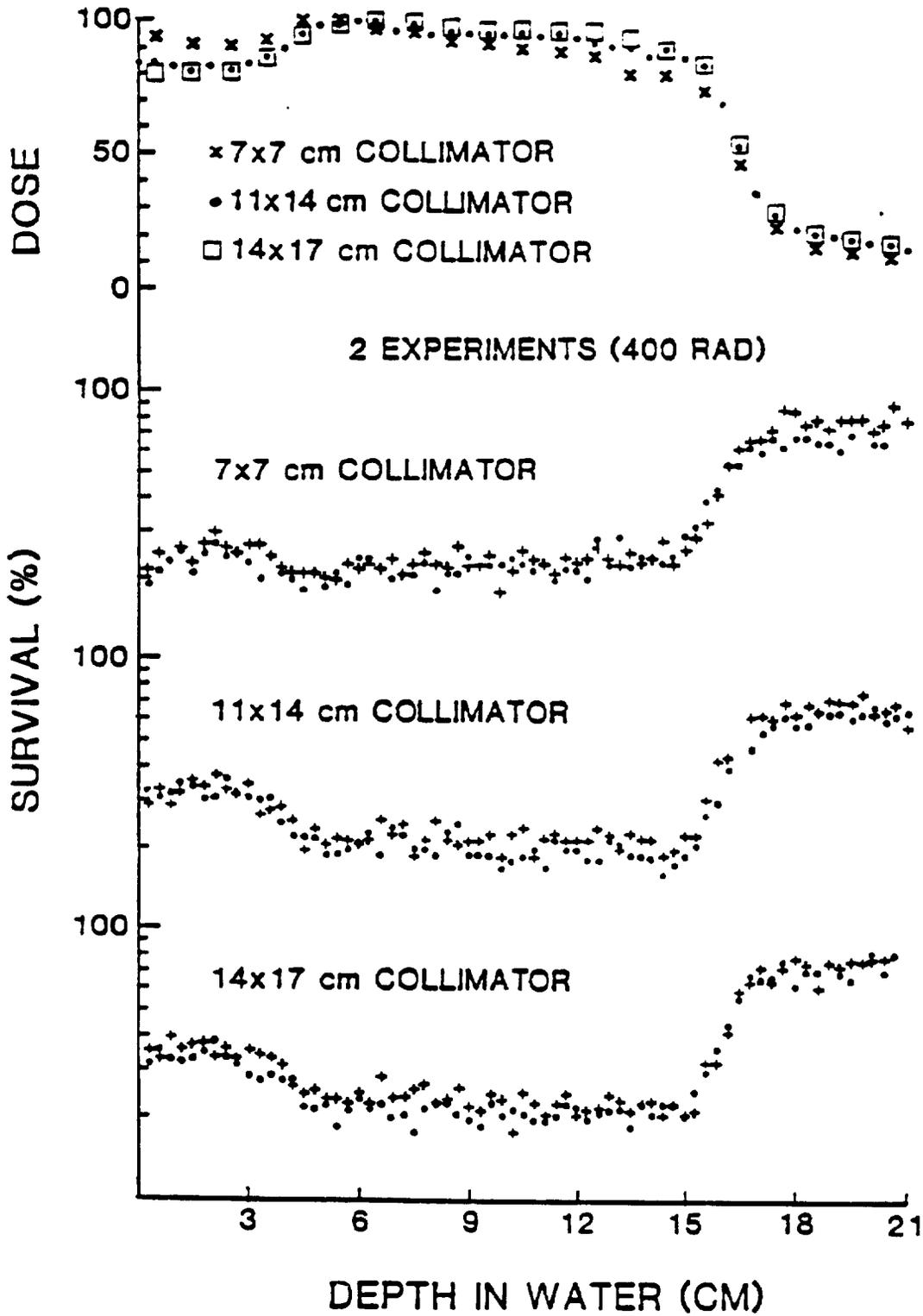


Figure 57. Dose distribution and cell-killing as a function of depth and collimation, Tunc 16B, 10-cm peak

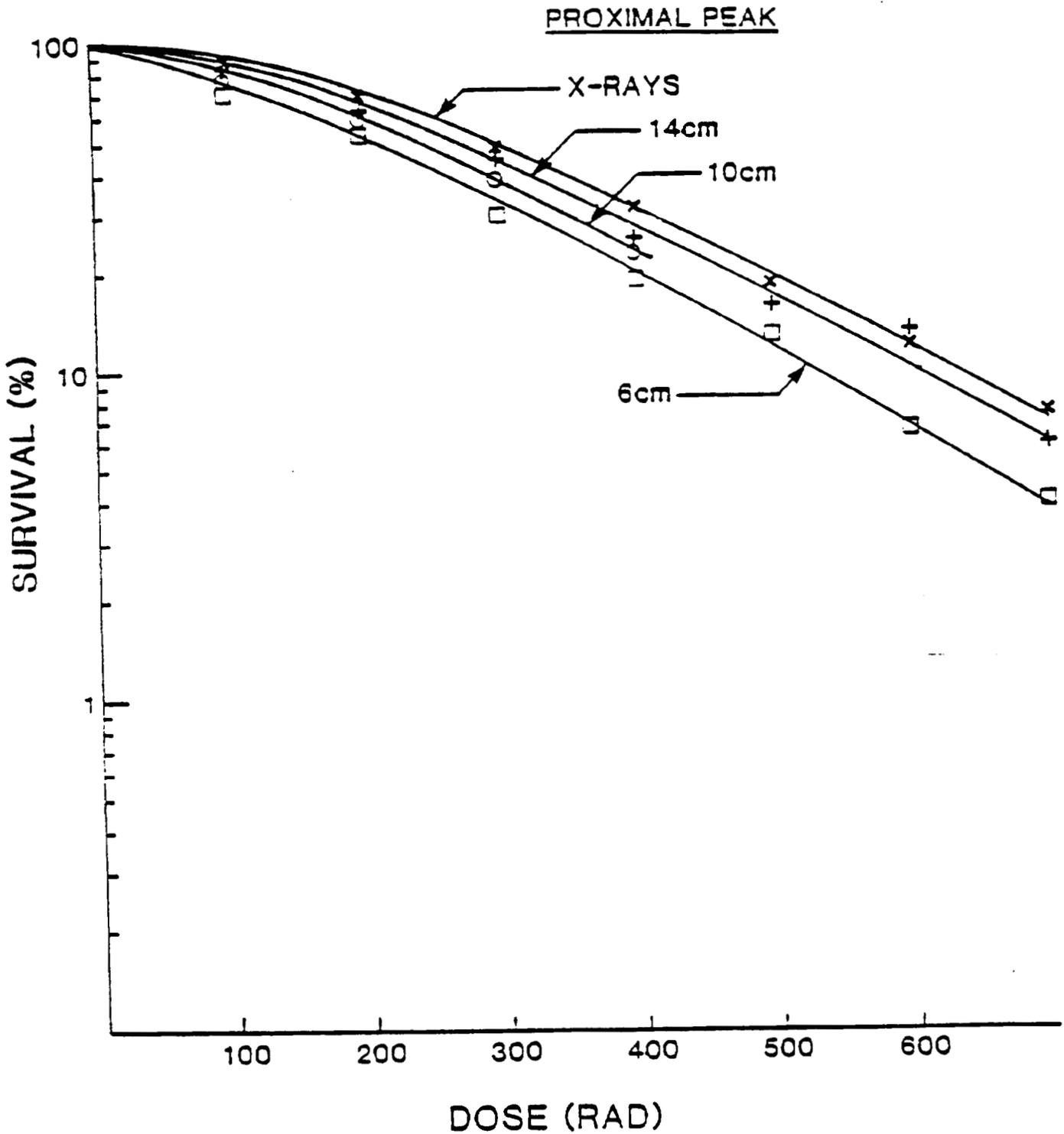


Figure 58. Cell survival curves for proximal position of 6-, 10-, and 14-cm pion peaks (Tune 16B) versus x-rays

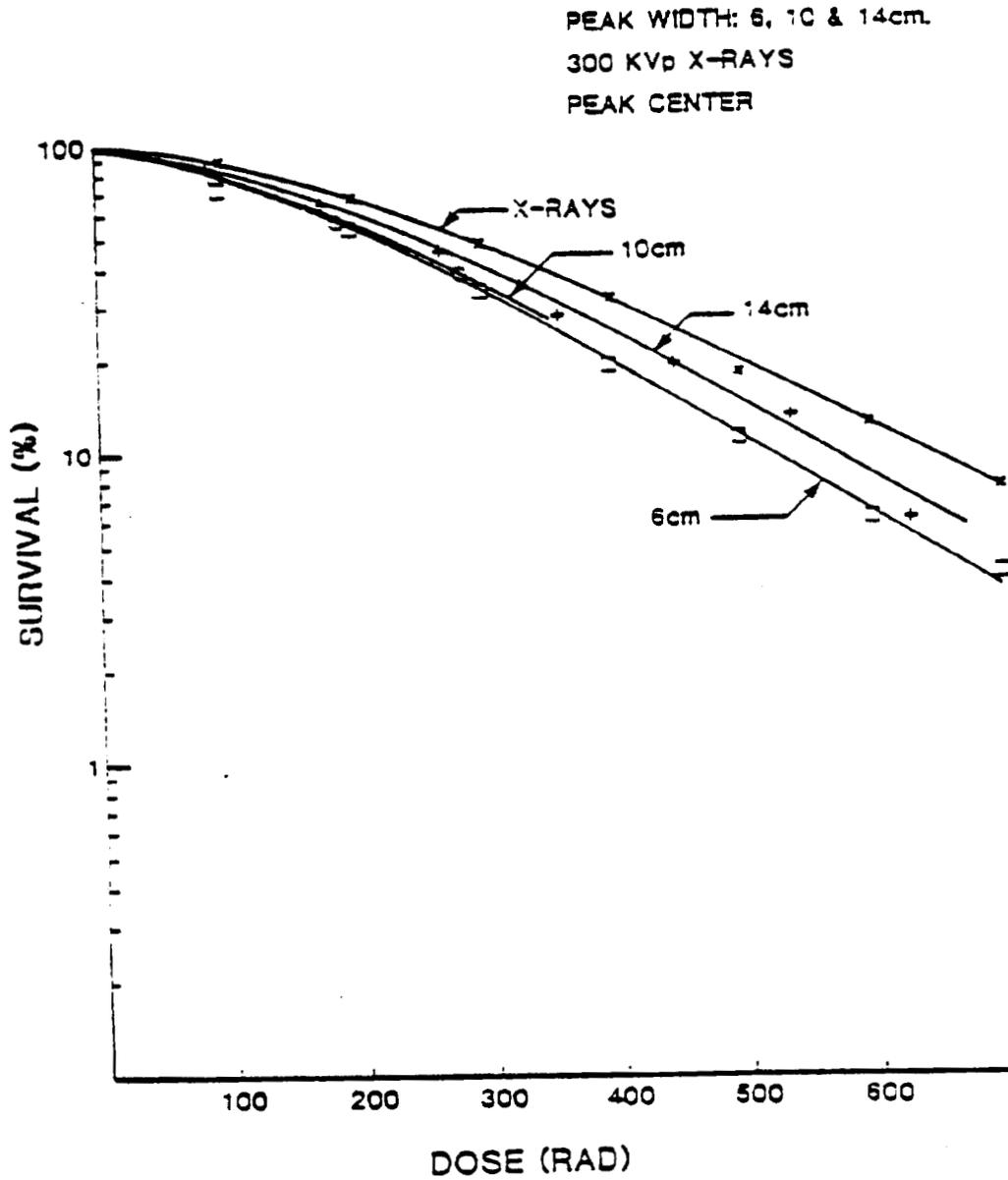


Figure 59. Cell survival curves for center position of 6-, 10-, and 14-cm pion peaks (Tune 16B) versus x-rays

PEAK WIDTH: 6, 10 & 14cm.

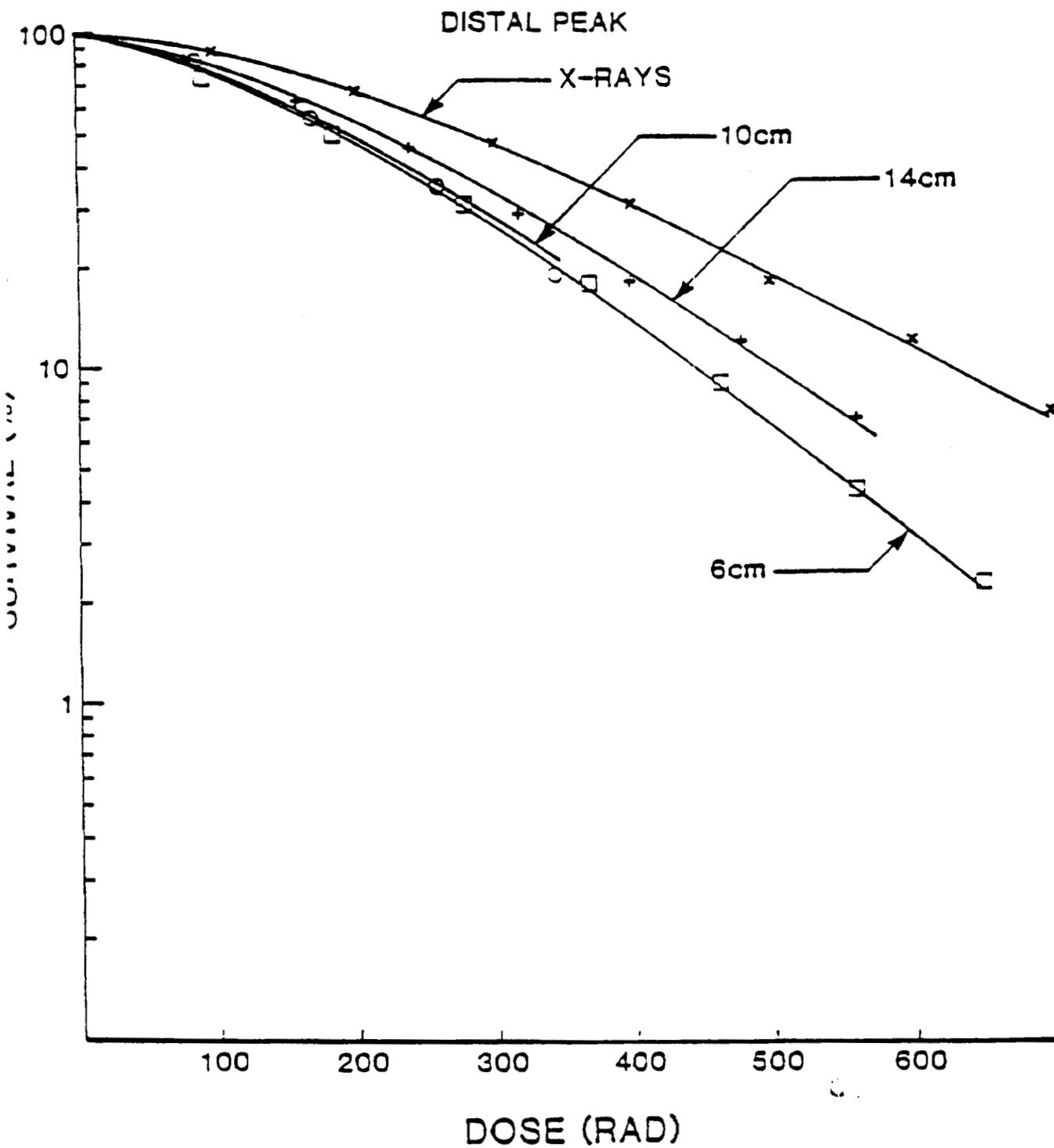


Figure 60. Cell survival curves for distal position of 6-, 10- and 14-cm peaks (Tune 16B) versus x-rays

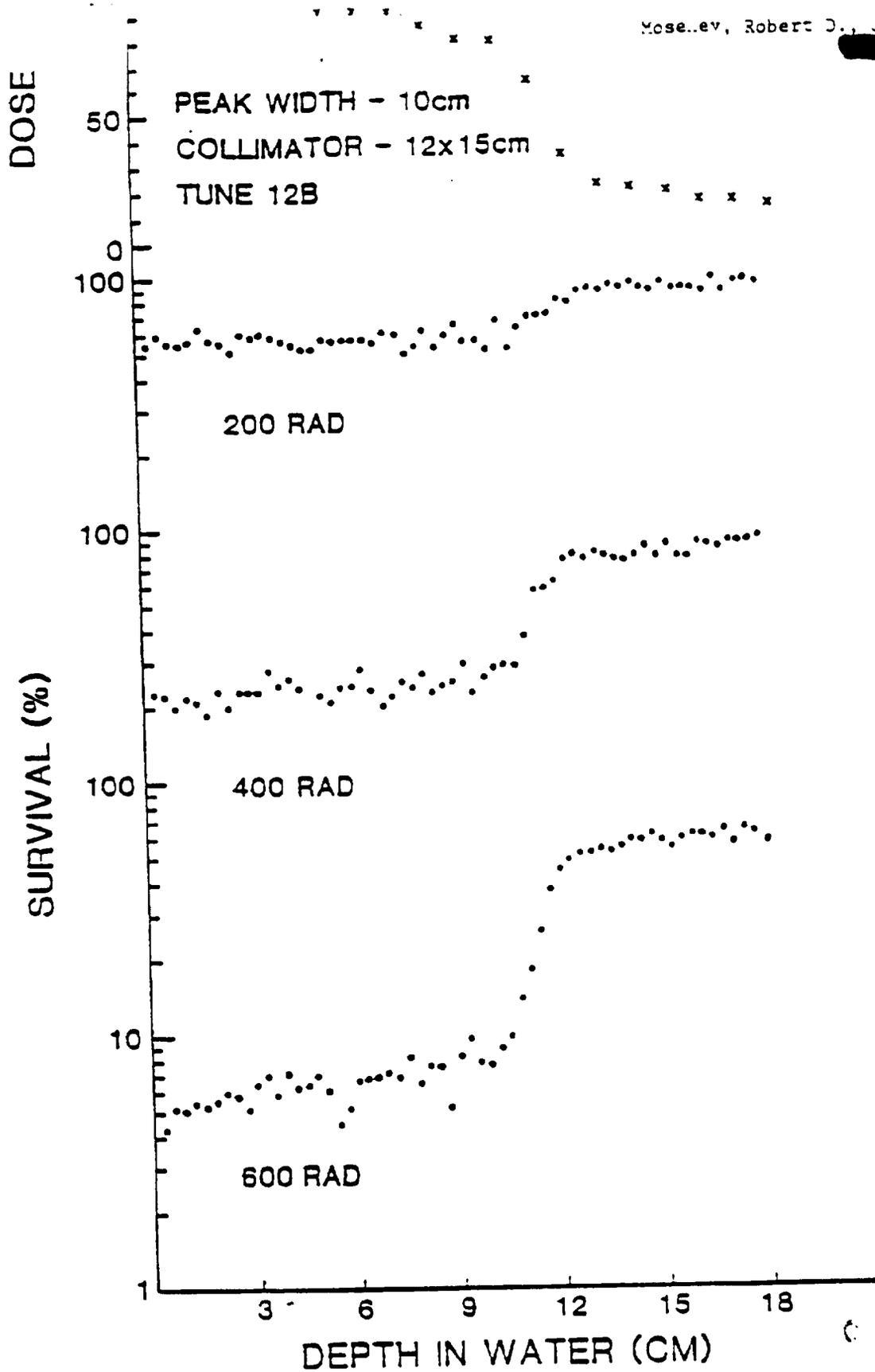


Figure 61. Dose distribution and cell survival as a function of dose and depth, Tune 12B. 10-cm peak

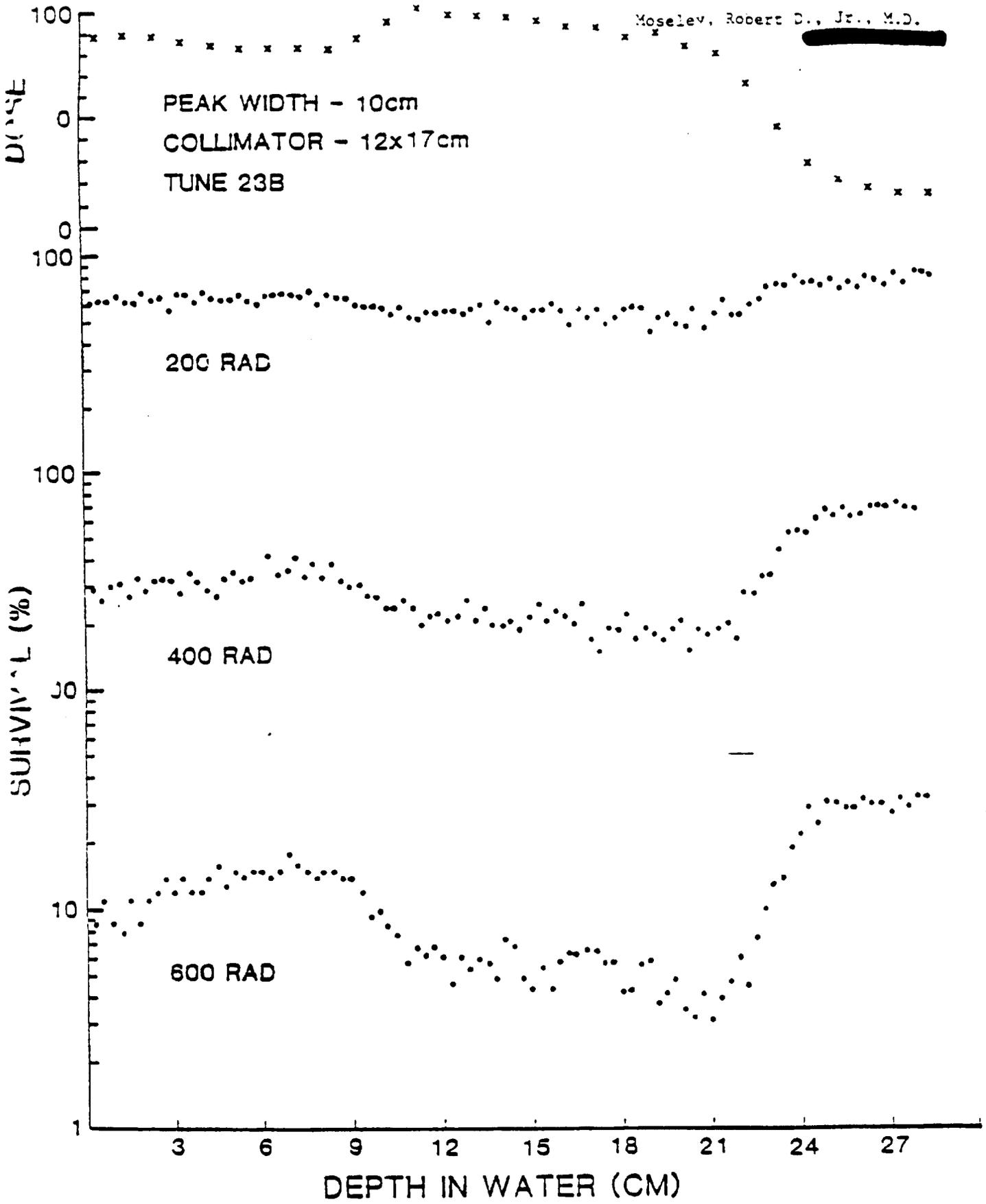


Figure 62. Dose distribution and cell survival as a function of dose and depth, Tune 23B, 10-cm peak

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□ 7x7cm COLLIMATOR
○ 14x17cm COLLIMATOR
300 kVp X-RAYS
PEAK CENTER

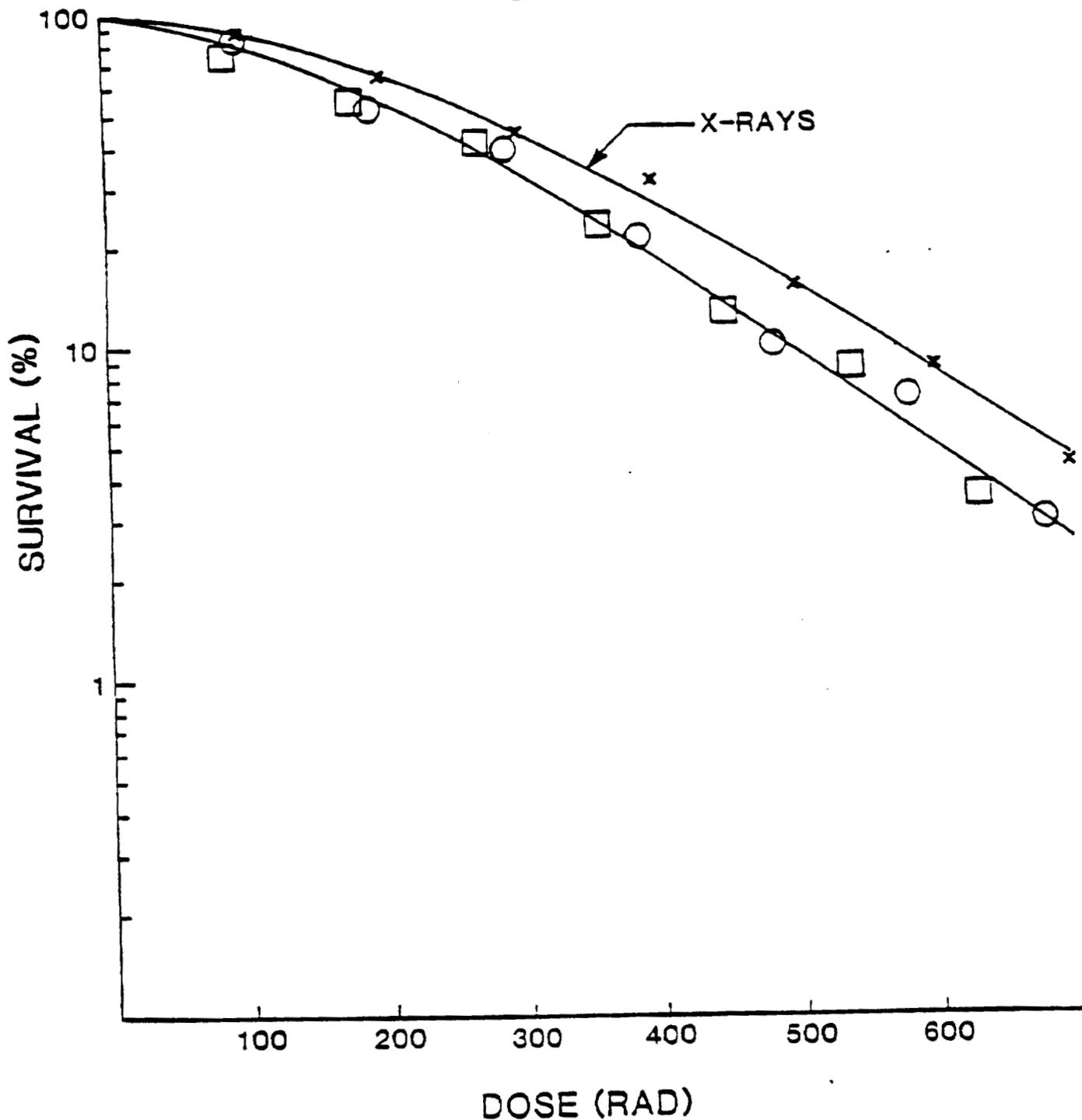


Figure 63. Cell survival curves for central position of pion beam (Tune 16B, 10-cm peak) with two different collimators versus x-rays

in the single-dose studies and that the delay induced by three daily doses of pions is almost as large as that induced by single pion doses, while that for x-rays shows far greater tumor recovery from fractionation.

(b) Kidney. These studies have been described by Jordan *et al.*^{126,127} In brief, the remaining kidney of unilaterally nephrectomized mice was exposed to peak pions or x-rays one month after nephrectomy. Six months after exposure they were sacrificed for histologic examination and semi-quantitative grading of their kidney injury. Figure 64 is a plot of the RBE of pions as a function of the number of daily fractions in this system. Studies involving up to 15 daily fractions are in progress.

(c) Spinal cord. A study of spinal cord injury was initiated as soon as suitable pion dose rates became available. Two-cm segments of the lumbar spine in Fisher 344 rats were irradiated with graded doses of either pions or x-rays, at dose rates of 80 rad/min. One-, 5- and 15-fraction treatment schedules were used. Animals were observed weekly for signs of paralysis, for up to one year post-irradiation.

The results are summarized in Figure 65. The percentage of paralyzed animals in each irradiation group (5-12 mice per group) is plotted as a function of dose for 1-, 5-, and 15-fraction treatment schedules. Corresponding values of ED₅₀ and RBE are given in Figure 66. As can be seen, the RBE of pions for spinal cord paralysis increases from 1.3 for single-fraction exposure to 2.1 and 3.2 for 5 and 15 fractions, respectively. These RBE values are indeed higher than values that have been measured for other normal tissues. They are, however, consistent with data obtained by van der Kogel for neutrons.¹²⁸ This is shown in Figure 67, which plots ED₅₀ versus fraction number for pions, neutrons, and x-rays.

It should be noted that the increase in RBE with fraction number for both pions and neutrons is primarily the result of an increase in the ED₅₀'s for the control irradiations. The ED₅₀ for pions or other high-LET radiation, e.g., neutrons, varies slowly with fraction number.

(d) Colon. A system for studying late fibrotic and vascular injury in the colon of rats has been described by Black *et al.*,¹⁴ and preliminary pion studies (one, two, and three daily fractions) were reported previously.

A 10-fraction colon experiment in rats has recently been completed. The high total doses required for a 10-fraction experiment (2500-7000 rad) proved to be problematic, as most animals in the high-dose groups died due to overexposure of the gut before long-term colon injury could be manifest. Consequently, the 10-fraction study was repeated, using an improved collimator design for both pions and x-rays. In the repeat experiment, animal survival rates were satisfactory, and both pion and x-irradiated animals were sacrificed at 4½ months post-exposure. Results are being analyzed.

(e) Brain. Several possibilities have been explored for studying the late effects of pion irradiation to the brain. There are two problems involved: (1) the choice of a suitable biological endpoint, and (2) dosimetric difficulties of irradiation. For small animals,

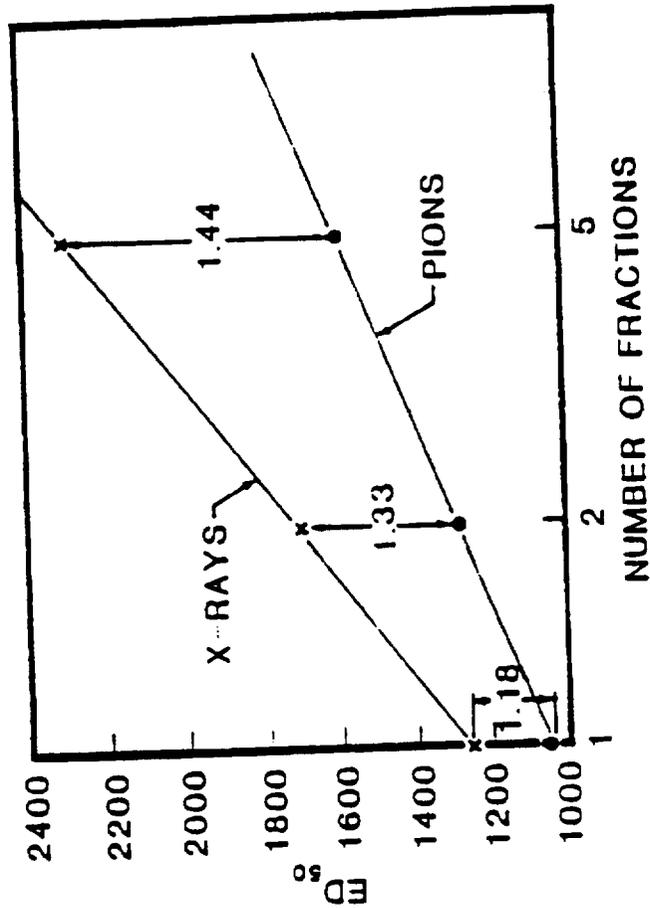


Figure 64. RBE of pions as a function of number of daily fractions in chronic injury to mouse kidney

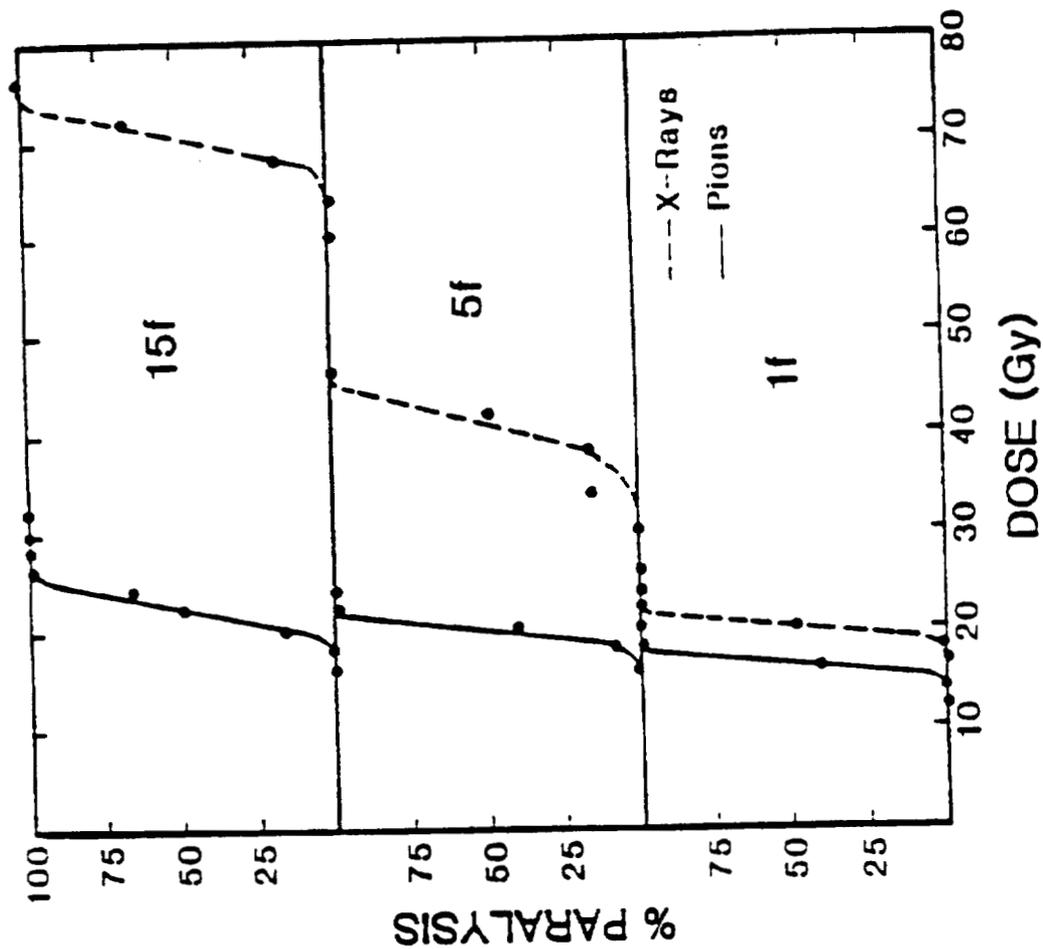


Figure 65. Spinal cord injury from fractionated pion and x-ray exposures

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	X	DOSE, ED ₅₀	TT	RBE
1f	2083 ± 117	1604 ± 117	1.3	
5f	4176 ± 315	2012 ± 166	2.1	
15f	7103 ± 217	2236 ± 184	3.2	

Figure 66. RBE for spinal cord injury at ED₅₀ for fractionated phon and x-ray exposures

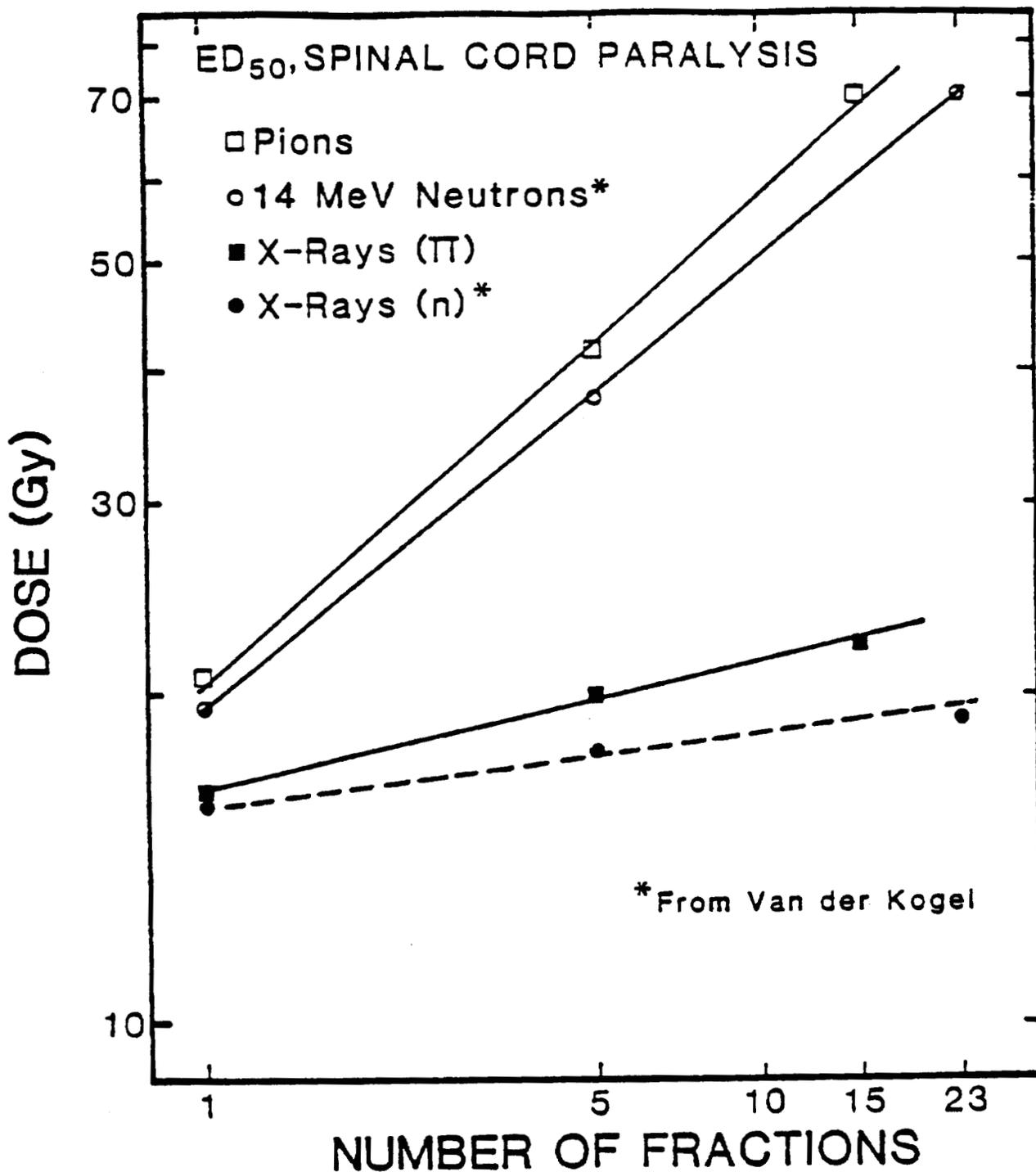


Figure 67. Spinal cord injury after fractionated neutron, pion, and x-ray exposures

such as rats, it is difficult to ensure long-time survival after whole brain irradiation, because of concurrent radiation injury to the oral cavity and esophagus.

Using a finely collimated pion beam and a specially designed bolus, single-fraction test irradiations of whole brain were made on a group of nine rats, at doses of 1000-2500 rad. Concurrent irradiation of control animals to x-irradiation of 1500-3000 rad was also performed. All animals were sacrificed, and gross morphological and vascular damage to the brain is being evaluated.

(f) Lung. Three studies involving radiation-induced lung death and/or collagen deposition initiated by Yuhas et al., but none of the mice successfully survived the treatment. The mice uniformly developed chronic pneumonia and die. A new series of lung experiments have been started, as described under Methods of Procedure.

(3) Mechanism studies

(a) Negative versus positive pions. Bagshaw initiated a series of studies on growth delay of MCa-11 MTS exposed to negative pions, positive pions, and x-rays. As described above, the primary difference between negative pions and x-rays was a smaller threshold for pions before detectable growth delay was observed. Positive pions in these experiments produced results indistinguishable from those of x-rays. This finding indicates that the "star" formation produced by pions is largely responsible for the reduction in threshold.

(b) Radioprotection against pions. The responsiveness of CHO cells to sulfhydryl (cysteine) radioprotection was compared for 2-cm peak pions and x-rays. Results of this study, summarized in Table 34, demonstrate that cysteine is nearly as effective in protecting against pions as against x-rays. This is consistent with the fact that the vast majority of peak pion radiation is low LET.

ii. Publications

(1) Amols, H.I., and Yuhas, J.M.: Induction of spinal cord paralysis by negative pi mesons. British Journal of Radiology, in press.

(2) Black, W.C.; Gomez, L.; Yuhas, J.M.; and Kligerman, M.M.: Quantitation of the late effects of x-irradiation on the rectum of the rat. Cancer 45: 444-451, 1980.

(3) Jordan, S.W.; Key, C.R.; Gomez, L.S.; Agnew, J.; and Barton, S.L.: Late effects of radiation on the mouse kidney. Experimental Molecular Pathology 29: 115-129, 1978.

(4) Jordan, S.W.; Yuhas, J.M.; and Key, C.R.: Late effects of unilateral radiation on the mouse kidney. Radiation Research 76: 429-435, 1978.

TABLE 34

ABILITY OF CYSTEINE (8mM) TO PROTECT
CHO CELLS AGAINST EITHER 2-CM PEAK PIONS OR X-RAYS

	<u>D₀</u>		<u>Dose Reduction Factor</u>
	<u>Control</u>	<u>Cysteine</u>	
X-rays	127±13	231±11	1.82
Pions	132±11	223±14	1.71
Neutrons*	63±7	90±4	1.43

*Performed at ORNL in 1974 and presented for comparison.

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3. Specific Aims

a. To establish the RBE for pions as compared to kilovoltage x-rays for fractionated pion irradiation in the induction of acute injury to the mouse skin and intestinal mucosa.

b. To study the late effects of clinically useful pion beams on the rat cervical spinal cord by analysis of physiological and histological endpoints.

c. To study the late effects of clinically useful pion beams on the rat kidney by means of serial, noninvasive radioisotope scanning and correlation with histopathologic findings.

d. To study the late effects of clinically useful pion beams on the mouse lung as assayed by physiological and histopathological endpoints.

e. To study the late effects of clinically useful pion beams on the rat rectum by means of morphometric analysis.

f. To study the late effects of pion irradiation on the mouse lens.

g. To characterize the patterns of cell-killing and RBE for clinically employed pion beams including static, fan, and spot beams, as well as varying field sizes and range-modulated peaks using cultured cells in gel.

h. To study mutagenesis and transformation by pions using cultured cells and carcinogenesis by pions using the same animals irradiated in the late effects studies.

i. To facilitate cooperation between other institutions involved in pion biomedical research in Vancouver, B.C., Canada, and Villigen, Switzerland and this project in terms of comparison of biology protocols and results as well as development of complementary programs.

4. Methods of Procedure

Cell culture studies using the gel-tube suspension system similar to studies reported in the progress report will be used to characterize the spectrum of static and dynamic beam tunes used in therapy. These studies complement dosimetry studies and guide the development of range-shifter functions and treatment planning.

Cell culture studies performed during September and October 1980, have established that the distal region of the Bragg peak is more biologically effective than the proximal region and that the biological effectiveness of pions decreases significantly with increasing peak width. The differences in biological effects could be larger for fractionated doses. We propose to study the RBE for acute reactions to fractionated doses of pions

for various peak widths commonly used in radiotherapy, using techniques assessing survival of mouse intestinal crypt cells and desquamation of mouse skin.

Since the late effects studies are very costly, we propose to study the late effects of pion radiation on normal tissues (rat cervical spine, kidney, and colon and mouse lung and lens) using a pion beam with the smallest peak width (6 cm) used in therapy. A larger peak width of 14 cm will also be used for cervical spinal cord studies later. The response of murine tumors as compared to mouse skin and gut will also be studied with pion beams of 6-cm peak width to document the relationship of RBE for tumor and normal tissue in the same system.

a. Beam uniformity studies. Some of the range-shifter functions used in conjunction with the static beams currently used in therapy have been verified as producing uniform cell-killing across the peak region by studies of cultured hamster cells (V79) suspended in gelatin (see the progress report). Such measurements will be made for additional treatment tunes required for thorough characterization of beams employed in patient treatment. Dynamic treatment plans using "fan tunes" and "spot tunes" are under development. The response of cultured cells to these focused beams will also be measured by exposing several tubes containing cell suspensions in gel oriented in different directions with respect to the beam. The results for large static beams will be compared with those for dynamic treatment beams.

b. Normal tissue effects

i. Acute effects

(1) Intestinal crypt cells. Cultured cell experiments indicated decreases in RBE with increasing peak width (see the progress report). These differences are expected to be larger for fractionated doses. Ideally, such measurements should be carried out with beams that are used clinically. Withers' technique¹²⁴ will be used for intestinal crypt cell-survival measurements. Since there are no differences between abdominal irradiation and whole body irradiation in intestinal crypt cell survival, there is no need to use any additional collimation that could change the beam quality; hence this system is appropriate for measurements of differences in RBE as a function of peak width ranging from 6 to 16 cm. In addition, extensive background data using the Withers technique are available for comparison with neutrons,¹²⁴ pions,¹²⁹ and heavy ions.¹³⁰ Since limited time periods are available on the biomedical channel for dosimetry and radiobiology experiments (approximately 8 hours daily, from midnight to 8:00 a.m., and about 32 hours during weekends), fractionated experiments can be performed only during weekends. Studies with single-fraction, two- and four-fractions, separated by three-hour time intervals, and a limited number of experiments using up to 10 fractions will be conducted. The effects of variation of range-shifter functions will also be studied using four-fraction exposures at the proximal, mid, and distal regions of the peak.

(2) Mouse skin. The mouse foot system¹²⁵ has been found to be useful for studying the acute effects of heavy particles¹³¹ and pions.¹³² It is proposed to use this system also to measure RBE of pion beams of 6- and 14-cm peak widths for single and fractionated exposures. Four daily fractions will be used, since the RBE obtained for four fractions is not significantly different from that for a larger number of fractions for pions.¹³³

ii. Late effects. Late effects of radiation in general develop in tissues with a slow turnover of cells, such as the lung, kidney, brain, and spinal cord. These organs are the most critical dose-limiting normal tissues, since severe damage may lead to serious morbidity or death. In contrast to acute effects observed, for example, in skin or intestine, mechanisms involved in the development of late damage are not well understood. In the pion radiobiology program, the following tissues of direct importance to clinical treatment will be studied: (1) central nervous system (CNS), (2) kidney, (3) lung, (4) colon, and (5) lens.

(1) CNS. This is one of the most important dose-limiting tissues in treatment of a variety of tumors, including those of the brain, head/neck, lung, esophagus, and pancreas. For studies on the radiation tolerance of the brain and spinal cord, the rat cervical spinal cord has been observed to be a clinically relevant model.^{128,134,135} Various syndromes of radiation myelopathy may develop, depending on radiation dose or time after irradiation. These syndromes are remarkably similar to those described in patients, with regard to histopathological characteristics and time of appearance. The two major types of irreversible delayed damage are:

(a) Early delayed damage consisting of demyelination and white matter necrosis. This develops 5-6 months after irradiation, with neurological signs of a rapidly progressing paralysis

(b) Late delayed damage, mainly characterized by vascular injury such as telangiectasia, thrombus formation and focal hemorrhages. The latent period shows great variation, but usually is from 1 to 1.5 years. In most animals, the neurological signs are mild, but severe paralysis may also occur as a result of a hemorrhagic infarction.

Irradiation of the rat lumbar spine containing the lower lumbosacral part of the cord and a part of the cauda equina results in a completely different histological picture as compared to the cervical cord. In this region, the main damage is necrosis of the nerve roots, with the spinal cord itself well preserved, even with single doses of x-rays as high as 6000 rad. Despite some gross similarities in dose response relationships with the early delayed response in the cervical cord, the lumbar cord is not a representative model for the whole CNS. Also, the late vascular response of cervical cord and brain is not observed in the lumbar region.

Until now, most studies with high-LET radiation on the spinal cord have been performed on the lumbar region. Results were reported for fast neutrons,^{128,136,137} heavy ions,¹³⁸ and, recently, pions.¹³⁹ The RBE values obtained with pions of a small volume Bragg peak are almost as high as those obtained with 15-MeV neutrons (see progress report). However, for clinical therapy, these small Bragg peaks will not be used; a spread peak of about 6 cm is expected to be the smallest beam used. Therefore, experiments on CNS tolerance will be performed with the latter beam tune, using the rat cervical spinal cord as the most relevant model for human CNS. Since a further increase in peak width will show a decrease of RBE, the results obtained with the smallest clinical beam to be used should give an upper limit of RBE.

In the first series of experiments, irradiation will be carried out with 1, 2, 5, 10, and 20 fractions of pions and x-rays with doses per fraction as low as 1 Gy.

For determination of ED₅₀ values with an accuracy of 5-10 percent, each experiment will use about 50 rats with 5-6 radiation doses. This totals 400 rats for the four fractionation schemes with x-rays and pions. On the average, half of these rats will develop paralysis within six months; the others have to be observed for a minimum of 1-1.5 years.

In a later stage, it is envisioned to repeat a 5- or 10-fraction experiment with a larger volume pion beam. This depends on whether significant differences in RBE values are found for acute reactions in skin and intestine.

Other aspects are residual damage and amount of long-term recovery. In split-dose experiments with 300-kV x-rays and 15-MeV neutrons on the rat cervical spinal cord, the repair capacity after neutrons was strongly reduced for a 24-hr interval between two fractions. However, with increasing time intervals, additional recovery was observed to a similar or even greater extent for neutrons as compared to x-rays (Figure 68). Experiments with x-rays and pions will be carried out to further elucidate the mechanisms of long-term recovery after low- and high-LET irradiation of the CNS.

(2) Kidney. In the pion radiobiology program, development of late damage in the mouse kidney has been studied for up to 15 fractions of pions (2-cm peak width) and x-rays. The model used was that developed by Phillips,¹⁴⁰ in which one kidney is irradiated about 30 days after unilateral nephrectomy. Instead of evaluating LD₅₀ values, which is a simple but crude endpoint, a quantitative histological scoring system was developed.¹²⁶ The advantage of this system is that dose response relationships are also derived for doses below the lethal range. Isoeffect curves for dose versus the number of fractions shows a log-linear relationship for up to 15 fractions of pions and x-rays.¹²⁷ The steep curve for x-rays (slope 0.49) indicates a great capacity of the mouse kidney for repair of subeffective damage--even greater than that observed for the spinal cord (slope 0.42). Pion irradiation reduces the amount of repair, but to a lesser extent than that observed in the lumbar spinal cord.¹³⁹ A disadvantage of the unilateral nephrectomy model is that the radiobiological characteristics of the remaining, hypertrophied kidney may not be representative of a normal kidney. For example, the results obtained by Hopewell¹⁴¹ for the pig kidney show a significant rise in tolerance when the overall treatment time is increased from 16 to 30 days, presumably due to repopulation. This effect was not seen by Phillips¹⁴⁰ in the unilaterally nephrectomized mice, which suggests a decreased proliferation potential in the hypertrophic kidney.

In a new series of experiments, another approach will be the irradiation of one kidney in the rat, with the other kidney remaining intact. A system will be developed for monitoring kidney function with radioactive tracers at various time intervals after irradiation. The function of the irradiated left kidney will be compared with the unirradiated right kidney as an internal control. Dynamic studies with radioisotopes are

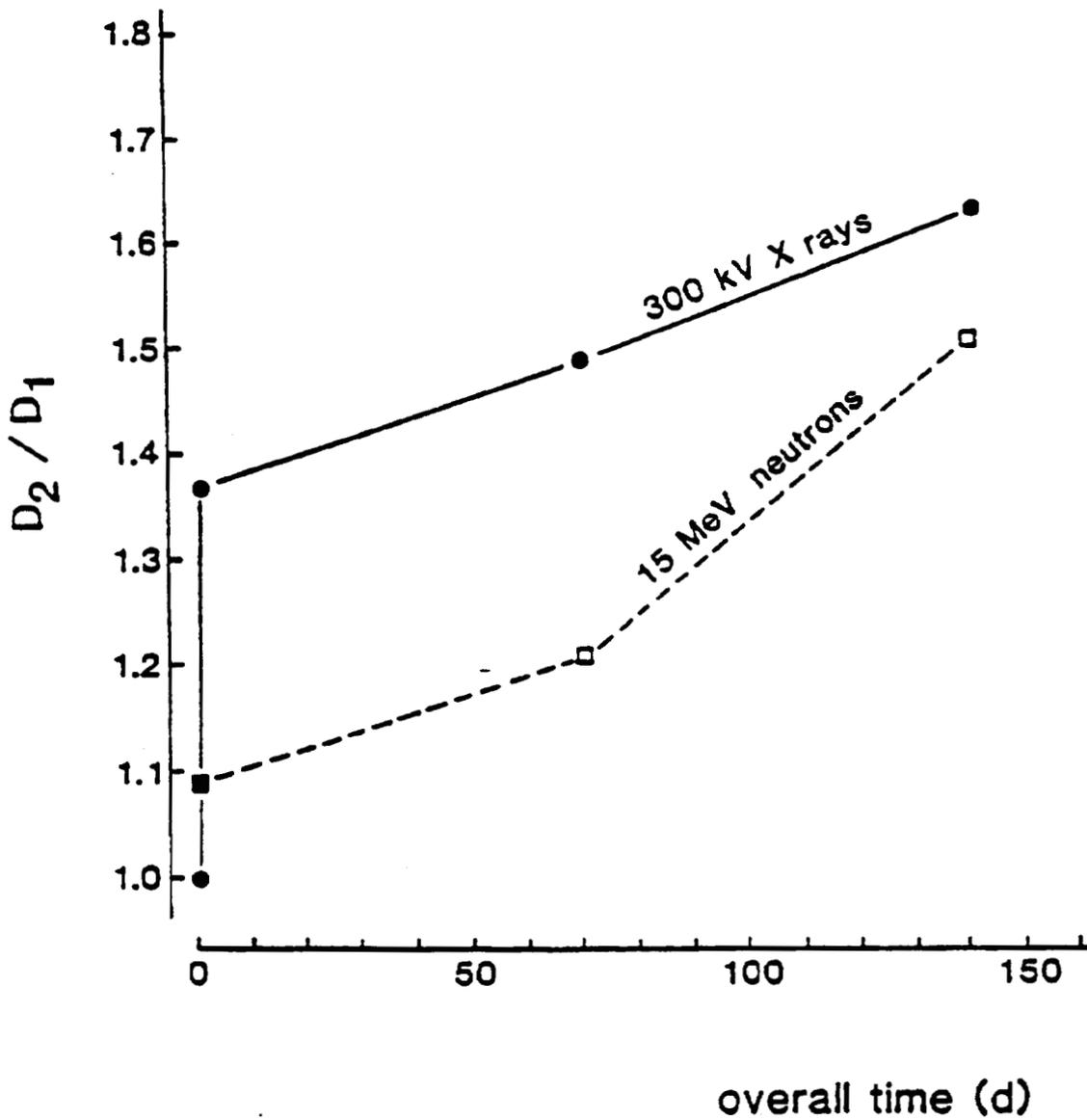


Figure 68. Time-dependent recovery for spinal cord necrosis

most sensitive for testing loss of function, even at doses which do not cause irreversible, lethal damage. Different tracers can be used, which are specific for the function of kidney compartments, e.g., Hippuran for tubular secretion and DTPA (diethylene triamine penta-acetic acid) for glomerular filtration. Since these techniques are noninvasive, different functions can be assessed regularly, which allows the evaluation of acute and late phases in the development of damage. Parallel to these functional assays, rats will be sacrificed and development of kidney damage will be studied with the quantitative scoring technique used in previous mouse kidney experiments.

(3) Lung. Since carcinoma of the lung is locally controlled by conventional radiotherapy in only about 50 percent of cases, these tumors are included in the clinical pion program. Experiments had been initiated by Yuhas and his associates to study the effect of pions and x-rays on the mouse lung (LD₅₀ endpoint), but severe infections hampered the progress of these studies.

The effect of high-LET radiation on lung has been studied extensively by Field and Hornsey¹⁴² and Phillips,¹⁴³ using death at 160-180 days as an endpoint, which is mainly related to acute pneumonitis. Recently, a more specific model has been developed by Travis et al.,^{144,145} combining quantitative histology and a noninvasive assay of lung function in the mouse. This method employs whole body plethysmography for monitoring respiratory frequency. Dose-response curves were derived after irradiation with x-rays and fast neutrons. With this system the occurrence of early and late waves of damage has been quantitatively assessed.

Recently, a pilot experiment was carried out with 1, 2, 5, 10, and 20 fractions of x-rays and pions. From two months after irradiation, animals started to die with radiation pneumonitis without signs of infection. Dose-response curves for the early phase of damage are expected mid 1982.

The whole body plethysmography system is now used in Los Alamos, and base-line data are similar to other strains of mice. A more detailed analysis of the respiratory pattern in early and late waves of damage is planned.

(4) Colon and rectum. Late fibrosis and mucosal injury to the lower intestinal tract is a serious complication after irradiation of pelvic tumors with x-rays or fast neutrons. To evaluate the effect of pions, a system for histological scoring of changes in the mucosa and submucosa of the rectum has been developed.¹⁴ The main components of the observed submucosal damage are fibrosis and vascular sclerosis. Single dose and fractionated pion irradiations (up to 10 fractions) have been done with a narrow (2-cm) Bragg peak. Additional experiments will be carried out with a clinically relevant beam of 6 cm.

(5) Lens. A significant amount of radiation may be given to the lens of the eye during the course of pion radiotherapy for tumors in the head and neck or brain. Major concern is that high-LET radiations have a high RBE for lens opacification.¹⁵⁴ Experiences with neutrons indicate that the RBE of fast neutrons is a function of dose (varying from 10 to 50, with a higher RBE at lower dose regions). Although one can alleviate the incidence

of cataract formation by using fractionated treatment.¹⁵⁵ It is yet to be tested if such fractionation can lower the incidence of lens opacification for pions. We propose to study the effects of pions on mouse lens using single and four fraction doses. We intend to use nonanesthetized mice under the study design proposed by the group at TRIUMF.¹⁵⁶ The endpoint for the RBE determination is the time required to achieve cataracts in 50 percent of the mice irradiated. Preliminary studies involving single-fraction x-rays as well as pions are in progress at Los Alamos.

iii. Mutagenicity and oncogenicity studies

(1) In vitro studies. Mutagenic and oncogenic properties are important aspects in evaluating new therapeutic modalities. For x-rays, experience has shown that the oncogenic risk from such therapy is considerably surpassed by the potential benefits. Mutagenicity and oncogenicity studies using cultured mammalian cells may not be of clinical relevance. However, with significant prior experience in oncogenicity of x-irradiation, in vitro comparative studies between x-rays and pions will provide a clue in the evaluation of mutagenic/oncogenic characteristics of pion beams. Previous studies by Li have indicated that the slope for mutants per 10^6 survivors versus dose is three times steeper for pions than it is for x-rays using the hypoxanthine-guanine phosphoribosyl transferase (HGPRTase) locus in CHO cells (see the progress report). When the mutagenicity of alpha particles from plutonium was compared to that of x-rays using the same cell system, plots of mutation frequency against survival showed that, relative to x-rays, the probability is greater that a lesion from alpha particle irradiation will result in an inactivation (cell death) than in a mutagenic event.¹⁵⁷ Extensive review of in vitro transformation studies involving high-LET radiation has been published by Yang and Tobias.¹⁵⁸

Because of variations in neutron contribution, radiobiological properties of pion beams vary, depending on the peak width for a given field size. Therefore, we intend to continue to measure the mutagenic characteristics of pion beams with different peak widths. For mutagenicity studies, CHO and human embryonic fibroblasts will be used, and, for transformation studies, Syrian hamster cells (3T3) will be used. Cells will be irradiated in water phantom at 37°C with one fraction or two fractions given three hours apart. The data obtained will be matched with the survival data to correlate the mutagenicity or transformation rates in the surviving fractions. Preliminary studies using x-rays and alpha particles for one and two fractions are in progress, in collaboration with the members of the Molecular Biology Group in the LANL Life Sciences Division.

(2) In vivo studies. As described earlier, the rats that will be exposed to pions or x-rays for CNS late effects and other normal tissue late effects studies will also be followed for radiation-induced tumors. All the animals that develop tumors will be examined histologically.

c. Pion RBE and tumor cell differentiation. Historically, the rationale for proposing cancer therapy with high-LET radiations was to overcome the resistance of hypoxic cells. The rationale for using high-LET particles is that they may produce greater effect on tumor cells for a given effect on normal tissues. The radiobiologic and clinical experience with fast neutrons indicates that the RBE on normal tissues, especially for late effects,

is rather large; hence, there may not be a uniform therapeutic advantage for high-LET radiations for all tumors. The Amsterdam group concluded after an extensive series of investigations with human pulmonary metastases that there is a correlation between histologic tumor grade and volume-doubling time and between RBE and volume-doubling time, suggesting an advantage for high-LET radiations only for slow-growing, well differentiated tumors.¹⁵⁹ We believe this important observation should be explored in high-LET programs. About 7,000 patients have been treated with fast neutrons, but a definitive answer is still not available as to whether fast neutrons improve local tumor control, as compared to local control with conventional megavoltage radiotherapy. The Amsterdam group has speculated that good results for some tumors may be counter-balanced by bad results for other tumors, thereby confounding a resolution to the assessment of improved local control.

Since it is difficult to accumulate such extensive clinical experience with pions or heavy ions, it is of paramount importance to develop methods that would help screen patients who would have a better prognosis with high-LET particles than with conventional radiation. We propose to initiate such a research program in a small scale. We intend to start with our existing rodent tumor lines (well differentiated and poorly differentiated adenocarcinomas) and to extend these studies with more relevant tumor systems and to measure RBE of these tumors by means of growth delay/colony formation in vitro. These RBE data will be compared to the RBE of normal tissues such as skin and gut to test whether there is any correlation between response to pions and tumor differentiation. We will also examine, from patient records, the tumor response of patients treated with pions or x-rays in this program for any correlation between tumor differentiation and tumor response.

5. Anticipated Results

Anticipated results from the biology component of the program are:

a. Biological dosimetry information will be obtained by means of cell culture systems and experimental animal systems to verify and/or modify pion therapy beams of various dimensions to enhance uniformity of cell-killing across the peak.

b. RBE values of fractionated doses of pion beams for acute effects (mouse skin and gut) and late effects (rat cervical spinal cord, kidney, and colon and mouse lung and lens) will be determined to provide guidance on late normal tissue responses for the therapy program.

c. Studies in cell systems and in rodents will provide information for comparison with the expectation of mutagenicity and oncogenicity after x-irradiation.

d. Determination of tumor RBE for well or poorly differentiated tumors compared to RBE's for normal tissues will provide information on expected therapeutic gain with pions.

6. Significance

The biological component of this proposal is primarily aimed at assisting the clinical program. Experimental data obtained will be used to assist the therapy program in terms of biological dosimetry (uniform cell-killing across the beams), RBE values for various dose-limiting normal tissues (including isoeffect slopes so that RBE values can be extrapolated to different fractionation schemes), and information on carcinogenesis.

7. Facilities Available

The LANL Life Sciences Division has excellent laboratory facilities for the proposed study, in addition to the expertise in the fields of molecular biology, cellular biology, mammalian biology, and flow cytometry. Excellent facilities in pathology are available at UNM. Animal facilities, accredited under NIH guidelines, are available at LANL and at the UNM Medical Center for housing animals irradiated in these studies.

8. Collaborative Arrangements

Collaborative arrangements with E. Travis, Ph.D., of the M.D. Anderson Cancer Center, Houston, for late effects studies of lung are described under Methods of Procedure. The collaboration between the LANL Life Sciences Division and the UNM Department of Pathology, as well as the addition of Dr. van der Kogel from the Radiobiological Institute of the Organisation for Health Research, TNO, Rijswijk, The Netherlands, are also described above. Other potential collaborators who may be able to contribute new information and/or techniques to these studies will be sought as the need indicates.

D. Core Component1. Investigators

<u>Name</u>	<u>Title</u>
Robert D. Moseley, Jr., M.D.	Co-Principal Investigator
TBA	Co-Principal Investigator Chief, Radiation Oncology, CRTC
Kincaid Davidson, M.S.	Program Manager, CRTC/Los Alamos
TBA	Grants Management Specialist, CRTC/Los Alamos
Antoinette Garcia	Program Specialist II, Protocol Office, CRTC/Albuquerque
TBA	Program Specialist II, Protocol Office, CRTC/Los Alamos

2. Introduction

a. Objective The objective of this component is to provide adequate administrative, logistics, and data management support so that clinical trials of pion radiotherapy can be conducted as expeditiously and cost-effectively as possible.

b. Rationale. The conduct of the clinical trials program as a cooperative effort between the UNM/CRTC in Albuquerque and LANL in Los Alamos creates the need for an administrative structure capable of supporting the staffing, patient interchange, and communications between two institutions 90 miles apart, as well as the usual requirements associated with scientific documentation, patient data management, technical administration and fiscal administration.

Administration, CRTC/Los Alamos. Logistical support and technical and fiscal administration for the Los Alamos-based components of the pion clinical and scientific program are supervised by the Administrative Office, CRTC/Los Alamos Kincaid Davidson, Program Manager. The group handles technical/fiscal monitoring, accounting, budgeting, patient reimbursements, reimbursements to health care providers, purchasing, personnel, and related matters for the CRTC/Los Alamos staff. All documentation flows through the appropriate units of the CRTC/Albuquerque (F. Jackson, Administrator, CRTC/Albuquerque) and then to appropriate units of the UNM Medical Center. The group also assists in arrangements for patient and staff housing and transportation in Los Alamos, arrangements for visiting scientists, and liaison with the NCI, LANL, the Los Alamos Medical Center, members of the Pion Program External Advisory committee, the Radiation Therapy Oncology Group, and other organizations, as appropriate.

Mechanisms for billing appropriate medical costs for pion patients to third-party providers are being streamlined to maximize recovery of costs at rates comparable to those for routine radiotherapy, and to document costs not recoverable from third parties. These improvements are resulting in more timely and complete billing and improved collections. Funds received from this source are credited to the grant in proportion to money collected.

The administrative staff is housed in offices in the Pion Biomedical Facility. With funds provided by the DOE, LANL implemented major modifications to the Pion Biomedical Facility to accommodate installation of the EMI 7070 whole-body CT scanner and associated peripherals and a new treatment planning area. The pion channel control room was expanded to accommodate a new PDP 11/70 computer and physics data acquisition equipment. The staging area was expanded to permit the simultaneous set-up of two patients. Another room was converted for use as a patient casting room, permitting separation of Lightcase manufacture from bolus/collimator work. A new kitchenette was installed for on-site preparation of patients' meals. As a result of these space conversions, new quarters were added to replace lost office and conference room space. LANL procured a prefabricated building and a trailer, located next to the Pion Biomedical Facility, to provide offices for displaced staff and conference space.

The CRIC Protocol Office will be staffed with one person in Albuquerque (A. Garcia), and one half FTE in Los Alamos to provide logistics, scheduling data management, and related support to the pion program. The difficulty of coordinating patients and records between the Los Alamos and Albuquerque facilities, and the fact that patients are coming from throughout the United States for pion therapy and follow-up, has required logistical support in excess of that normally needed for data management in conjunction with clinical research protocols.

3. Specific Aims

- a. to provide fiscal, personnel, logistical, and other operational support related to delivery of pion radiation therapy in Los Alamos.
- b. To serve as UNM/CRIC liaison with various LANL units participating in or supporting the pion program.
- c. To assist in planning and coordination of the pion research program.
- d. To serve as liaison with referring institutions, visiting scientists, members of advisory groups, the RTOG, the NCI, and other organizations and agencies concerned with the pion program.
- e. To prepare and process protocols, consent forms and progress reports for the pion program, for assurance of protection of human subjects.
- f. To monitor (technically and fiscally) expenditures incurred in the pion program, to ensure cost-effective utilization of resources.
- g. To serve as liaison with medical providers and agencies providing third-party payment, to promote cooperation in provision of and reimbursement for services to patients participating in the pion clinical studies.

C. 10

4. Methods of Procedure

The Los Alamos administrative offices of the CRTC are located at LAMPF, within the Pion Biomedical Facility. The staff serve all CRTC personnel working in Los Alamos, and LANL scientists working on the program as needed.

Communications between the CRTC in Albuquerque and CRTC staff based in Los Alamos are simplified by having access to the LANL centrex phone system (which permits direct dialing to any phone in Albuquerque at no charge to this program); access to the FTS for long-distance calls (other than Albuquerque); access to official use of Ross Aviation for transporting correspondence and patient records and films by plane; and access to official taxi service for transporting patients and staff to and from the Los Alamos airport and business locations (e.g., Los Alamos Medical Center, Pion Biomedical Facility, patient apartments, etc.) for patients and staff who do not have automobile transportation. Many CRTC staff routinely drive to and from Los Alamos in their own or UNM vehicles. These staff also routinely transport correspondence, packages, and small equipment between the two cities.

The LANL administrative staff has been most cooperative and helpful to this project in procurement of space, office equipment, and surplus scientific equipment; freight transfers between Albuquerque and Los Alamos; and in various other ways. Lines of communication and cooperation between the CRTC and LANL administrative staffs for the conduct of this program are well established.

All CRTC administrative paperwork that originates in Los Alamos flows through regular channels of the CRTC and UNM, so that CRTC operations in Los Alamos are a satellite extension of the UNM/CRTC, not a separate operation. As clinical operations have become more routine and sufficient information has become available to justify reimbursement from third parties for costs patients would incur if they were to receive conventional therapy, the billing program for pion protocol patients has been expanded to promote maximum recovery of costs from third parties. The funds generated through this program offset the amount of support requested from the NCI.

Patients who come to Albuquerque from pretreatment evaluation or follow-up are housed in a local motel for procedures performed in Albuquerque and then either fly via Ross Airlines or are transported by car to Los Alamos for clinical examination, casting, CT scanning, and simulation (new patients). Those who are in Albuquerque for diagnostic work-up, clinical examination and/or CT scanning (new and follow-up patients) are brought to the CRTC each day by cab.

In Los Alamos, patients are housed in one-room efficiency apartments each with two beds, located next to (and owned by) the Los Alamos Medical Center. Patients may cook their own meals or eat in the hospital cafeteria. Two patients can be housed in each unit. However, when a CRTC physician certifies that it is medically indicated to have a family member accompany the patient, the efficiency unit is assigned to the patient and his family member. In the past, this has resulted in cost savings because it reduces the need for home nursing care and often makes the difference between

whether or not a patient needs to be admitted to the hospital. The same policies apply to out-of-town patients being given conventional treatment in Albuquerque as an adjunct to pion therapy.

Patients who require hospitalization in Los Alamos are hospitalized at the LAMC; the LAMC also provides ambulance service and emergency service when needed. Clinical consultation is also provided by Los Alamos specialists (e.g., internists, cardiologists, surgeons, etc.) as indicated and as experienced specialists are locally available. Patients are taken by governmental-paid (DOE) taxi service to the Pion Biomedical Facility for their daily treatment at no expense to this project. Local American Cancer Society volunteers provide transportation for shopping and sight-seeing, and arrange social gatherings for patients with local residents.

Patients who need hospitalization in Albuquerque are admitted to the eight-bed cancer research unit at the UNM Hospital, when appropriate. However, they may be placed on other services, such as the surgical service or intensive care unit if needed. Most patients see one or more specialists, e.g., gastroenterologists, head and neck surgeons, or gynecologists, in Albuquerque as indicated by their condition before, during or after the course of their treatment. Patients who may have difficulties with the altitude in Los Alamos are referred for cardiac and pulmonary function studies prior to treatment. All patients assigned to pion therapy receive an ophthalmologic exam to assess baseline lens opacity. This is re-evaluated annually to determine changes which may be due to high-LET radiation dose to the lens during pion treatment. To date, no such changes have been seen. All diagnostic studies to evaluate local disease or possible metastases are performed at the CRTC or the UNM Hospital in Albuquerque.

All the above arrangements are scheduled by the Protocol Office staff according to the instructions of the responsible CRTC radiation oncologist or other physician. In addition, the staff completes detailed forms on patients after their treatment for input to the computerized pion patient data system, as well as follow-up forms after each follow-up visit. This system provides the data base required for analysis of a variety of clinical parameters associated with treatment and outcome. The staff also completes, with guidance from the appropriate CRTC radiation oncologist, all forms required by the RTOG and various human research review committees regarding patients accessed to the pion program. Detailed CT scan files and other files related to treatment are maintained by the Protocol Office staff for reference by the CRTC radiation oncologists, physicists, and others as needed.

5. Anticipated Results

It is anticipated that methods and procedures for continued support of the pion clinical trials through the remainder of the experimental phase, and beyond as a routine medical treatment if the results of clinical trials so warrant, are firmly established, but will continue to be streamlined and otherwise improved during the course of the proposed project period.

6. Significance

The administrative and logistics processes and procedures developed as part of this cooperative effort between the CRTC and LANL are transferable to other sites where heavy particles are being investigated in cancer therapy as a cooperative effort between major medical centers and accelerator facilities. There has already been considerable cross-transfer of information with other facilities, and this will continue. More significantly, services proficed by the core component help to ensure the success of a joint scientific effort conducted by the CRTC and LANL physically speparated by 90 miles.

7. Facilities Available

The full administrative facilties of UNM, CRTC and LANL are available to this project. Office space for the CRTC staff in Los Alamos is provided by LANL at no cost to this program, along with utilities, phone service, and other support.

8. Collaborative Arrangements

Collaborative arrangements are well established with health care providers in Albuquerque and Los Alamos, as well as vendors of necessary supplies and equipment. The Los Alamos Medical Center provides the majority of the logistical support to the clinical component of this program (e.g., patient housing, inpatient serviced, outpatient services, clinical supplies, etc.), under a blanket purchase agreement with UNM. Arrangements are also well established with the Los Alamos chapter of the American Cancer Society for personal assistance to patients and their families while they are in Los Alamos, particularly to those who do not have access to an automobile.

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154. Bateman, J.L., and Bond, V.P.: Lens opacification in mice exposed to fast neutrons. Radiation Research (Supplement) 7: 239-249, 1967.
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158. Yang, T.C.H., and Tobias, C.A.: Radiation and cell transformation in vitro. Advances in Biology and Medical Physics 17: 417-461, 1980.
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Moseley, Robert D., Jr., M.D.

VII. BIOGRAPHICAL SKETCHES OF PROFESSIONAL PERSONNEL

BIOGRAPHICAL SKETCH

Give the following information for key professional personnel listed on page 2, beginning with the Principal Investigator/Program Director. Photocopy this page for each person.

NAME	TITLE	BIRTHDATE (mm, day, year)
Robert E. Anderson, M.D.	Co-Director, CRIC Professor & Chairman, Pathology	[REDACTED]

EDUCATION (Begin with baccalaureate training and include postdoctoral)

INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	FIELD OF STUDY
[REDACTED]	B.A.	[REDACTED]	Chemistry
[REDACTED]	M.D.	[REDACTED]	Medicine

RESEARCH AND/OR PROFESSIONAL EXPERIENCE: Concluding with present position, list in chronological order previous employment, appointments, and honors. Include present membership on any Federal Government Public Advisory Committee. List, in chronological order, the titles and complete references to recent representative publications, especially those most pertinent to this application. Do not exceed 2 pages.

- [REDACTED] Fellowship (for research on carbon metabolism, Department of Biochemistry, [REDACTED] Ph.D., preceptor)
- 1960-64 Instructor and Assistant Professor of Pathology, [REDACTED]
- 1962-64 Surgeon (I) [REDACTED]
- 1964-66 Assistant Professor of Pathology, [REDACTED]
- 1966-72 Markle Scholar in Academic Medicine
- 1966-69 Associate Professor of Pathology, [REDACTED]
- 1971-72 Sabbatical leave, [REDACTED]
- 1974 Research leave, [REDACTED]
- 1978-79 Sabbatical leave, [REDACTED]
- 1980 Research leave, [REDACTED]
- 1966-present Consultant in Pathology, Radiation Effects Research Foundation, Hiroshima and Nagasaki, Japan
- 1968-present Chairman, Department of Pathology, University of New Mexico, School of Medicine, Albuquerque
- 1969-present Professor, Department of Pathology, University of New Mexico, School of Medicine, Albuquerque
- 1974-present Pathology Consultant Panel, Veterans Administration Central Office, Washington, D.C.
- 1977-present Physician-in-Residence Program, Veterans Administration Central Office, Washington, D.C.
- 1979-present Member, Pathology B Study Section National Institutes of Health
- 1980-present Co-Director, Cancer Research and Treatment Center, University of New Mexico, Albuquerque

PUBLICATIONS

1. Anderson, R.E.: Radiation Injury. In Pathology. J. Kissane and W.A.D. Anderson, eds. C.V. Mosby Company, 7th Edition, pp. 326-368, 1977.

- Anderson, R.E.; Olson, G.B.; Autry, J.R.; Howarth, J.L.; Troup, G.M.; and Bartels, P.H.: Radiosensitivity of T and B Lymphocytes. IV. Effect of Whole Body Irradiation upon Various Lymphoid Tissues and Numbers of Recirculating Lymphocytes. Journal of Immunology 118: 1191-1200, 1977.
- Anderson, R.E.; Standefer, J.C.; and Scaletti, J.V.: Radiosensitivity of Defined Populations of Lymphocytes. VI. Functional, Structural and Biochemical Consequence of In Vitro Irradiation. Cellular Immunology 33: 45-61, 1977.
- Anderson, R.E., and Williams, W.L.: Radiosensitivity of T and B Lymphocytes. V. Effects of Whole Body Irradiation on Numbers of Recirculating T Cells Sensitized to Primary Skin Grafts in Mice. American Journal of Pathology 89: 367-378, 1977.
- Anderson, R.E.; Standefer, J.C.; and Scaletti, J.V.: The Phospholipid and Glycoprotein Composition of T and B Cells. Laboratory Investigation 37: 329-338, 1977.
- Anderson, R.E.; Howarth, J.L.; and Troup, G.M.: Effects of Whole-body Irradiation upon Neonatally Thymectomized Mice: Incidence of Benign and Malignant Tumors. American Journal of Pathology 91: 217-227, 1978.
- Olson, G.B.; Anderson, R.E.; and Bartels, P.H.: Computer Analysis of Defined Populations of Lymphocytes Irradiated In Vitro. III. Evaluation of Human T and B Cells in Peripheral Blood Origin. Human Pathology 10: 179-190, 1979.
- Anderson, R.E.; Weston, J.T.; Craighead, J.E.; Lacy, P.E.; Wissler, R.W.; and Hill, R.B.: The Autopsy: Past, Present and Future. Journal of the American Medical Association 242: 1056-1059, 1979.
- Anderson, R.E., and Lefkovits, I.: In Vitro Evaluation of Radiation-induced Augmentation of the Immune Response. American Journal of Pathology 96: 456-472, 1979.
0. Anderson, R.E.; Howarth, J.L.; and Troup, G.M.: Radiation-induced Life Shortening in Neonatally Thymectomized Germfree Mice. Archives of Pathology and Laboratory Medicine 104: 145-149, 1980.
1. Anderson, R.E., and Lefkovits, I.: Effects of Irradiation on the In Vitro Immune Response. Experimental Cell Biology 48: 255-273, 1980.
2. Anderson, R.E.: Radiation Injury: A Model for the Study of Environmental Insults. In Topics of Environmental Pathology. Universities Associated for Research and Education in Pathology, pp. 107-119, 1980.
3. Anderson, R.E.; Lefkovits, I.; and Troup, G.M.: Radiation-induced Augmentation of the Immune Response. Contemporary Topics in Immunobiology 11: 245-274, 1980.
4. Anderson, R.E., and Standefer, J.C.: Ionizing Radiation and the Plasma Membrane of Lymphocytes. In The Immune System (Festschrift in Honour of Niels Kaj Jerne, on the Occasion of his 70th Birthday), Basel: S. Karger, 1981, in press.
5. Anderson, R.E., and Standefer, J.C.: Radiation Injury of the Immune System. In Cytotoxic Insult to Tissue. C.S. Potten and J.H. Hendry, eds., England: Churchill Livingstone, 1981, in press.

BIOGRAPHICAL SKETCH

Give me following information for key professional personnel listed on page 2, beginning with the Principal Investigator/Program Director. Photocopy this page for each person.

NAME	TITLE	BIRTHDATE: mo., day, year
Petar A. Berardo, Ph.D.	Physicist, LANL	[REDACTED]

EDUCATION (Begin with secondary school training and include postdoctoral)

INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	FIELD OF STUDY
[REDACTED]	B.S.	[REDACTED]	Physics
[REDACTED]	M.S.	[REDACTED]	Physics-Nuclear Physics
[REDACTED]	Ph.D.	[REDACTED]	Physics-Elementary Particles

RESEARCH AND/OR PROFESSIONAL EXPERIENCE: Concluding with present position, list in chronological order previous employment, occupation, and honors. Include present membership on any Federal Government Public Advisory Committee. List, in chronological order, the titles and complete references to recent representative publications, especially those most pertinent to this application. Do not exceed 2 pages.

- 1970-73 Physicist in electron dosimetry [REDACTED]
- 1973-1976 Physicist, Joint Strategy Target Planning Staff, [REDACTED]
- 1975-present Physics staff member in charge of computerized treatment planning, Los Alamos National Laboratory, New Mexico

PUBLICATIONS

1. Berardo, P.A., et al.: Measurement of Inverse Pion Photoproduction Near the P₃₃ (1236) resonance. Physical Review Letters 26: 201, 1971.
2. Berardo, P.A., et al.: Analysis of Negative Pion Photoproduction near the P₃₃ resonance; test of the $\Delta I \leq 1$ Rule and Time-reversal Invariance. Physical Review Letters 26: 205, 1971.
3. Berardo, P.A., et al.: Measurement of the Differential Cross-section for $\pi^-p \rightarrow \pi^0$ at 317, 452, and 491 MeV/c. Physical Review D6: 756, 1972.
4. Berardo, P.A., et al.: Differential Cross-sections for $\pi^-p \rightarrow \pi^0$ at 317, 452, and 491 MeV/c. Physical Review D9: 621, 1974.
5. Cahput, R.L., and Berardo, P.A.: Increased Brain Radioresistance after Supralethal Irradiation. Medical Physics 1: 148, 1974.
6. Zeller, M.E.; Berardo, P.A., et al.: Measurement of the Differential Cross-section for $\pi^-p \rightarrow \pi^0$ at 360 MeV. Bulletin of the American Physical Society II 14: 108, 1969.
7. Parson, A.S.L.; Truol, P.; Berardo, P.A.; et al.: Measurement of the Differential Cross-section for Pion-proton Charge Exchange by 200, 320, and 360 Pions. Bulletin of the American Physical Society II 14: 108, 1969.
8. Verhey, L.J.; Berardo, P.A.; et al.: Measurement of the Differential Cross-section for $\pi^-p \rightarrow \pi^0$ at 200 and 320 MeV. I. Experimental Results. Bulletin of the American Physical Society II 14: 637, 1969.
9. Truol, P.; Parson, A.S.L.; Berardo, P.A.; et al.: Measurement of the Differential Cross-section for $\pi^-p \rightarrow \pi^0$ at 200 and 320 MeV. II. Analysis. Bulletin of the American Physical Society II 14: 637, 1969.

1. Vefkens, B.M.K.; Berardo, P.A.; et al.: In Search of the Roper Resonance in $\pi N^* p$ - πN . Paper Contributes to the International Symposium on Electron and Photon Interactions at High Energies, Daresbury, England, 1969. (Lawrence Radiation Laboratory Report: UCRL-19281).
2. Verhey, L.J.; Berardo, P.A.; et al.: Measurement of Charge Exchange Scattering of Negative Pions by Hydrogen at 1245, 1357, and 1363 MeV Center-of-Mass Energy. Bulletin of the American Physical Society II 16: 635, 1971. (University of California, Los Angeles Report: UCLA-34P106-51).
3. Berardo, P.A.: Irradiation Techniques and Dosimetry at the AFRRRI LINAC. Presented to Symposium on Recent Developments in Practical Dosimetry and Standards, National Bureau of Standards, Gaithersburg, Md., 1971.
4. Berardo, P.A., and Willis, J.A.: Real-time Monitor of Radiation Field Shape and Intensity. Presented to 1972 Winter Meeting of the American Association of Physicists in Medicine, Chicago, ILL.
5. Berardo, P.A., and Willis, J.A.: Real-time Monitor of Radiation Field Shape and Intensity. AFRRRI Technical Report 73-10, August 1973. Medical Physics 3: 259, 1976.
6. Smith, A.R.; Rosen, I.I.; Hogstrom, K.R.; Lane, R.G.; Kelsey, C.A.; Amols, H.I.; Richman, C.; Berardo, P.A.; Heland, J.A.; Kistel, R.S.; Paciotti, M.A.; and Bradbury, J.N.: Dosimetry of Pion Therapy Beams. Medical Physics 4: 408, 1977.
7. Kelsey, C.A.; Berardo, P.A.; et al.: Clinical Treatment Planning with Static Pion Beams. Presented at 62nd RSNA/AAPM Meeting, November 1976.
8. Berardo, P.A., et al.: The Effect of Inhomogeneities on Static Pion Dose Distribution. Presented at 62nd RSNA/AAPM Meeting, November 1976.
9. Smith, A.R.; Kligerman, M.M.; Kelsey, C.A.; Lane, R.G.; and Berardo, P.A.: Treatment Planning for Negative Pi-meson Radiation Therapy: UNM-LASL Experience. International Journal of Radiation Oncology, Biology, and Physics 3: 307, 1977.
10. Hogstrom, K.R.; Smith, A.R.; Simon, S.L.; Somers, J.W.; Lane, R.G.; Rosen, I.I.; Kelsey, C.A.; von Essen, C.F.; Kligerman, M.M.; Berardo, P.A.; and Zink, S.M.: Static Pion Beam Treatment Planning of Deep Seated Tumors Using Computerized Tomographic Scans at LAMPF. International Journal of Radiation Oncology, Biology, and Physics 3: 875-886, 1979.

BIOGRAPHICAL SKETCH

Give the following information for key professional personnel listed on page 2, beginning with the Principal Investigator/Program Director. Photocopy this page for each person.

NAME William C. Slack, M.D.	TITLE Chief, CRIC Oncologic Pathology Assoc. Prof. Pathology	BIRTHDATE (mm, dd, yy) [REDACTED]
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EDUCATION (Begin with baccalaureate training and include postdoctoral)

INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	FIELD OF STUDY
[REDACTED]	B.A.	[REDACTED]	
[REDACTED]	M.D.	[REDACTED]	Medicine

RESEARCH AND/OR PROFESSIONAL EXPERIENCE: Concluding with present position, list in chronological order previous employment, experience, and honors. Include present memberships on any Federal Government Public Advisory Committee. List, in chronological order, the titles and complete references to recent representative publications, especially those most pertinent to this application. Do not exceed 2 pages.

- [REDACTED] Intern in Pathology, [REDACTED]
- [REDACTED] Resident in Pathology, [REDACTED]
- [REDACTED] Resident in Surgical Pathology, [REDACTED]
- [REDACTED] Resident in Clinical Pathology, [REDACTED]
- 1961-1962 Clinical Instructor in Pathology, [REDACTED]
- 1962-1964 Chief, Pathology Section, [REDACTED]
- [REDACTED] Trainee in Electron Microscopy, Department of Pathology, Division of Surgical Pathology, [REDACTED] (preceptor: [REDACTED])
- 1964-1966 Assistant Professor of Pathology, [REDACTED]
- 1966-1967 Instructor in Pathology, [REDACTED]
- 1967-1969 Assistant Pathologist, [REDACTED]
- 1967-1969 Assistant Pathologist, [REDACTED]
- 1967-1969 Assistant Professor of Pathology, [REDACTED]
- 1974-present Chief, Oncologic Pathology, Cancer Research and Treatment Center, University of New Mexico
- 1969-present Associate Professor of Pathology, University of New Mexico

PUBLICATIONS

1. Kalodney, L.; Eaton, P.; and Black, W.C.: Exacerbation of Cushing's Syndrome during Pregnancy: Report of a Case. Journal of Clinical Endocrinology and Metabolism 36: 81-86, 1973.
2. Olds, J.; Langley, J.; Black, W.C.; and Lueter, R.: Malignant Mesothelioma Producing Intractable Pulmonary Congestion. Archives of Internal Medicine 134: 142, 1974.
3. Black, W.C.; Introduction to Neoplasia, Parts 1 and 2, Audio Visual Presentation (60 minutes). Produced by the Given Institute of Pathology, Aspen, Colorado; University of Colorado, 1974.
4. Black, W.C., and Meuswen, R.: Neoplasms of the Ovary. Audio Visual Presentation (45 minutes). Produced by the Given Institute of Pathology, Aspen, Colorado; University of Colorado, 1974.
5. Black, W.C.: The Cytological Basis of Cancer Diagnosis. Audio Visual Presentation (30 minutes). Produced by the Given Institute of Pathology, Aspen, Colorado, University of Colorado, 1974.

1. Black, W.C.: Audio-Digest, Chronic Liver Disease: Pathological Classification. Family Practice Series, Volume 22, Number 47, 1974.
2. Tung, K.S., and Black, W.C.: Association of Renal Glomerular and Tubular Immune Complex Disease and Antitubular Basement Membrane Antibody, Laboratory Investigation. International Academy of Pathology 32: 166, 1975.
3. Strickland, R.C.; Black, W.C.; Husby, G.; and Williams, Ralph Jr.: Peripheral Blood and Intestinal Lymphocyte Subpopulations in Crohn's Disease. GUT 16: 847, 1975.
4. Black, W.C., and Gomez, L.: Late Effects of X-Irradiation on the Rectum of the Rat. Proceedings of the Radiation Research Society, June, 1976.
5. Black, W.C.: Flyfishing the Rockies. Pruett Press, Boulder, Colorado, 1976.
6. Black, W.C.; Key, C.; Carmany, T.; and Herman, D.: Carcinoma of the Gallbladder in a Population of Southwestern American Indians. Cancer 39: 1267, 1977.
7. Kligerman, M.M.; Black, W.C.; Yuhas, J.M.; Doberneck, R.C.; Bradbury, J.; and Kelsey, C.A.: Current Status of Clinical Pion Radiotherapy. Radiology 125: 439-492, 1977.
8. Black, W.C.; Bordin, G.M.; Varsa, E.; and Herman, D.: Histological Comparison of Breast Carcinomas Among a Population of Southwestern American Indian, Spanish American and Anglo Women. American Journal of Clinical Pathology, 71:142-145, 1979.
9. Black, W.C.; Gomez, L.; Yuhas, J.M.; and Kligerman, M.M.: Quantitation of the Late Effects of X-radiation on the Large Intestine. Cancer, 45:444-451, 1980
10. Black, W.C.; Key, C.R.: Epidemiologic Pathology of Cancer in New Mexico's Tri-Ethnic Population, Pathology Annual, in press.
11. Black, W.C.: Hooked on Flies. Winchester Press, in press.
12. Kligerman, M.M.; Tsujii, H.; Bagshaw, M.; Wilson, S.; Black, W.C.; Mettler, F.; and Hogstrom, K.: Current Observations of Pion Radiotherapy at LAMPF. In Treatment of Radioresistant Cancers, eds., M. Abe, K. Sakamoto, and T.E. Phillips. Amsterdam: Elsevier/North-Holland Biomedical Press, 1979. pp. 145-157
13. Black, W.C.: The Morphogenesis of Gallbladder Carcinoma, Festschrift for Dr. Raffaele Lattes, American Journal of Surgical Pathology, in press.

Give the following information on key professional personnel:
Principal Investigator/Program Director. Photocopy this page for each person.

NAME: Pless Stuart Bowling		TITLE: Staff Member, MP-3, Medium Energy Physics Division, LANL	BIRTHDATE (mo., day, year): [REDACTED]
EDUCATION (Begin with baccalaureate training and include postdoctoral)			
INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	FIELD OF STUDY
[REDACTED]	B.S.E.E.	[REDACTED]	Engineering
[REDACTED]	M.S.E.E.	[REDACTED]	Electrical & Biomedic

RESEARCH AND/OR PROFESSIONAL EXPERIENCE: Concluding with present position, list in chronological order previous employment, research, and honors. Include present membership on any Federal Government Public Advisory Committee. List, in chronological order, the titles and complete references to recent representative publications, especially those most pertinent to this application. Do not exceed 2 pages.

1962-1966 Russian Translator, [REDACTED]
 1966-1967 Card Punch Operator, [REDACTED]
 1968 Research Assistant, [REDACTED]
 1969 Electronics Technician, [REDACTED]
 1969 Engineering Assistant, [REDACTED]
 1970-1974 Systems Design Engineer, [REDACTED]
 1974-1975 Computer Engineer, [REDACTED]
 1976-1978 Project Manager, [REDACTED]
 1978-1979 Staff Member, Nevada Test Site, Los Alamos National Laboratory, New Mexico
 1979-present Staff Member, MP-3 Medium Energy Physics Division, Los Alamos National Laboratory

BIOGRAPHICAL SKETCH

Give the following information for key professional personnel listed on page 1, beginning with the Principal Investigator/Program Director. Photocopy this page for each person.

NAME	TITLE	BIRTHDATE (mo., day, year)
James N. Bradbury, Ph.D.	Group Leader, LANL	[REDACTED]

EDUCATION (Begin with baccalaureate training and include postdoctoral)

INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	FIELD OF STUDY
[REDACTED]	B.A.	[REDACTED]	Physics
[REDACTED]	Ph.D.	[REDACTED]	Physics

RESEARCH AND/OR PROFESSIONAL EXPERIENCE: Concluding with present position, list in chronological order previous employment, research areas, and honors. Include present memberships on any Federal Government Public Advisory Committee. List, in chronological order, the titles and complete references to recent representative publications, especially those most pertinent to this application. Do not exceed 2 pages.

- 1953-1966 Research Assistant, High-Energy Physics Laboratory, [REDACTED]
- 1974-1976 Alternate Group Leader, Practical Applications Group, Medium Energy Physics Division, Los Alamos Scientific Laboratory, New Mexico
- 1976-present Group Leader, Practical Applications Group, Medium Energy Physics Division, Los Alamos National Laboratory, New Mexico

PUBLICATIONS

Leon, M.; Bradbury, J.N.; Gram, P.A.M.; Hutson, R.L.; Schillaci, M.E.; Hargrove, C.K.; and Reidy, J.J.: Observation of the Repulsive Nature of the P-Wave Pion-Nucleus Interaction at Large Z. Physical Review Letters 37: 1135, 1976.

Bradbury, J.N.; Knapp, E.A.; and Rosen, L.: Technology Programs at a Meson Factory. Physics in Industry : 75-79, 1976.

Daniel, H.; Reidy, J.; Hutson, R.; Bradbury, J.; and Helland, J.: Two-Dimensional Visualization of Stopping Pion Distributions. Radiation Research 68: 171-176, 1976.

Amols, H.I.; Awschalom, M.; Bradbury, J.; Boyd, T.J.; Bush, E.; Coulson, L.; Dicello, J.F.; Faulkner, R.; Jameson, R.A.; Johnsen, S.; Kanpp, E.A.; Smith, A.; Stovall, J.; Swenson, D.A.; and Theus, R.: Fast Neutrons Dosimetry and Ion Linear Accelerators. Proceedings of Workshop of Physical Data for Neutron Dosimetry, 1976.

Kligerman, M.M.; Black, W.C.; Yuhas, J.M.; Doberneck, R.C.; Bradbury, J.M.; and Kelsey, C.A.: Current Status of Pion Radiotherapy. Radiology 125: 489, 1977.

Smith, A.R.; Rosen, I.I.; Hogstrom, K.R.; Lane, R.G.; Kelsey, C.A.; Amols, H.I.; Richman, C.; Berardo, P.A.; Helland, J.A.; Kittell, R.S.; Paciotti, M.A.; and Bradbury, J.N.: Dosimetry of Pion Therapy Beams. Medical Physics 4: 408, 1977.

Paciotti, M.A.; Bradbury, J.N.; Knapp, E.A.; Hutson, R.L.; Rivera, O.M.; and Laubacher, D.: Tuning the Beam Shaping Section of the LAMPF Biomedical Channel. IEEE Transactions of Nuclear Science 24: 1058, 1977.

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8. Hanson, K.M.; Bradbury, J.N.; Cannon, T.M.; Hutson, R.L.; Laubacher, D.B.; Macek, R.; Paciotti, M.A.; and Taylor, C.A.: The Application of Protons to Computed Tomography. IEEE Transactions of Nuclear Science NS-25: 657-660, 1978
9. Rosen, I.; Smith, A.; Lane, R.; Kelsey, C.; Lake, D.; Helland, J.; Kittell, R.; Amols, H.; Bradbury, J.; and Richman, C.: An Automated Dosimetry Data Acquisition and Analysis System for the LAMPF Pion Therapy Facility. Medical Physics 5: 120-123, 1978.
10. Allred, J.C.; Bradbury, J.N.; Rosen, L.; Hungerford, E.V.; Kidder, H.R.; Osborne, W.Z.; Phillips, G.C.: Pion Radiotherapy: Studies with Nuclear Emulsions. Physics in Medicine and Biology 23: 4, 1978.
11. Amols, H.I.; Bradbury, J.N.; Dicello, J.F.; Helland, J.A.; Kligerman, M.M.; Lane, T.F.; Paciotti, M.A.; Roeder, D.L.; and Schillaci, M.E.: The Dose Outside of the Treatment Volume for Patients Irradiated with Negative Pions. Physics in Medicine and Biology 23: (3), 385, 1978.
12. Leon, M.; Bradbury, J.N.; Gram, P.A.M.; Hutson, R.L.; Schillaci, M.E.; Hargrove, C.K.; and Reidy, J.J.: Observation of the E2 Nuclear Resonance Effect in Some Pionic Atoms. Nuclear Physics A322: 397-407, 1979.
13. Bradbury, J.N.: Biomedical Applications of Medium Energy Particle Beams at LAMPF. IEEE Transactions of Nuclear Science NS-26: 139-145, 1979.
14. Dicello, J.F.; Zaider, M.; and Bradbury, J.N.: Meson Factories. Proceedings of the 6th International Congress of Radiation Research: 1009-1012, 1979.
15. Paciotti, M.; Amols, H.; Bradbury, J.; Rivera, O.; Hogstrom, K.; Smith, A.; Inoue, H.; Laubacher, D.; and Sandford, S.: Pion Beam Development for the LAMPF Biomedical Project. IEEE Transactions of Nuclear Science NS-26: 1979.

BIOGRAPHICAL SKETCH

Give the following information for key professional personnel listed on page 2, beginning with the Principal Investigator/Program Director. Photocopy this page for each person.

Name: Will M. Foreman	Title: Staff Member, MP-3, Medium Energy Physics Division, Los Alamos National Laboratory	Birthdate: [REDACTED]
-----------------------	---	-----------------------

EDUCATION (Begin with baccalaureate training and include postsecondary)

INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	FIELD OF STUDY
[REDACTED]	B.S.	[REDACTED]	Math/Physics
			2 yrs. graduate work towards Masters in Math
			Math

RESEARCH AND/OR PROFESSIONAL EXPERIENCE: Concluding with present position, list in chronological order previous employment, positions, and honors. Include present memberships on any Federal Government Public Advisory Committee. List, in chronological order, the titles and complete references to recent representative publications, especially those most pertinent to this application. Do not exceed 2 pages.

- 967-1973 Manager of Operations, Systems Programmer, [REDACTED]
- 973-1977 [REDACTED]
- 977-1980 Data Processing Manager, [REDACTED]
- 980-1981 Systems Programmer, [REDACTED]
- February 1981 Staff Member, MP-3, Medium Energy Physics Division, Los Alamos National Laboratory, New Mexico
- present

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Give the following information for key professional personnel listed on page 2, beginning with the Principal Investigator/Program Director. Photocopy this page for each person.

NAME	TITLE	BIRTHDATE (Mo., Day, Year)
Christopher J. Gilman, M.D.	Radiation Oncologist	[REDACTED]

EDUCATION (Begin with secondary training and include postdoctoral)

INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	FIELD OF STUDY
[REDACTED]	A.B.	[REDACTED]	Chemistry, Biology
[REDACTED]	M.D.	[REDACTED]	Medicine
[REDACTED]	Internship	[REDACTED]	Family Practice I
[REDACTED]	Residency	[REDACTED]	Family Practice
[REDACTED]	Residency	[REDACTED]	Radiation Therapy

RESEARCH AND/OR PROFESSIONAL EXPERIENCE: Concluding with present position, list in chronological order previous employment, research, and honors. Include present membership on any Federal Government Public Advisory Committee. List, in chronological order, the titles and complete references to recent representative publications, especially those most pertinent to this application. Do not exceed 2 pages.

- 1979-1981 Volunteer Teaching Staff, Attending Staff, Department of Family Practice, [REDACTED]
- 1980-1981 Instructor, [REDACTED]
- 1981-present Radiation Oncologist, University of New Mexico, Cancer Research and Treatment Center, Los Alamos

BIOGRAPHICAL SKETCH

Give the following information for key professional personnel listed on page 2, beginning with the Principal Investigator/Program Director. Photocopy this page for each person.

Robert A. Hilko, Ph.D.	TITLE Senior Research Scientist. Biomed	BIRTHDATE (Mo., Day, Yr.) [REDACTED]
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EDUCATION (Begin with baccalaureate training and include postdoctoral)

INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	FIELD OF STUDY
[REDACTED]	B.A.	[REDACTED]	Physics
[REDACTED]	Ph.D.	[REDACTED]	Experimental Nuclear Physics

RESEARCH AND/OR PROFESSIONAL EXPERIENCE: Concluding with present position, list in chronological order previous employment, experience, and honors. Include present membership on any Federal Government Public Advisory Committee. List, in chronological order, the titles and complete references to recent representative publications, especially those most pertinent to this application. Do not exceed 1 page.

- 64-75 Research Associate, Physics Department, [REDACTED]
Postdoctoral Fellow, Dept. de Physique, [REDACTED]
- [REDACTED] Trainee, Radiological Sciences Division, [REDACTED]
- 78-79 Physicist, [REDACTED]
- 79-date Senior Research Scientist, Cancer Research and Treatment Center, Biomed Facility, Los Alamos New Mexico

PUBLICATIONS

Morgan, G.L., Mitchell, G.E., Tilley, D.R., Hilko, R.A., and Roberson, N.R.: The $^{14}\text{C}(\alpha, \alpha)Y^{14}\text{HC}$ Reaction from 4 to 8 MeV. Bulletin of the American Physics Society 14: 508, 1969.

Morgan, G.L., Mitchell, G.E., Tilley, D.R., Hilko, R.A., and Roberson, N.R.: Elastic Scattering of Alpha Particles on ^{14}C from 3.5 to 16.5 MeV. Bulletin of the American Physics Society (1969 Winter Meeting in West) 14: 1221, 1969.

Morgan, G.L., Tilley, D.R., Mitchell, G.E., Hilko, R.A., and Roberson, N.R.: States in ^{18}O Excited by the $^{14}\text{C}({}^7\text{Li}, \tau)$ Reaction. Physics Letters 329: 353, 1970.

Morgan, G.L., Tilley, D.R., Mitchell, G.E., Hilko, R.A., and Roberson, N.R.: Study of ^{18}O through $^{14}\text{C} + \alpha$ Reaction. Nuclear Physics A148: 480, 1970.

Nelson, R.O., Roberson, N.R., and Hilko, R.A.: Measurement of Spectroscopic Factors in the $^{24}\text{Mg}(d, \tau)^{23}\text{Mg}$ and $^{24}\text{Mg}(d, {}^3\text{He})^{23}\text{Na}$ Reaction. Bulletin of the American Physics Society (1971 Spring Meeting in Washington, D.C.) 16: 621, 1971.

Hilko, R.A., Nelson, R.O., Dzubay, T.G., and Roberson, N.R.: Mass Identification of Charged Particles by Time of Flight. Bulletin of the American Physics Society (1972 Spring Meeting in Washington, D.C.) 17: 461, 1972.

Nelson, R.O., Roberson, N.R., and Hilko, R.A.: Inelastic Effects in the Study of ^{23}Na and ^{23}Mg . Bulletin of the American Physics Society (1972 Spring Meeting in Washington, D.C.) 17: 532, 1972.

3. Hilko, R.A., Roberson, N.R., Nelson, R.O., and Gould, C.R.: Inelastic Effects in the Study of ^{29}Al and ^{29}Si . Bulletin of the American Physics Society (1973 Spring Meeting in Washington, D.C.) 18: 604, 1973.
9. Hilko, R.A. and Divadeenam, M.: γ -Decay of a Rotator-Particle Doorway Resonance in ^{29}Si . Bulletin of the American Physics Society (1974 Fall Divisional Meeting of Nuclear Physics at Pittsburgh, Pa.) 19: 1017, 1974.
10. Hilko, R.A., Roberson, N.R., and Nelson, R.O.: Incident and Exit Channel Effects in the $^{30}\text{Si}(d,t)^{29}\text{Si}$ Reaction and Their Effect on Spectroscopic Factors. Bulletin of the American Physics Society (1974 Fall Divisional Meeting of Nuclear Physics at Pittsburgh, Pa.) 19: 1033, 1974.
11. Cusson, R.Y. and Hilko, R.A.: Realistic Heavy Ion Potentials from Constrained Self-Consistent B.H.F. Calculations. Bulletin of the American Physics Society 20: , 1975.
12. Cusson, R.Y., Kolb, D., and Hilko, R.A.: Realistic Heavy Ion Adiabatic Potentials. Nuclear Physics A270: 437, 1975.
13. Hilko, R.A.; Ramavataram, K.; and Rangacharyulu, C.: $^{68}\text{Zn}(p,\gamma)$ Study of the Ground State Isobaric Analogue Resonance of ^{69}Zn . Bulletin of the American Physics Society 21: 581, 1976.
14. Ramavataram, K.; Rangacharyulu, C.; Szogy, I.; St.-Pierre, C.; and Hilko, R.A.: Isobaric Analog Resonances in the $^{68}\text{Zn}(p,\gamma)^{69}\text{Ga}$ Reaction. Physiological Reviews 17: 1583, 1976.

BIOGRAPHICAL SKETCH

Give the following information for key professional personnel listed on page 2, beginning with the Principal Investigator/Program Director. Photocopy this page for each person.

46	Mario Kornfeld, M.D.	TITLE Neuropathologist, CRIC Professor of Pathology	BIRTHDATE (mm-dd-yy) [REDACTED]
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EDUCATION (Begin with secondary training and include postdoctoral)

INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	FIELD OF STUDY
Med. Faculty of the Univ., [REDACTED]	-	-	Medicine
Medical Faculty in [REDACTED]	M.D.	[REDACTED]	Medicine
Residency Internship, Univ. Hosp., [REDACTED]	-	[REDACTED]	Medicine
Residence, Gen. Path., Institute of Pathology General Hospital, [REDACTED]	-	[REDACTED]	Pathology

RESEARCH AND/OR PROFESSIONAL EXPERIENCE: Concluding with present position, list in chronological order previous employment, appointments, and honors. Include present membership on any Federal Government Public Advisory Committee. List, in chronological order, the titles and honors referenced in recent representative publications, especially those most pertinent to this application. Do not exceed 2 pages.

- 59-64 General Pathology, Institute of Pathology, General Hospital, [REDACTED]
- [REDACTED] Trainee, Division of Neuropathology, College of Physicians and Surgeons, [REDACTED]
- [REDACTED] Fellow, Division of Neuropathology and Otolological Research Laboratory, College of Physicians and Surgeons, [REDACTED]
- 57-68 Instructor, Neuropathology, College of physicians and Surgeons, [REDACTED]
- 68-70 Assistant Professor, Pathology, [REDACTED]
- 70-80 Associate Professor, Pathology, [REDACTED]
- 79 Present Pathologist, Cancer Research and Treatment Center, University of New Mexico, Albuquerque
- 80-present Professor, Pathology, University of New Mexico, School of Medicine, Albuquerque

PUBLICATIONS

Appenzeller, O., and Kornfeld, M.: Macroductyly and Localized Hypertrophic Neuropathology. Neurology 24: 767-771, 1974.

Vorherr, R.; Vorherr, U.F.; McConnell, T.S.; Goldberg, N.M.; Kornfeld, M.; and Jordan, S.W.: Localization and Origin of Antidiuretic Principle in Para-Endocrine-Active Malignant Tumors. Oncology 29: 201-218, 1974.

Kornfeld, M.; Snyder, R.D.; MacGee, J.; and Appenzeller, O.: The Oculo-Cerebral-Renal Syndrome of Love. Archives of Neurology 32: 103-107, 1975.

Kornfeld, M.; Appenzeller, O.; Saiki, J.; and Troup, G.M.: Sea-Blue Histiocytes and Sural Nerve in Neurovisceral Storage Disorder with Vertical Ophthalmoplegia. Journal of Neurological Science 25: 291-302, 1975.

Appenzeller, O.; Kornfeld, M.; and Snyder, R.: Acromutilating, Paralyzing Neuropathy with the Corneal Ulceration in Navajo Children. Archives of Neurology 33: 733-738, 1976.

6. Kornfeld, M.; Snyder, R.D.; and Wenger, D.: Fucosidosis with Angiokeratoma: Electron Microscopic Changes in the Skin. Archives of Pathology and Laboratory Medicine 101: 478, 1977.
7. Vorherr, H.; Messer, R.H.; Vorherr, U.F.; Jordan, S.W.; and Kornfeld, M.: Diethylstilbestrol-Induced Teratogenesis and Carcinogenesis in Rats. Federation Proceedings 35: 567, 1976.
8. Davis, L.E.; Snyder, R.D.; Orth, D.N.; Nicholson, W.E.; Kornfeld, M.; and Seelinger, D.F.: Adrenoleukodystrophy and Adrenomyeloneuropathy Associated with Partial Adrenal Insufficiency in Three Generations of a Kindred. American Journal of Medicine 66: 342-347, 1979.
9. Vorherr, H.; Messer, R.J.; Vorherr, U.; Jordan, S.W.; and Kornfeld, M.: Teratogenesis and Carcinogenesis in Rat Offspring after Transplacental and Transmammary Exposure to Diethylstilbestrol. Biochemical Pharmacology 28: 1365-1377, 1979.
10. Rosenberg, G.A.; Kornfeld, M.; Stovring, J.; and Bickness, J.M.: Subcortical Arteriosclerotic Encephalopathy (Binswanger): Computerized Tomography. Neurology 29: 1102-1106, 1979.
11. Appenzeller, O.; Kornfeld, M.; and Atkinson, R.: Pure Axonal Neuropathy: Nerve Xenograft and Clinical Pathological Study of Family with Peripheral Neuropathy, Hereditary Ataxia, Focal Necrotizing Encephalopathy and Spongy Degeneration of Brain. Annals of Neurology 7: 251-261, 1980.
12. McConnell, T.S.; Kornfeld, M.; McClellan, G.; and Abase, J.: Partial Deletion of Chromosome 2 Mimicking a Phenotype of Trisomy 18: Case Report with Autopsy. Human Pathology 11: 202-205, 1980.
13. Davis, L., and Kornfeld, M.: Influenza A Virus and Reye's Syndrome in Adults. Journal of Neurology, Neurosurgery and Psychiatry 43: 516-521, 1980.
14. Kornfeld, M.: Mixed Nemaline-mitochondrial "Myopathy." Acta Neuropathologica (Berlin) 51: 185-189, 1980.
15. Davis, L.; Johnsson, L.; and Kornfeld, M.: Cytomegalovirus Labyrinthitis in an Infant: Histological, Virological and Immunofluorescence Studies. Submitted to Journal of Neuropathology and Experimental Neurology.

BIOGRAPHICAL SKETCH

Give the following information for key professional personnel listed on page 1 beginning with the Principal Investigator/Program Director. Photocopy this page for each person.

James E. Lambert	TITLE MP-7 Staff Member, LANL	BIRTHDATE (Mo., Day, Yr.) [REDACTED]
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EDUCATION (Begin with baccalaureate training and include postgraduate)

INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	FIELD OF STUDY
[REDACTED]	B.S.	[REDACTED]	Mechanical Engineering

RESEARCH AND/OR PROFESSIONAL EXPERIENCE: Concluding with present position, list in chronological order previous employment, experience, and honors. Include present membership on any Federal Government Public Advisory Committee. List, in chronological order, the titles and authors references to recent representative publications, especially those most pertinent to the application. Do not exceed 2 pages.

- 1956-1957 Engineer, [REDACTED]
- 1967-1970 Staff Member, N-3 and J-9, Los Alamos Scientific Laboratory, New Mexico
- 1970-1976 Staff Member, ENG-6, Device Positioning and Mechanical Design, Los Alamos Scientific Laboratory, New Mexico
- 1976-present Staff Member, MP-7, Mechanical Design and Remote Handling Equipment Supervision Los Alamos National Laboratory, New Mexico

C. L. [REDACTED]

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BIOGRAPHICAL SKETCH

Give the following information for key professional personnel listed on page 2, beginning with the Principal Investigator/Program Director. Photocopy this page for each person.

NAME Frederick A. Mettler, Jr., M.D.	TITLE Chief, Diagnostic Imaging Assoc. Prof., Radiology	BIRTHDATE (mo., day, year) [REDACTED]
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EDUCATION (Begin with baccalaureate training and include postdoctoral)

INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	FIELD OF STUDY
[REDACTED]	A.B.	[REDACTED]	Mathematics
[REDACTED]	M.D.	[REDACTED]	Medicine
[REDACTED]	M.P.H.	[REDACTED]	Industrial Health

RESEARCH AND/OR PROFESSIONAL EXPERIENCE: Concluding with present position, list in chronological order previous employment, positions, and honors. Include present membership on any Federal Government Public Advisory Committee. List, in chronological order, the titles and complete references to recent representative publications, especially those most pertinent to this application. Do not exceed 2 pages.

- 1969 Guest Investigator, [REDACTED]
- [REDACTED] Rotating Radiology Internship, [REDACTED]
- [REDACTED] Radiology Resident, [REDACTED]
- 1972-1974 Radiologist, [REDACTED]
- 1974-1976 Medical Consultant, [REDACTED]
- [REDACTED] NIH Clinical Fellow, [REDACTED]
- [REDACTED] Graduate, Nuclear Engineering Courses, [REDACTED]
- 1975-1977 Manager, Health Services Division, [REDACTED]
- 1976-1977 Assistant Clinical Professor, Department of Radiology, [REDACTED]
- 1977-1978 Acting Chief, Division of Nuclear Medicine, Department of Radiology, [REDACTED]
- 1977-1979 Chief, Diagnostic Imaging, [REDACTED]
- Assistant Professor of Radiology, [REDACTED]
- 1978-1982 Picker Foundation Scholar
- 1980-present Chief, Diagnostic Imaging and Associate Professor of Radiology, University of New Mexico, Albuquerque

Publications

1. Kligerman, M.M.; Tsujii, H.; Bagshaw, M.; Wilson, S.; Black, W.C.; Mettler, F.A.; and Hogstrom, K.: Current Observations of PION Radiation Therapy at LAMPF. Treatment of Radioresistant Cancers. Elsevier/North Holland Biomedical Press, 1979.
2. Mettler, F.; Schultz, K.; and Kelsey, C.A.: Gray Scale Ultrasonography in Evaluation of Carcinoma of the Base of the Tongue. Radiology 133(3): 781-784, 1979.
3. Mettler, F.A.: Radiographic Manifestations of Drug Toxicity. Current Problems in Diagnostic Radiology, Year Book Publishers, July-August, 1979.

berts, K.T., and Mettler, F.A.: Evaluation of the Pelvic and Abdominal Lymphatic System. Current Problems in Diagnostic Radiology, Year Book Publishers, Sept.-October, 1979.

Tsujii, N.; Bagshaw, M.A.; Smith, A.R.; von Essen, C.F.; Mettler, F.A.; and Kligerman, M.M.: Localization of Structures for PICON Radiotherapy by Computerized Tomography and Orthodiagraphic Projection. International Journal of Radiation Oncology, Biology, and Physics 6: 319-325, 1980.

Requard, K., and Mettler, F.A.: Sonographic Diagnosis and Evaluation of Therapy in Trophoblastic Disease. Radiology 135: 419-422, 1980.

Mettler, F.A.: Low Level Radioactive Waste: Generator's Experience. Nuclear Regulatory Commission NUREG/CP 0013, July 1980.

Mettler, F.A. and Christie, J.H.: Scintigraphic Pattern of Acute Renal Vein Thrombosis. Clinical Nuclear Medicine, August 1980.

Mettler, F.A., and Christie, J.H.: Another Cause of Hepatic Hot Spot: Isolated Innominate Vein Obstruction. Clinical Nuclear Medicine, October 1980.

Crawford, E.D.; Peters, P.C.; Mettler, F.A., et al.: Clinicopathologic Conference: Renal Mass in a Man with Eosinophilic Granuloma. Urology 15: 520-525, 1980.

Ball, W.S.; Wicks, J.; and Mettler, F.A.: Positional CT Scanning for Radiotherapy Planning. American Journal of Roentgenology 135: 815-820, 1980.

Mettler, F.A.: Biological Risks of Medical Irradiation. UNSCEAR Update. APM Monograph Series, November 1980.

Wicks, J.D.; Mettler, F.A.; and Schultz, K.H.: Bacterial Contamination of an Automated Water Path B-scanner. Radiology 136: September 1980.

Mettler, F.A.; Wicks, J.D.; and Christie, J.H.: Biliary Imaging: A New Look. Current Problems in Diagnostic Radiology, Year Book Publishers, Sept-Oct, 1980.

Mettler, F.A.; Thornbury, J.R.; and Wicks, J.D.: Diagnostic Radiologic Evaluation. In Genitourinary Cancer Surgery, Philadelphia: Lea & Febiger.

Mettler, F.A.; Wicks, J.D.; Thornbury, J.R.; and Crawford, D.E.: Co-existent Renal Eosinophilic Granuloma and Renal Adenocarcinoma. Urologic Radiology, in press.

Kelsey, C.A.; Moseley, R.D.; Mettler, F.A.; and Briscoe, D.E.: Cost Effectiveness of Stereoradiographs in Lung Tumor Detection. Radiology, in press.

Kelsey, C.A.; Moseley, R.D.; Mettler, F.A.; and Briscoe, D.E.: Observer Performance as a Function of Viewing Distance. Investigative Radiology, in press.

Requard, C.K.; Mettler, F.A.; and Wicks, J.D.: Preoperative Sonographic Evaluation of Malignant Ovarian Tumors. Submitted to American Journal of Roentgenology.

Rosen, I.; Hall, T.C.; Mettler, F.A.; et al.: A Computerized Database System for Medical Diagnostic Studies (DIASTU). Submitted to Computer Programs in Biomedicine.

BIOGRAPHICAL SKETCH

Give the following information for each professional person in the Principal Investigator Program Director's office. Give this data for each person.

NAME	TITLE	ADDRESS (City, State, Zip)
Moseley, Robert D., Jr.	Professor and Chairman	[REDACTED]

EDUCATION (Begin with postgraduate training and include an institution)

INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	FIELD OF STUDY
[REDACTED]	M.D.	[REDACTED]	Medicine

RESEARCH AND/OR PROFESSIONAL EXPERIENCE: Conclude with present position. List in chronological order previous employment, positions, and honors. Include present memberships on any Federal Government Public Advisory Committee. List, in chronological order, the titles and complete references, to recent representative publications, especially those most pertinent to this application. Do not exceed 1000.

EXPERIENCE:

- 5/78 - present Chairman Department of Radiology, University of New Mexico
- 6/71 - present Professor of Radiology, University of New Mexico
- 3/58 - 6/71 Professor and Chairman Department of Radiology, [REDACTED]
- 7/57 - 7/58 Associate Professor Department of Radiology [REDACTED]
- President, Board of Directors James Picker Foundation
- Member, Board of Directors National Council on Radiation Protection and Measurements
- Chairman US Delegation to United Nations Scientific Committee on the Effects of Atomic Radiation
- 7/68 - 6/71 Director Biomedical Computation Facilities, [REDACTED]

Moseley, R.D., Jr.: Kurt Rossmann, In Memoriam. Med. Physics 4: 268-269, May-June, 1977.

Kelsey, C.A.; Moseley, R.D., Jr.; Brogdon, B.G.; Shave, D.G.; and Hallberg, J.R.: Effect of size and positron on chest lesion detection. Am. J. Roentgenol. 129: 205-208, August, 1977.

Moseley, R.D., Jr., and Linton, O.W.: The federal government's impact on radiology. Am. J. Roentgenol. 129: 171-174, July, 1977.

Moseley, R.D., Jr.: Second Image Receptor Conference: Radiographic Film Processing, Report of Workshop I, pp. 125-127, HEW Publication (FDA) 77-8036, August, 1977.

Brogdon, B.G.; Moseley, R.D., Jr.; Kelsey, C.A.; and Hallberg, J.R.: Perception of simulated lung lesions. Investigative Radiology, 13: 12-15, January-February, 1978.

Brogdon, B.G.; Kelsey, C.A.; and Moseley, R.D., Jr.: Effect of fatigue and other physiologic factors on observer perception. Am. J. Roentgenol. 130: 971-974, May, 1978.

Moseley, R.D., Jr.: Editorial: Radiation effects and radiologic personnel. Applied Radiology, 8: 14, November-December, 1979.

Kelsey, C.A.; Moseley, R.D., Jr.; Mettler, F.A.; Briscoe, D.E.: Cost Effectiveness of Stereoradiographs in Lung Tumor Detection. Radiology To Be Published 1982.

Kelsey, C.A.; Moseley, R.D., Jr.; Mettler, F.A.; Garcia, J.F.; Parker, T.W.; Briscoe, D.E.: Comparison of Nodule Detection with 70 and 120 kVp Chest Radiographs Submitted to Radiology 1981.

Kelsey, C.A.; Moseley, R.D., Jr.; Mettler, F.A.; Parker, T.W.; Garcia, J.F.; Juhl, J.H.; Briscoe, D.E.: The Effect of Anticross-over Emulsions on Observer Performance Submitted to Investigative Radiology 1981.

Kelsey, C.A.; Mettler, F.A.; Moseley, R.D., Jr.; Briscoe, D.E.: Measured Effect of Antireflective Eyeglass Coatings on Observer Performance Submitted to Radiology 1981.

Parker, T.W.; Kelsey, C.A.; Moseley, R.D., Jr.; Mettler, F.A.; Garcia, J.F.; Briscoe, D.E.: Directed vs Free Search for Nodules in Chest Radiographs Accepted for publication in Invest Radiol 1982.

BIOGRAPHICAL SKETCH

Give the following information for key professional personnel listed on page 2, beginning with the Principal Investigator/Program Director. Photocopy this page for each person.

NAME	TITLE	BIRTHDATE (Mo., Day, Yr.)
Michael A. Paciotti, Ph.D.	Physicist, LANL	[REDACTED]
EDUCATION (Begin with baccalaureate training and include postdoctoral)		
INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED
[REDACTED]	B.S.	[REDACTED]
[REDACTED]	Ph.D.	[REDACTED]

RESEARCH AND/OR PROFESSIONAL EXPERIENCE: Concluding with present position, list in chronological order previous employment, positions, and honors. Include present memberships on any Federal Government Public Advisory Committee. List, in chronological order, the titles and complete references to recent representative publications, especially those most pertinent to this application. Do not exceed 2 pages.

- [REDACTED] Graduate Student Research Assistant, pion and kaon physics. [REDACTED]
- 1970-72 Staff Member, MP-3, experimental accelerator development, Los Alamos National Laboratory, New Mexico
- 1972-present Staff Member, MP-3, biomedical facilities development and channel tuning, Los Alamos National Laboratory, New Mexico

PUBLICATIONS

1. Dorfman, D.; Enstrom, J.; Raymond, D.; Schwartz, M.; Wojcicki, S.; Miller, D.; and Paciotti, M.: Charge Asymmetry in the Muonic Decay of the K₂₀. Physical Review Letters 19: 987, 1967.
2. Paciotti, M.A.: Charge Asymmetry in the Muonic Decay of the K₂₀. UCRL-19446, [REDACTED].
3. Trump, M.A.; Machen, D.R.; Paciotti, M.A.; and Swenson, D.A.: Bead Perturbation Measurement. Proceedings of the 1970 Particle Accelerator Conference NAL, September 28, 1970.
4. Swenson, D.A.; Goplen, B.C.; Paciotti, M.A.; and Stovall, J.E.: Beam Measurements of the First Tank of LAMPF. Proceedings of the 1971 Particle Accelerator Conference, Chicago, March 1-3, 1971.
5. Stevens, R.R., Jr.; Palermo, J.; Paciotti, M.A.; Mueller, D.W.; Mills, R.S.; Meyer, E.A.; Kohl, D.K.; and Goplen, B.C.: Beam Measurements on the High-Intensity Proton Injector of LAMPF. LANS Report No. LA-4961-MS, May 1972.
6. Paciotti, M.A.; Bradbury, J.M.; Helland, J.A.; Hutson, R.L.; Rivera, O.M.; and Laubacher, D.: Tuning of the First Section of the Biomedical Channel at LAMPF. IEEE Transactions on Nuclear Science NS-22: 1784, 1975.
7. Paciotti, M.A.; Bradbury, J.M.; Knapp, E.A.; Hutson, R.L.; Rivera, O.M.; and Laubacher, D.: Tuning the Beam Shaping Section of the LAMPF Biomedical Channel. IEEE Transactions on Nuclear Science NS-24: 1058, 1977.

Michael A. Paciotti, Ph.D.
Biographical Sketch
Page 2

Moseley, Robert D., Jr., M.D.

Smith, A.R.; Kligerman, M.M.; Kelsey, C.A.; Lane, R.G.; Berardo, P.A.; Paciotti, M.A.;
and Richman, C.: Treatment Planning for Negative Pi Meson Radiation Therapy: UNM-LASL
Experience. International Journal of Radiation Oncology, Biology, and Physics 3: 307-314
1977.

Amols, H.I.; Bradbury, J.; Dicello, J.F.; Holland, J.A.; Kligerman, M.M.; Lane, T.F.;
Paciotti, M.A.; Roeder, D.L.; and Schillaci, M.A.: The Dose Outside of the Treatment
Volume for Patients Irradiated with Negative Pions. Physics in Medicine and Biology
23: 385-396, 1978.

BIOGRAPHICAL SKETCH

Give the following information for key professional personnel listed on page 2, beginning with the Principal Investigator/Program Director. Photocopy this page for each person.

NAME Mudundi E. Raju, Ph.D.	TITLE LS-1 Group, Los Alamos National Laboratory	BIRTHDATE (mm, day, year) [REDACTED]
--------------------------------	---	---

EDUCATION (Begin with baccalaureate training and include postdoctoral)

INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	FIELD OF STUDY
[REDACTED]	B.S., M.A.	[REDACTED]	Physics
[REDACTED]	M.S.	[REDACTED]	Physics
[REDACTED]	Ph.D.	[REDACTED]	Nuclear Physics

RESEARCH AND/OR PROFESSIONAL EXPERIENCE: Concluding with present position, list in chronological order previous employment, experience, and honors. Include present membership on any Federal Government Public Advisory Committee. List, in chronological order, the titles and complete references to recent representative publications, especially those most pertinent to this application. Do not exceed 2 pages.

- [REDACTED] Post Doctoral Research Fellow in Biophysics, [REDACTED]
- [REDACTED] Post Doctoral Research Fellow in Biophysics, [REDACTED]
- 1964-1966 Biophysicist, [REDACTED]
- 1966-1968 Assistant Professor, [REDACTED] and Guest Scientist at [REDACTED]
- July-Dec. 1976 Visiting Scientist, [REDACTED] Supported by the U.S. Atomic Energy Commission and the Medical Research Council of England
- 1968-1971 Associate Professor, [REDACTED] and Guest Scientist at [REDACTED]
- 1971-present Staff Member, LS-1 Group, Los Alamos National Laboratory

PUBLICATIONS

1. Raju, M.R.; Gnanapugani, M.; Martins, B.T.; Richman, C.; and Barendsen, G.W.: Measurement of RBE and OER of π^- Mesons with Cultured Human Cells. British Journal of Radiology 45: 178-181, 1972.
2. Tobias, C.A.; Lyman, J.T.; Chatterjee, A.; Howard, J.; Maccabee, H.D.; Raju, M.R.; Smith, A.R.; Sperinde, J.M.; and Welch, G.P.: Radiological Physics Characteristics of the Extracted Heavy Ion Beams of the Bevatron. Science 174: 1131-1134, 1971.
3. Raju, M.R.: Negative Pions in Radiotherapy: A Brief Review. European Journal of Cancer 10: 211-215, 1974.
4. Madhavanath, U.; Raju, M.R.; and Kelley, L.S.: Survival of Human Lymphocytes Following Exposure to Densely Ionizing Radiation. ERDA Symposium Series 37: 125-139, 1976.
5. Raju, M.R., and Jett, J.H.: RBE and OER Variations of Mixtures of Plutonium Alpha Particles and X-Rays for Damage to Human Kidney Cells (T-1). Radiation Research 60: 473-481, 1974.
6. Raju, M.R.; Tobey, R.A.; Jett, J.H.; and Walters, R.A.: Age Response for line CHO Chinese Hamster Cells Exposed to X-Irradiation and Alpha Particles from Plutonium. Radiation Research 63: (422), 161-167, 1975.

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- Raju, M.R.; Frank, J.P.; Bain, E.; and Trujillo, T.T.: The Use of Hypoxic Cell Radiosensitizers with Mixed X and α Radiations. Radiation Research 71: 233-239, 1977.
- Raju, M.R.; Amols, H.I.; and Carpenter, S.: A Combination of Sensitizers with High LET Radiations. British Journal of Cancer 37: Supp. III, 189-193, 1977
1. Raju, M.R.; Amols, H.I.; Bain, E.; Carpenter, S.; Cox, R.A.; and Robertson, J.B.: OER and RBE for Negative Pion Beams of Different Peak Widths. British Journal of Radiology 52: 494-498, 1979.
2. Raju, M.R.; Amols, H.I.; Tobey, R.A.; and Walters, R.A.: Age Response for Line CHO Chinese Hamster Cells Exposed to Peak Negative Pions. Radiation Research 75: 219-233, 1973.
3. Raju, M.R.; Amols, H.I.; Dicello, J.F.; Howard, J.; Lyman, J.T.; Koehler, R.; Graves, R.; and Smathers, J.B.: A Heavy Particle Comparative Study. Part I. Depth Dose Distributions. British Journal of Radiology 51: 699-703, 1978.
4. Raju, M.R.: Differences in Cell-Cycle Progression Delays After Exposure to ^{228}Pu -Alpha Particles Compared to X-Rays. Radiation Research 84: 16-24, 1980.
5. Raju, M.R.; Bain, E.; Carpenter, S.G.; Jett, J.; and Walters, R.A.: Effects of Argon Ions on Synchronized Chinese Hamster Cells. Radiation Research 84: 152-157, 1980.
6. Raju, M.R.; Carpenter, S.; Tokita, N.; Dicello, J.F.; Jackson, D.; Frohlick, E.; and Van Ersen, C.: Effect of Fractionated Doses of Pions on Normal Tissues. International Journal of Radiation Oncology, Biology, and Physics 6: 1663-1666, 1980.
7. Raju, M.R., and Richman, C.: Physical and Biological Aspects of Negative Pions with a View to Their Use in Radiotherapy. Current Topics in Radiation Research 8: 159-233, 1972.

BIOGRAPHICAL SKETCH

Give the following information for key professional personnel listed on page 2, beginning with the Principal Investigator/Program Director. Photocopy this page for each person.

NAME	TITLE	BIRTHDATE (mm-dd-yy)
Robert S. Seigel, M.D.	Chief, Neuroradiology Section, Assistant Prof. Radiology	[REDACTED]

EDUCATION (Begin with postgraduate training and include postdoctoral)

INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	FIELD OF STUDY
[REDACTED]	B.A.	[REDACTED]	Political Science, History
[REDACTED]	M.D.	[REDACTED]	Medicine

RESEARCH AND/OR PROFESSIONAL EXPERIENCE: Concluding with present position, list in chronological order previous employment, positions, and honors. Include present membership on any Federal Government Public Advisory Committee. List, in chronological order, the titles and complete references to recent representative publications, especially those most pertinent to this application. Do not exceed 2 pages.

1976-77 Instructor, Radiology, [REDACTED]
 1977-78 Instructor, [REDACTED]
 1978-79 Assistant Professor of Radiology, [REDACTED]
 1979 Acting Chairman, Department of Radiology, [REDACTED]
 1979-80 Attending Physician, [REDACTED]
 1980-present Chief, Neuroradiology Section, University of New Mexico School of Medicine, Albuquerque.

PUBLICATIONS

- Seigel, R.S.; Thrall, J.; and Sisson, J.: Thyroid Acrophachy: 99 mTc Pyrophosphate Scan and Radiographic Correlation. Journal of Nuclear Medicine 17: 791-793, 1976.
- Seigel, R.S., and Wolson, A.: The Radiographic Manifestations of Chronic Pneumocystic Carinii Pneumonia. American Journal of Roentgenology 128: 150-152, 1977.
- Borlaza, G.; Siefel, R.S.; Fischer, B.; and Kuhns, L.R.: A New Double Exposure Technique for Demonstration of Osseous and Pulmonary Structures on a Single CT Film. American Journal of Roentgenology 130: 375-376, 1978.
- Kuhns, L.R.; Siegel, R.S.; and Borlaza, G.: A Simple Method of Localizing the Level of Computed Tomography Cross Sectioning. Journal of Computer Assisted Tomography 2: 233-234, 1978.
- Kuhns, L.R.; Seigel, R.S.; and Borlaza, G.: A Simple Method for Production of Slides of CT Images from Multifformat Radiographs. Computerized Tomography 2: 45-46.
- Kuhns, L.R.; Borlaza, G.; Seigel, R.S.; and Cho, R.J.: Localization of the Head of the Pancreas Using the Junction of the Left Renal Vein and the Inferior Vena Cava. Journal of Computer Assisted Tomography 2: 170-172, 1978.
- Kuhns, L.R.; Borlaza, G.S.; Seigel, R.S.; and Thornbury, J.R.: Relationships of External Anatomical Landmarks of the Abdomen to Vertebral Segments. American Journal of Roentgenology 131: 115-118, 1978.

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1. Kuhns, L.R.; Borlaza, G.S.; Seigel, R.S.; Pozderac, R.; and Simmons, J.: Lack of Visualization of the Portal Venous Tree in Cirrhosis of the Liver: a CT Finding with Possible Diagnostic Significance. Journal of Computer Assisted Tomography 2: 400-403, 1978.
2. Seigel, R.S.; Seeger, J.F.; Gabrielsen, T.O.; and Allen, R.J.: Cerebral Computed Tomography in Oculocraniosomatic Disease (Kerns-Sayre Syndrome). Radiology 130(1): 159-164, 1979.
3. Kuhns, L.R.; Seigel, R.S.; Borlaza, G.S.; and Rapp, R.: Visualization of the Longitudinal Fold of the Duodenum by CT. Journal of Computer Assisted Tomography 3(3): 345-347, 1979.
4. Borlaza, G.S.; Kuhns, L.R.; Seigel, R.S.; and Rapp, R.: The Posterior Pararenal Space: An Escape Route for Retrocrural Masses. Journal of Computer Assisted Tomography 3(4): 470-473, 1979.
5. Kuhns, L.R.; Borlaza, G.S.; and Seigel, R.S.: Rapid Sequence Display of CT Images: An Aid in the Diagnosis of Pulmonary Metastases. Radiology 747-748, 1979.
6. Borlaza, G.S.; Kuhns, L.R.; and Seigel, R.S.: CT and Angiographic Demonstration of Gastroduodenal Artery Pseudoaneurysm in a Pancreatic Pseudocyst. Journal of Computer Assisted Tomography 3(5): 612-614, 1979.
7. Borlaza, G.S.; Seigel, R.S.; Paramugul, C.; and Berger, P.E.: An In Vitro Comparison of Computerized Tomography, Xeroradiography, and Radiography in the Detection of Soft Tissue Foreign Bodies. Radiology 132(1): 218-219, 1979.
8. Kuhns, L.R.; Thornbury, J.R.; and Seigel, R.S.: Variation of Position of the Kidneys and Diaphragm in Patients Undergoing Repeated Suspension of Respiration: A Radiological Study. Journal of Computer Assisted Tomography 3(5): 620-621, 1979.
9. Seigel, R.S.; McCormick, T.L.; Kuhns, L.R.; and Borlaza, G.S.: Computed Tomography and Angiography in Ileal Carcinoid Tumors and Retractable Mesenteritis. Radiology 134(2): 437-440, 1980.
10. McCormick, T.L.; Seigel, R.S.; and Forrest, M.E.: Subclavical Steal Syndrome: Is Venous Phase Angiography Worthwhile? Radiology, in press.
11. Borlaza, G.S.; Seigel, R.S.; Kuhns, L.R.; Kawanishi, H.: Case Report: Intramural Diverticulum of the Esophagus Simulating an Esophageal Lipoma. American Journal of Roentgenology, in press.
12. Kroll, P.D., and Seigel, R.S.: Cerebral Cortical Atrophy in Alcoholic Men. Journal of Clinical Psychiatry, in press.
13. Borlaza, G.S.; Seigel, R.S.; Kuhns, L.R.; Good, A.E.; Rapp, R.; and Martel, W.: Computed Tomography in the Evaluation of Sacroiliac Arthritis. Radiology, in press.

BIOGRAPHICAL SKETCH

Give the following information for key professional personnel listed on page 2, beginning with the Principal Investigator/Program Director. Photocopy this page for each person.

NAME	TITLE	BIRTHDATE (Mo., Day, Yr.)
Alfred R. Smith, Ph.D.	Associate Professor Radiology	[REDACTED]

EDUCATION (Begin with baccalaureate training and include postdoctoral)

INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	FIELD OF STUDY
[REDACTED]	B.A.	[REDACTED]	Mathematics
[REDACTED]	M.S.	[REDACTED]	Physics
[REDACTED]	Ph.D.	[REDACTED]	Physics

RESEARCH AND/OR PROFESSIONAL EXPERIENCE: Concluding with present position, list in chronological order previous employment, positions, and honors. Include present membership on any Federal Government Public Advisory Committee. List, in chronological order, the titles and complete references to recent representative publications, especially those most pertinent to this application. Do not exceed 2 pages.

- 1963-64 [REDACTED] Instructor, Physics Laboratory, [REDACTED]
[REDACTED] Fellow, [REDACTED]
- 1966-67 Physics Instructor, [REDACTED]
- 1967-70 [REDACTED] Research Assistant [REDACTED] (Research Grant), [REDACTED]
[REDACTED] Advanced Senior Fellow in Medical Physics, [REDACTED]
- 1971-74 Assistant Physicist and Assistant Professor of Biophysics, [REDACTED]
- 1972-75 Associate to the Faculty, [REDACTED]
- 1974-75 Associate Physicist and Assistant Professor of Biophysics, [REDACTED]
- 1975-78 Assistant Professor of Radiology, [REDACTED]
- 1975-present Biomedical Physicist, Cancer Research and Treatment Center, University of New Mexico, Albuquerque
- 1976 Co-author of paper which received the Farrington Daniels Award for best paper published in Medical Physics
- 1976-present Chairman of the AAPM Charged Particle Physics Dosimetry Group
- 1979-present Associate Professor of Radiology, University of New Mexico, Albuquerque

PUBLICATIONS

1. Smith, A.R., and Richman, C.: W Values, Stopping Power Ratios and Kerma Values for the LAMPF Therapy Beam. Biological Sciences Monograph on Basic Physical Data for Neutron Dosimetry. Edited by J.J. Broerse. The Commission of the European Communities, Luxembourg. (EUR 5629C), 1976.
2. Smith, A.R.; Rosen, I.I.; Hogstrom, K.R.; and Prichard, H.W.: The Silicon Diode as an In Vivo Dosimeter for Fast Neutrons. International Journal of Radiation Oncology, Biology, and Physics 2: 111-116, 1977.
3. Smith, A.R.; Kligerman, M.M.; Kelsey, C.A.; Lane, R.G.; Berardo, P.A.; Paciotti, M.A.; and Richman, C.: Treatment Planning for Negative Pi Meson Radiation Therapy: UNM-LASL Experience. International Journal of Radiation Oncology, Biology, and Physics 3: 307-314, 1977.

- Kligerman, M.M.; Smith, A.R.; Yuhas, J.M.; Wilson, S.; Sternhagen, C.J.; and Helland, J.A.: The Relative Biological Effectiveness of Pions in the Acute Response of Human Skin. International Journal of Radiation Oncology, Biology, and Physics 3: 335-339, 1977.
- Smith, A.R.; Rosen, I.I.; Hogstrom, K.R.; Lane, R.G.; Kelsey, C.A.; Amols, H.I.; Richman, C.; Berardo, P.A.; Helland, J.A.; Kittell, R.S.; Paciotti, M.A.; and Bradbury, J.N.: Dosimetry of Pion Therapy Beams. Medical Physics 4: 408-413, 1977.
- Kligerman, M.M.; von Essen, C.F.; Khan, M.K.; Smith, A.R.; Sternhagen, C.J.; and Sala, J.M.: Experience with Pion Radiotherapy. Cancer 43: 1043-1051, 1979.
- Hogstrom, K.R.; Smith, A.R.; Somers, J.; Lane, R.G.; Rosen, I.I.; and Kelsey, C.A.: Measurement of the Effect of Inhomogeneities and Compensating Bolus in Clinical Pion Beams. Medical Physics 6: 26-31, 1979.
- Hogstrom, K.R.; Smith, A.R.; Simon, S.L.; Somers, J.W.; Lane, R.G.; Rosen, I.I.; Kelsey, C.A.; von Essen, C.F.; Kligerman, M.M.; Berardo, P.A.; and Zink, S.M.: Static Pion Beam Treatment Planning of Deep Seated Tumors Using Computerized Tomographic Scans. International Journal of Radiation Oncology, Biology, and Physics 5: 875-886, 1979.
- Smith, A.; Hogstrom, K.; Simon, S.; Berardo, P.; Zink, S.; Somers, J.; Kligerman, M.; and Tsujii, H.: Dosimetry and Treatment Planning for Pion Radiotherapy at LAMPF. Proceedings, Third Meeting on Fundamental and High LET Radiations in Clinical Radiotherapy, Pergamon Press, Oxford, pp. 233-234, 1979.
- Paciotti, M.; Amols, H.; Bradbury, J.; Rivera, O.; Hogstrom, K.; Smith, A.; Inoue, H.; Taubacher, D.; and Sandford, S.: Pion Beam Development for the LAMPF Biomedical Project. IEEE Transactions in Nuclear Science, Vol. NS-26, No. 3, 3071-3073, 1979.
- Kligerman, M.M.; Sala, J.M.; Tanaka, Y.; Khan, M.; Smith, A.R.; Sternhagen, C.J.; Akanuma, A.; von Essen, C.F.; Knapp, E.A.; Tsujii, H.; Bagshaw, M.A.; Bradbury, J.M.; and Wilson, S.: Tissue Reaction and Tumor Response with Negative Pi Mesons. Journal of the Canadian Association of Radiologists 31: 13-18, 1980.
- Richman, C.; Kligerman, M.; von Essen, C.; and Smith, A.R.: High LET Dose Measurements in Patients Undergoing Pion Radiotherapy. Radiation Research 81: 455-472, 1980.
- Tsujii, H.; Bagshaw, M.A.; Smith, A.R.; von Essen, C.F.; Mettler, F.A.; and Kligerman, M.M.: Localization of Structures for Pion Radiotherapy by Computerized Tomography and Orthodiographic Projection. International Journal of Radiation Oncology, Biology, and Physics 6: 319-325, 1980.
- Smith, A.R.: Particle Accelerators for Radiotherapy - A Review. Proceedings of Sixth Conference on the Application of Accelerators in Research and Industry, in press.
- Kelsey, C.A., and Smith, A.R.: Neutrons and Heavy Charged Particles Used in Radiotherapy. Submitted to Handbook of Medical Physics.
- Hogstrom, K.R.; Paciotti, M.A.; Smith, A.R.; and Collier, M.: A Comparison of Static and Dynamic Treatment Modes for the Pion Therapy Beam at LAMPF. Submitted to Medical Physics.
- Hills, J.; Hendee, W.R.; Smith, A.R.; and Hogstrom, K.R.: Converting CT Numbers to Water-equivalent Thicknesses for Pion Therapy Treatment Planning. Submitted to Medical Physics.

Give the following information for key professional personnel listed on page 2, beginning with the Principal Investigator/Program Director. Photocopy this page for each person.

NAME	TITLE	ADDRESS (Inc., Dept., etc.)
Nobuhiko Tokita	Staff Member	[REDACTED]

EDUCATION (Begin with baccalaureate training and include postdoctoral)

INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	FIELD OF STUDY
[REDACTED]			Premedical Studies
[REDACTED]	M.D.	[REDACTED]	Medicine and Surgery
[REDACTED]	D.Sc.	[REDACTED]	Biophysics-Radiology
[REDACTED]	Residency & Fellowship in	[REDACTED]	Radiation Oncology

RESEARCH AND/OR PROFESSIONAL EXPERIENCE: Concluding with present position, list in chronological order previous employment, positions, and honors. Include present membership on any Federal Government Public Advisory Committee. List, in chronological order, the titles and complete references to recent representative publications, especially those most pertinent to this application. Do not exceed 2 pages.

- [REDACTED] Medicine and Surgery Intern, [REDACTED]
- [REDACTED] Therapeutic Radiology Resident, [REDACTED]
- 1975-77 [REDACTED] Radiation Research Fellow, therapeutic radiology, [REDACTED]
- 1978-present Staff Member, Life Sciences Division, Los Alamos National Laboratory, University of California, New Mexico

PUBLICATIONS:

1. Kim, J.H.; Hahn, E.; Tokita, N.; and Nisce, L.: Local Tumor Hyperthermia in Combination with Radiation Therapy: Malignant Cutaneous Lesions. Cancer 40: 161-169, 1977.
2. Hilaris, B.; Whitmore, W.; Batata, M.; Barzell, W.; and Tokita, N.: I-125 Implantation of the Prostate: Dose-response Considerations. Frontiers in Radiation Therapy and Oncology 12: 82-90, 1978.
3. Hilaris, B.; Anderson, L.; and Tokita, N.: Interstitial Implantation of Pancreatic Cancer. Frontiers in Radiation Therapy and Oncology 12: 62-71, 1978.
4. Antich, P.; Tokita, N.; Kim, J.H.; and Hahn, E.: Selective Tumor Tissue Heating by Radiofrequency Inductive Hyperthermia. IEEE MTT-26(8): 569-572, 1978.
5. Tokita, N.; Nisce, L.; Simpson, L.; Huh, H.; D'Angio, G.J.; and Lewis, J., Jr.: Techniques Employed to Diminish Ovarian Dose in the Radiation Therapy of Hodgkin's Disease. In Abstracts of the Annual Meeting of the Radiological Society of North America, Chicago, Illinois, November, 1976.
6. Kim, J.H.; Hahn, E.; and Tokita, N.: Clinical Trial with Hyperthermia and Radiotherapy: Cutaneous Cancers as a Model System. In Abstracts of the Second National Symposium on Cancer Therapy by Hyperthermia and Radiation, Essen, West German, June, 1977.
7. Cassir, J.; Hilaris, B.; Tokita, N.; Anderson, L.; Freel, J.; and Lewis, J.: Time-dose Relationship on the Radiation Treatment of Cancer of the Cervix: Normal and Neoplastic Tissue Response. In Abstracts of the Annual Meeting of the ASTR, Denver, Colorado, November, 1977.

1. Kim, J.H.; Hahn, E.W.; and Tokita, N.: Combination Hyperthermia and Radiation Therapy for Cutaneous Malignant Melanomas. Cancer 41: 2143-2148, 1978.
2. Raju, M.R.; Amols, H.; Bain, E.; Carpenter, S.; Cox, R.; Dicello, J.; Robertson, J.; Tokita, N.; and von Essen, C.: Pion Radiobiology Studies. Poster Session at the Third Meeting on Fundamental and Practical Aspects of Fast Neutrons and Other High LET Particles in Clinical Radiotherapy. European Journal of Cancer, 1979.
3. Tokita, N.; Kim, J.H.; and Hilaris, B.: Time-dose-volume Considerations in Iodine-125 Interstitial Brachytherapy. International Journal of Radiation Oncology, Biology and Physics, in press.
4. Kim, J.H.; Hahn, E.; and Tokita, N.: A Model System for Combined Radiation Hyperthermia Studies. In Cancer Therapy by Hyperthermia and Radiation, Urban & Schwarzenberger Publishing Co., Baltimore, MD., pp. 325-336, 1979.
5. Tokita, N.; Skogen-Hagenson, M.J.; Johnson, T.S.; and Raju, M.R.: Flow Cytometric Measurement of Adriamycin Fluorescence for Determining Drug Cytotoxicity. (Abstract) Automated Cytology VII, Engineering Foundation and Society for Analytical Cytology, Asilomar, Ca., November, 1979.
6. Raju, M.R.; Carpenter, S.G.; Tokita, N.; Dicello, J.; Jackson, D.; Fröhlich, E.; and von Essen, C.: Effects of Fractionated Doses of Pions on Normal Tissue. Part I. Mouse Skin. International Journal of Radiation Oncology, Biology and Physics, in press.
7. Raju, M.R.; Johnson, T.S.; Tokita, N.; Carpenter, S.G.; and Jett, J.H.: Differences in Cell Cycle Progression Delays After Exposure to 238-Pu Alpha Particles Compared to X-rays. Radiation Research, in press.
8. Raju, M.R.; Johnson, T.S.; Tokita, N.; and Gillette, E.L.: Flow Cytometric Applications of Tumor Biology: Prospects and Pitfalls. Proceedings of the 9th L.M. Gray Memorial Conference on Quantitation of Tumor Response: A Critical Appraisal. British Journal of Cancer 41 Suppl. IV: 171-176, 1980.
9. Tokita, N.; Jett, J.H.; Raju, M.R.; and Belli, J.A.: Correlations Between Cell Cycle Perturbations and Survival Levels after Exposure to Adriamycin for Two Chinese Hamster Cell Lines. Submitted to Cell and Tissue Kinetics.
10. Tokita, N.; Skogen-Hagenson, M.J.; Wilder, M.E.; Raju, M.R.; and Belli, J.A.: Direct Quantitation of Intracellular Adriamycin by Flow Cytometry. Submitted to Cytometry.
11. Tokita, N.; Bain, E.; Carpenter, S.; and Raju, M.R.: Effects of Hypoxia on Cell-cycle Progression and Radiosensitivity of Chinese Hamster Cells. Submitted to International Journal of Radiation Biology.

COPY

BIOGRAPHICAL SKETCH

Give the following information for key professional personnel listed on page 2, beginning with the Principal Investigator/Program Director. Photocopy this page for each person.

NAME	TITLE	BIRTHDATE (mo./day/yr)
A.J. van der Kogel	Visiting Associate Professor, Radiology*	[REDACTED]

EDUCATION (Begin with baccalaureate training and include postdoctoral)

INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	FIELD OF STUDY
[REDACTED]	Ph.D. (equivalent)	[REDACTED]	Biology

RESEARCH AND/OR PROFESSIONAL EXPERIENCE: Concluding with present position, list in chronological order previous employment, occupation, and honors; include present membership on any Federal Government Public Advisory Committee. List, in chronological order, the titles and complete references to recent representative publications, especially those most pertinent to this application. Do not exceed 2 pages.

- [REDACTED] Postdoctoral Fellowship from the [REDACTED]
- 1980 Consultant in Experimental Radiotherapy, [REDACTED]
- 1975-present Staff Member, Radiobiological Institute TNO Rijswijk

PUBLICATIONS

1. van der Kogel, A.J., and Barendsen, G.W.: Late Effects of Spinal Cord Irradiation with 300 kV X-rays and 15 MeV Neutrons. British Journal of Radiology 47: 393-398, 1974.
2. van der Kogel, A.J., and Barendsen, G.W.: Long-term Effects After X-ray Exposure of the Spinal Cord. In Proc. XII International Congress of Radiology, Madrid, vol. 1, pp. 637-639, 1973.
3. Burek, J.D.; van der Kogel, A.J.; and Hollander, C.F.: Degenerative Myelopathy in Three Strains of Aging Rats. Veterinary Pathology 13: 321-331, 1976.
4. van der Kogel, A.J.: Radiation Tolerance of the Rat Spinal Cord: Time-Dose Relationships. Radiology 122: 505-509, 1977.
5. van der Kogel, A.J.; van Bekkum, D.W., and Barendsen, G.W.: Tolerance of CNS to Total Body Irradiation Combined with Chemotherapy Applied for the Treatment of Leukemia. European Journal of Cancer 12: 675-677, 1976.
6. van der Kogel, A.J.: Radiation Tolerance of the Spinal Cord: The Dependence on Fractionation and Extended Overall Times. In Radiobiological Research and Radiotherapy. In Proceedings of the International Symposium on Radiobiological Research Needed for the Improvement of Radiotherapy, IAEA, Vienna, vol. I, pp. 85-91, 1977.
7. van der Kogel, A.J.: Radiation-induced Nerve Root Degeneration and Hypertrophic Neuropathy in the Lumbosacral Spinal Cord of Rats: The Relation with Changes in Aging Rats. Acta Neuropathologica 39: 139-145, 1977.

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1. Walner, H., and van der Kogel, A.J.: Early Effects and Possible Therapy of Radiation Injury in Man and Animals. Prepared for United Nations Scientific Committee of the Effects of Atomic Research, 1976.
2. van der Kogel, A.J.: Mechanisms of Late Radiation Injury in the Spinal Cord. In Radiation Biology in Cancer Research. R.E. Meyn and H.R. Withers, eds. Raven Press: New York, pp. 461-470, 1980.
3. van der Kogel, A.J.: Late Effects of Radiation on the Spinal Cord. Dose-effect Relationships and Pathogenesis. Thesis. [REDACTED] Publication of the Radiobiological Institute TNO, Rijswijk, the Netherlands, [REDACTED]
4. Kal, H.B., and van der Kogel, A.J.: Fast Neutron Radiobiology. In High LET Radiations in Clinical Radiotherapy. G.W. Barendsen, J.J. Broerse and K. Breur, eds. Regamon Press: Oxford, pp. 187-191, 1979.
5. Beentjes, L.B.; Broerse, J.J.; van der Kogel, A.J., and van der Wielen, A.: Age Dependence of the Risk of Radiation Induced Fatal Malignancies. Health Physics 38: 229-241, 1980.
6. Ang, K.K.; van der Schueren, E., and van der Kogel, A.J.: Feasibility of Multiple Daily Fractionation in High Dose Radiotherapy of Malignant Gliomas. European Journal of Radiotherapy, in press.

BIOGRAPHICAL SKETCH

Give the following information for key professional personnel listed on page 1, beginning with the Principal Investigator/Program Director. Photocopy this page for each person.

NAME James D. Wing	TITLE High Voltage Test Facility Manager, LANL	BIRTHDATE (mo.-day-yr.) [REDACTED]
-----------------------	--	---------------------------------------

EDUCATION (Begin with highest grade training and include as structured)

INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	FIELD OF STUDY
[REDACTED]	B.S.	[REDACTED]	Electrical Engineering

RESEARCH AND/OR PROFESSIONAL EXPERIENCE: Concluding with present position, list in chronological order previous employment, experience, and honors. Include present membership on any Federal Government Public Advisory Committee. List, in chronological order, the titles and complete references to recent representative publications, especially those most pertinent to this application. Do not exceed 2 pages.

- 1957-59 Teacher, [REDACTED]
- 1959-65 Senior Products Designer, [REDACTED]
- 1965-67 Component Application Engineer, [REDACTED]
- 1967-present High Voltage Test Facility Manager, Los Alamos Scientific Laboratory

BIOGRAPHICAL SKETCH

Robert J. Moseley, Jr., M.D.

Give the following information for key professional personnel listed on page 2, beginning with the Principal Investigator/Program Director. Photocopy this page for each person.

Sandra Zink, Ph.D.	TITLE Staff Member, Adjunct Asst. Professor of Radiology	BIRTHDATE (Inc. Month) [REDACTED]
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EDUCATION (Begin with baccalaureate training and include postdoctoral)

INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	FIELD OF STUDY
[REDACTED]	B.S.	[REDACTED]	Physics
[REDACTED]	M.S.	[REDACTED]	Physics
[REDACTED]	Ph.D.	[REDACTED]	Physics

RESEARCH AND/OR PROFESSIONAL EXPERIENCE: Concluding with present position, list in chronological order previous employment, responsibilities, and honors. Include present membership on any Federal Government Public Advisory Committee. List, in chronological order, the titles and complete references to recent representative publications, especially those most pertinent to this application. Do not exceed 2 pages.

- [REDACTED] Research Fellow, Los Alamos Scientific Laboratory and [REDACTED]
- 1973-1975 Staff Member, Los Alamos Scientific Laboratory, New Mexico
Member of Space Physics Group Involved with Physics Studies and Monitoring of Solar Wind Parameters Through Data Received from Several Earth Satellites and Interplanetary Spacecraft
- [REDACTED] Research Fellow, [REDACTED]
- 1980 Consultant, Computer Services Section, [REDACTED]
- 1977-present Staff Member (MP-3), Los Alamos National Laboratory, New Mexico
- 1977-1981 Adjunct Assistant Professor of Radiology, [REDACTED]
- 1981-present Assistant Professor of Radiology, University of New Mexico, Albuquerque

PUBLICATIONS

- Zink (Moody), S., and Beckel, C.: Theoretical Determination of Vibration-Rotation Properties for the $B^1\Sigma_g^+$ State of H_2 . International Journal of Quantitative Chemistry 53: 469, 1970.
- Zink, S., and Beckel, C.: Extended Heuckel Beta Parameters Applied to Diatomic Molecules International Journal of Quantitative Chemistry 58: 209, 1974.
- Feldman, W.C.; Askbridge, J.R.; Bame, S.J.; Gary, S.P.; Montgomery, M.D.; and Zink, S.M.: Evidence for the Regulation of Solar Wind Heat Flux at 1 A.U. Journal of Geophysical Research 81: 5207, 1976.
- Rosenbauer, H.; Schwenn, R.; Marsch, E.; Meyer, B.; Miggenrieder, H.; Montgomery, M.D.; Muhlhauuser, K.; Piliipp, W.; Voges, W.; and Zink, S.: A Survey of Initial Results of the Helios Plasma Experiment. Journal of Geophysical Research 42: 561, 1977.
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Moseley, Robert D., Jr., M.D.

VIII. LETTER OF INTENT TO RENEW CONTRACT

University of New Mexico/Los Alamos National Laboratory

CC

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Los Alamos

Los Alamos National Laboratory
Los Alamos, New Mexico 87545

February 23, 1982

In reply refer to: DIR
Mail Stop: 100

Francis J. Mahoney, Ph.D.
Program Director for Radiation Branch
Division of Cancer Treatment
National Cancer Institute
Landow Building, Room 8C09
7910 Woodmont Avenue
Bethesda, MD 20205

Subject: Assurance of Intent to Renew Contract

Dear Dr. Mahoney:

The University of New Mexico (UNM) and the University of California (UC), parties to a cost reimbursable contract for work conducted both at UNM and at Los Alamos Laboratory, do hereby express their intent to extend the referenced contract for an additional period of five years from May 1, 1982 through April 30, 1987, subject to the approval of the U.S. Department of Energy and NCI and to any intervening changes in policies in such matters by either Agency. The statement of work for each grant period will be based upon the proposal presently being prepared, assuming appropriate funding for each period of the contract.

After receipt by UNM of Notices of Award, and provided the work to be performed and the funding provided are reasonably consistent with the proposals made, a formal Amendment to the contract will be entered into with appropriate revisions of the articles relating to the Statement of Work, Term, and Funding. It is not contemplated at this time that any other changes need to be made in the Terms and Conditions of the contract.

Dr. Francis J. Mahoney
DIR
Page 2

Subject to the conditions noted above, the parties see no obstacle to effecting this Amendment promptly upon receipt of firm information as to the terms of the NCI grant awards.

THE REGENTS OF THE UNIVERSITY OF
NEW MEXICO

Dated: 2 25 82

BY: [Signature]

John Perovich
TITLE: Vice President for Business
and Finance

THE REGENTS OF THE UNIVERSITY OF
CALIFORNIA

Dated: 2.24.82

BY: [Signature]

Donald M. Kerr
TITLE: Director, Los Alamos National
Laboratory

C. CR

CHECKLIST

This is the required last page of the application.

Check the appropriate boxes and provide the information requested.

TYPE OF APPLICATION:

- NEW application (This application is being submitted to the PHS for the first time.) (Based on discontinued support from P01 CA 16127)
- COMPETING CONTINUATION of grant number _____
(This application is to extend a grant beyond its original project period.)
- SUPPLEMENT to grant number _____
(This application is for additional funds during a funded project period.)
- REVISION of application number _____
(This application replaces a prior version of a new, competing continuation or supplemental application.)
- Change of Principal Investigator/Program Director.
Name of former Principal Investigator/Program Director: _____

ASSURANCES IN CONNECTION WITH:

Civil Rights	Handicapped Individuals	Sex Discrimination	Human Subjects General Assurance (if applicable)	Laboratory Animals (if applicable)
<input checked="" type="checkbox"/> Filled <input type="checkbox"/> Not filled				

INDIRECT COSTS:

Indicate the applicant organization's most recent indirect cost rate established with the appropriate DHHS Regional Office. If the applicant organization is in the process of initially developing or renegotiating a rate, or has established a rate with another Federal agency, it should, immediately upon notification that an award will be made, develop a tentative indirect cost rate proposal based on its most recently completed fiscal year in accordance with the principles set forth in the pertinent DHHS Guide for Establishing Indirect Cost Rates, and submit it to the appropriate DHHS Regional Office. Indirect costs will not be paid on foreign grants, construction grants, and grants to individuals, and usually not on grants in support of conferences.

- DHHS Agreement Dated: 7/1/80
_____ % Salary and Wages of 25.24 % Total Direct Costs. (Less Equipment and Purchased Services) over \$25,000
- Is this an off-site or other special rate, or is more than one rate involved? YES NO
Explanation: off-site research
- DHHS Agreement being negotiated with _____ Regional Office.
- No DHHS Agreement, but rate established with _____ Date _____
- No Indirect Costs Requested.

APPENDIX A

CLINICAL RESEARCH PROTOCOLS

- RTOG 79-23: Evaluation of Radiobiological Effects of Negative Pi Mesons on Miscellaneous Locally Advanced and/or Recurrent Human Solid Tumors and Surrounding Normal Tissues
- RTOG 79-24: Evaluation of Radiobiological Effects of Negative Pi Mesons on Miscellaneous Metastatic Lesions

RADIATION THERAPY ONCOLOGY GROUP
RTOG 79-23

EVALUATION OF RADIOBIOLOGICAL EFFECTS OF
NEGATIVE PI MESONS ON
MISCELLANEOUS LOCALLY ADVANCED AND/OR RECURRENT HUMAN SOLID TUMORS
AND SURROUNDING NORMAL TISSUES

Protocol for Human Radiobiology Studies of Pi Meson
Radiation Therapy at
University of New Mexico/Los Alamos Scientific Laboratory

Study Chairman: Steven E. Busn, M.D.
Phone: 505/277-6141

Activated: October 30, 1979
Current Edition: May 1, 1981

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Schema

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 - 2.0 Objectives
 - 3.0 Eligibility Criteria
 - 4.0 Pretreatment Evaluation
 - 5.0 Admission to Study
 - 6.0 Treatment
 - 7.0 Endpoints
 - 8.0 Statistical Considerations
 - 9.0 Follow-up Schedule
 - 10.0 Additional Therapy
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 - 13.0 Patient Consent and Peer Judgment
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RADIATION THERAPY ONCOLOGY GROUP
RTOG 79-23

EVALUATION OF RADIOBIOLOGICAL EFFECTS OF
NEGATIVE PI MESONS ON MISCELLANEOUS LOCALLY ADVANCED AND/OR RECURRENT
HUMAN SOLID TUMORS AND SURROUNDING NORMAL TISSUES

SCHEMA

Eligible Patients: Patients with biopsy-proven
locally advanced or recurrent neoplasms whose
projected survival is at least three months

Treatment:

Non-Randomized Negative Pi Meson
Radiotherapy Alone or as a Planned Boost
Following Conventional Radiotherapy

Endpoints:

Tumor regression and time to recurrence.
Local and regional tumor control.
Evaluation of tissue tolerances for pion radiotherapy
alone or as a planned boost following conventional
radiotherapy.
Quality and length of survival.
Adequacy of tumor localization, treatment planning,
and inhomogeneity correction.

1.0 INTRODUCTION

The rationale for pion radiotherapy is primarily related to two factors: (1) a different biologic response in the stopping region of the pion beam from that seen in conventional radiation, and (2) the capability for localizing this differential response within the target volume, largely sparing normal surrounding tissues.

With high-linear-energy-transfer (high-LET) radiation (for example, neutrons, pions, and heavy ions), there is increased irreparable damage of critical molecules (i.e., double-strand breaks in DNA), as compared to the type of damage caused by low-LET radiation (e.g., x-rays, gamma rays of cobalt, electrons, and protons). In addition, cells exposed to low-LET radiation exhibit up to three times more resistance to injury if they are not well oxygenated. Thus, hypoxic cells, large numbers of which are usually present in tumors, are less sensitive to damage than are well oxygenated cells of the tumor and the surrounding normal tissue. The dense ionization of high-LET radiation may overcome the protective effect of hypoxia, killing those cells almost as effectively as well-oxygenated cells. Further, cells are more resistant to low-LET radiation in certain phases of the cell cycle than in others. High-LET radiation reduces differences in cellular sensitivity due to cell cycle variations.

Heavy charged particles, such as pions and heavy ions, distribute their dose with a Bragg peak, a region of intense radiation which can be located in the tumor volume.

Pions have the advantages of both high-LET and low-LET radiation, because they deposit low-LET radiation as they pass through tissue (plateau region), but produce a high-LET component in the stopping (tumor) region. Due to their negative charge, the stopping pions are absorbed by the positively charged nuclei of oxygen, carbon, and nitrogen atoms. This excess energy makes the nuclei unstable and they disintegrate, producing neutrons, protons, deuterons, tritons, alpha particles, and heavy ions. These events increase

the total dose in the pion stopping region and alter the biological effectiveness of the dose in that region because of the dense ionization produced mainly by the alpha particles, heavy ions, and neutrons.

Phase II trials are proposed to study the efficacy of pion radiotherapy in improving local control and, thus, potentially survival for patients with a variety of locally advanced, non-metastatic neoplasms, and to assess acute and chronic normal tissue injury associated with such treatment. Sites of major interest include high grade gliomas (glioblastoma and astrocytoma Grade III and IV), inoperable esophageal carcinoma, inoperable epidermoid lung carcinoma, inoperable pancreatic carcinoma, carcinoma of the uterine cervix (Stage III and IVA) and locally advanced adenocarcinoma of the prostate (T3/T4, AJC).

Patients with lesions amenable to treatment with conventional radiotherapy and/or surgery with an anticipated five-year survival rate greater than approximately 40% would be excluded. Patients must be between 18 and 75 years of age and have a Karnofsky status of 60 or greater.

1.1 Summary of the Study.

This is a non-randomized pilot study to evaluate normal tissue and tumor response to pion radiotherapy in a wide variety of human tumor sites, all of which will be biopsy-proven, locally advanced or recurrent solid tumors. The study of local and regional tumor control as well as tissue tolerances will be the prime goal of this protocol. Additional valuable information will be gained regarding further refinement of techniques of treatment planning, patient set-up and immobilization, assessment of tissue inhomogeneities, and other technical aspects of pion therapy.

Patients previously treated with chemotherapy but not demonstrating objective response will be eligible provided they have a life expectancy of at least three months.

2.0 OBJECTIVES

- 2.1 To evaluate tumor response to pion radiation.
- 2.2 To study local and regional control of tumor.
- 2.3 To evaluate normal tissue response and tolerance to large field multi-fraction pion therapy, or to pion therapy delivered as a planned boost following conventional radiotherapy.
- 2.4 To evaluate important aspects of treatment planning and technical aspects of delivering the radiation in an attempt to maximize the therapeutic ratio by minimizing the normal tissue volume to be irradiated.

3.0 ELIGIBILITY CRITERIA

3.1 Conditions of Eligibility.

The following conditions must be met before a patient can be admitted in the study:

- 3.1.1 Biopsy-proven malignancy.
- 3.1.2 Locally advanced or recurrent cancer.
- 3.1.3 Patient age between 18 and 75.
- 3.1.4 Karnofsky Status \geq 60.
- 3.1.5 Little or no chance of cure with conventional radiotherapy alone.
- 3.1.6 Understanding by the patient of the provisions of the study and voluntary informed consent to participate in the study.

3.2 Conditions of Ineligibility.

- 3.2.1 Moderate to high chance of cure by other treatment modalities.
- 3.2.2 Ongoing chemotherapy.
- 3.2.3 Life expectancy less than three months or Karnofsky status of less than 60 and age $<$ 18 or $>$ 75.
- 3.2.4 Active uncontrollable infection in area of irradiation.
- 3.2.5 Medical, psychological or other contraindication to proposed treatment.

4.0 PRETREATMENT EVALUATION

Pretreatment evaluation will be performed at the University of New Mexico Cancer Research and Treatment Center (CRTC) or by the referring physician at another institution, with findings verified and studies augmented as required by the CRTC study team. The evaluation will include:

4.1 Medical history.

4.2 Physical examination.

4.3 Laboratory tests.

4.3.1 CBC (including differential)

4.3.2 Platelet count

4.3.3 Urinalysis

4.3.4 Serum chemistry profile

4.3.5 Others as indicated

4.4 Chest x-ray, other radiographs and radionuclide studies as indicated.

4.5 Staging procedures as indicated with careful mapping and clipping of tumor where possible.

4.6 An ophthalmologic examination to assess lens opacity (to be performed upon admission to the study).

5.0 ADMISSION TO THE STUDY

Any patient who meets the required eligibility and pretreatment evaluation criteria will be admitted to the protocol for pion radiotherapy at LAMPF. The following records will be generated by the study team and participating institutions for storage, retrieval and analysis:

1. Patient eligibility form.
2. Pretreatment evaluation form. This form, documenting the history and physical information, laboratory tests and special studies including surgery, will be submitted on those patients referred for treatment.
3. Study entrance form (patient name, address, referring institution, referring physician, etc.)

A study case number will be assigned to each patient by RTOG Headquarters (215-574-3191).

5.0 TREATMENT

All patients will receive non-randomized pion therapy at the Clinton P. Anderson Meson Physics Facility (LAMPF) in Los Alamos, New Mexico, either alone or as a planned boost in conjunction with conventional radiotherapy. Pion doses are based upon previous experience with pion irradiation of various human tumors¹ and for representative sites are outlined below.

Current Treatment Policy

<u>Site</u>	<u>Maximum Dose (Peak Pion Rad)</u>	<u>Minimum Dose (Peak Pion Rad)</u>	<u>Fractions</u>	<u>Days</u>
Pelvis*	4500	3500	36	50
Head & Neck**	4500	3500	35	50
Brain*				
Whole	2750	2200	22	32
Cone-down	4500	3600	36	50
Pancreas***				
Whole	2400	1920	24	35
Cone-down	3840	3072	24	35
Esophagus*				
Wide-field	3500	2800	28	38
Cone-down	4500	3600	36	50
Lung				
Wide-field	3250	2500	26	35
Cone-down	4500	3600	36	50

*May be treated by conventional wide-field irradiation and pion boost (approximately 1500 peak pion cGy (rad) maximum/12 fractions/2 1/2 weeks).

**Boost fields treated to 5000 peak pion cGy (rad) maximum

***Combined with planned external beam conventional therapy

Variations in total dose in the range of $\pm 10\%$ about the above doses will be explored to further evaluate tumor response and normal tissue tolerance. Doses in this range will be considered definitive and will be combined with other conventional therapy as outlined in Section 10.0 Additional Therapy, below.

Planned combinations of conventional radiation therapy with cone-down pion boost therapy will be applied in selected situations based upon previous experience regarding normal tissue tolerance in patients receiving pions alone. The estimated biological equivalent of combined pion and conventional treatment will not exceed that recognized as tolerance for pion or conventional therapy alone.

Treatment methods will be those developed previously for pion therapy with the fixed vertical beam at LAMPF with appropriate modifications and improvements consistent with improved techniques.² Single or multiple port therapy with or without cone-down therapy will be applied on an individualized basis to maximize normal tissue sparing and to accommodate particular difficulties with patient positioning or disease site.

Treatment planning will be performed by computerized calculation from CT data of necessary compensation for body and tumor contours and tissue inhomogeneities.³ Verification of treatment volumes will be accomplished by simulation using orthodiagraphic scanning⁴ and routine in vivo dosimetry.

7.0 ENDPOINTS

- 7.1 Tumor regression and time to recurrence.
- 7.2 Local and regional tumor control.
- 7.3 Evaluation of tissue tolerances for pion radiotherapy alone or as a planned boost following conventional radiotherapy.
- 7.4 Quality and length of survival.
- 7.5 Adequacy of tumor localization, treatment planning, and inhomogeneity correction.

8.0 STATISTICAL CONSIDERATIONS

This will be a non-randomized trial consisting of individual pilot studies comparing local control and survival statistics with best reported results using conventional treatment for those sites mentioned above. Approximately 15-30 patients will receive

optimized pion therapy for each of the disease sites of primary interest. Endpoints of interest in determining whether to proceed to Phase III trials will include a comparison of local control, median survival, and five-year survival rates for recently reported historical controls and pion-treated patients.

9.0 FOLLOW-UP SCHEDULE

9.1 The referring physician will be encouraged to see the patient in accordance with his customary schedule.

The patient will be seen at the Cancer Research and Treatment Center at one month after treatment, then every three months for 12 months counting from Day 1, and semi-annually thereafter until survival reaches five years. If the patient cannot return to the CRTC, arrangements will be made to have him examined at another hospital by his referring physician and preferably his radiotherapist and a report of this examination submitted to the CRTC.

9.2 Follow-up Information.

The following information will be recorded on the follow-up form at each visit:

- 9.2.1 Brief interval history related to disease.
- 9.2.2 Physical examination:
 - Weight, blood pressure
 - Temperature
 - Appropriate aspects of physical examination
 - Regression of palpable or visible tumor
- 9.2.3 Laboratory tests and routine x-rays; appropriate studies as indicated.
- 9.2.4 Specific diagnostic studies, or studies which gave the most reliable information regarding the initial extent of tumor will be repeated at periodic intervals.
- 9.2.5 Complications of treatment.
- 9.2.6 Recording and scoring of late reactions and pathologic studies by re-biopsy/autopsy as indicated.

9.2.7 Ophthalmologic exam to assess lens opacity (annually).

9.3 Study Parameters.

Parameters to be recorded throughout the study include:

9.3.1 Degree and time of regression and regrowth.

9.3.2 Assessment of acute radiation effects.

9.3.3 Assessment of long-term radiation effects.

Summary of Study Parameters

	<u>Pretreatment</u>	<u>Follow-Up</u>
History and Physical	x	x
Performance Status (Karnofsky Scale)	x	x
CBC, Differential, Platelet Count	x	x ^a
Urinalysis	x	
Chemistry Profile	x	x ^a
Diagnostic (radiographs, ultrasound, nuclear scans, etc.)	x ^a	x ^a
Staging/Localization Procedures	x ^a	
Ophthalmologic Exam	x	x ^b

a - As Indicated
b - Yearly

10.0 ADDITIONAL THERAPY

Clinical evidence of lack of tumor control should be documented by biopsy if possible. If such evidence is equivocal, re-exploration should be encouraged if the patient is a good surgical candidate, until such time as a pattern of recurrence is established and documented. In the event that surgery or biopsy is performed, the excised tissue or biopsy specimen should be carefully examined by the study pathologist with assistance from the involved radiation oncologist. If the primary tumor is not controlled or if distant metastases develop, subsequent therapy should proceed at the discretion of the patient's responsible physician. The patient or physician will notify the investigator of any treatment instituted that has not been prescribed by the investigator.

11.0 PATHOLOGY

11.1 Initial Surgical (Biopsy) Specimens.

Representative slides and copies of biopsy reports will be submitted to the study center and reviewed by the study pathologists. Copies of the reports from these pathologists will be forwarded to the referring and/or follow-up physician.

11.2 Subsequent Surgical Specimens.

Any tissue surgically removed from anatomic sites will be examined by pathologists at the participating institution where surgery was performed. Appropriate microscopic slides and pathological reports will be forwarded to the study center for review by the study pathologists.

11.3 Autopsies.

Autopsies are strongly urged on all study patients by pathologists at the participating institutions. Post-mortem studies should include a description of irradiated tissues and the character and extent of persistent, recurrent or metastatic tumor. Autopsy reports and representative microscopic slides will be forwarded to the study center for review by the study pathologists.

12.0 FORMS

Two copies of each study form must be submitted to RTOG Headquarters. Data will be recorded on standard forms to be supplied to participating institutions by RTOG Headquarters.

- a. Photocopy of patient consent form.
- b. Patient eligibility form.
- c. Pretreatment evaluation form.
- d. Study entrance form.
- e. Radiation treatment summary. A daily schedule of pion therapy will be prepared at LAMPF. This report will also include an end of treatment examination to include weight, pertinent general physical examination, performance status, current medications, and if possible, an assessment of tumor response.
- f. Follow-up examination form.
- g. Pathology forms.

13.0 PATIENT CONSENT AND PEER JUDGMENT

All institutional, Food and Drug Administration, and National Cancer Institute regulations requiring submission to the institutional human experimentation committee and the use of procedures for obtaining and recording informed consent will be followed. A patient may be removed from the study if the study is not in the best interest of the patient. A patient may withdraw voluntarily from the study at any time, as will be indicated in the consent form.

14.0 REFERENCES

1. Kligerman, M., Bush, S., Kondo, M., Wilson, S., Smith A.R.: Results of Phase I/II trials of pion radiotherapy. In Proceedings of the Second Rome International Symposium on Biological Bases and Clinical Implications of Radioresistance, in press.
2. Kligerman, M.M., Hogstrom, K.R., Lane, R.B., Scmers, J.: Prior immobilization and positioning for more efficient radiotherapy. Int J Radiat Oncol Biol Phys 2:1141-1144, 1977.
3. Hogstrom, K.R., Smith, A.R., Simon, S.L., Scmers, J.W., Lane, R.G., Rosen, I.I., Keisey, C.A., von Essen, C.F., Kligerman, M.M., Berardo, P.A., Zink, S.M.: Static pion beam treatment planning of deep seated tumors using computerized tomographic scans at LAMPF. Int J Radiat Oncol Biol Phys 5:875-886, 1979.
4. Tsujii, H., Bagshaw, M., Smith, A., von Essen, C., Mettler, F., Kligerman, M.: Localization of structures for pion radiotherapy by computerized tomography and orthodiagraphic projection. Int J Radiat Oncol Biol Phys 6:319-325, 1980.

APPENDIX I

KARNOFSKY PERFORMANCE STATUS

- 100 Normal; no complaints; no evidence of disease.
- 90 Able to carry on normal activity; minor signs or symptoms or disease.
- 80 Normal activity with effort; some sign or symptoms of disease.
- 70 Cares for self, unable to carry on normal activity or do active work.
- 60 Requires occasional assistance, but is able to care for most personal needs.
- 50 Requires considerable assistance and frequent medical care.
- 40 Disabled; requires special care and assistance.
- 30 Severely disabled; hospitalization is indicated, although death not imminent.
- 20 Very sick, hospitalization necessary; active support treatment is necessary.
- 10 Moribund; fatal process progressing rapidly.
- 0 Dead.

APPENDIX II

PATIENT CONSENT FORM FOR PI MESON RADIATION THERAPY FOR HUMAN CANCERS*

Patient's Name: _____

Address: _____

Hospital/Clinic: _____

Hospital/Clinic I.D. Number: _____

1. I, _____, agree to take part
Name of Patient
in a research study of pi meson radiation therapy for cancer. The pi meson radiation treatment will be given at the Clinton P. Anderson Meson Physics Facility in Los Alamos, New Mexico. Dr. Steven E. Bush and doctors he has chosen will do this study. Persons helping them will be supervised by a doctor at all times while treatment is being given.
2. The treatment to be given to me has been described to me by Dr. _____. It is as follows:
 - a. If I choose to be in the study and the physical examination and tests show that I am able to be in the study, I must agree to spend the needed time in Los Alamos for treatment. I must also agree to return to the University of New Mexico Cancer Research and Treatment Center for any check-ups and tests needed after the pi meson radiation therapy.
 - b. I will be given pi meson radiation treatments alone, usually five days a week for about eight weeks, or I will be given ordinary radiation, usually five days a week for about six weeks, followed by pion radiation, usually five days a week for about one to two weeks.
 - c. Before treatment, I will receive standard tests and examinations. These tests will include x-ray pictures and scans so that the persons treating me can see what area should be treated.
 - d. Before treatment, I will be placed in the exact position that I will be in during treatment. This set-up is done in a room near the treatment room. X-ray pictures will be taken to see if the treatment planned for me is correct.

*Sample Consent Form submitted by the Study Chairman.

- e. I will receive treatment in the same set-up position. There will be no pain or feeling from the pi meson beam during treatment. I will be alone in the treatment room, but persons treating me can see me on closed-circuit television. We will also be able to talk to each other through a microphone and speaker system. People will always be outside the treatment room and ready to help me.
- f. After the pi meson treatments end, I will receive standard medical tests to see what the treatments have done.
3. Dr. _____ has told me that I might not feel well after the pi meson radiation treatments. Complete information on problems and risks from pi meson treatment is not known. Tests with cells, animals, and patients have shown that pi meson radiation does not create problems much different from problems created by standard radiation treatments. Both pi meson and standard radiation could cause some or all of the following problems and risks: (Insert list for tumor site to be treated): _____ . Attach signed list to consent form.
4. Dr. _____ has told me about the good things this research study might do for me and for other people.
- a. Pi meson treatment might make me feel better while I am being treated.
- b. Pi meson treatment might shrink the tumor better than other treatments and improve chances for control of my disease.
5. Dr. _____ has told me about other treatments for me.
- a. Drug treatments.
- b. Standard radiation.
- c. Surgery.
6. Dr. _____ will answer any questions I have during the treatment.
7. I know that the treatment could harm me. No one has said that it wouldn't. I can stop having treatment at any time I want to.
8. Dr. _____ is in charge of my treatment. He can change the treatment at any time, or stop it.
9. If my body is injured by the research treatment, more than or different from that explained above, I understand that any emergency medical care I need will be given to me at no cost, but I will not be paid any money. Payments for medical costs will not continue after the emergency treatment is finished.

10. I understand that by signing this paper, I am not giving up my legal rights. State laws exist which may help people who think they have been treated carelessly. For information, I can write or call the Risk Management Division, Room 24, Lamy Building, Santa Fe, New Mexico 87503.

Date: _____ Time: _____ Place: _____

Signed: _____ Witness: _____

Parent or Guardian When Indicated _____
Witness: _____

Pion Protocol: Advanced/Recurrent Tumors, Phase I/II

PELVIC AND ABDOMINAL LESIONS, MALE PATIENTS

Possible Problems and Risks

1. I may get ulcers and other sores in my stomach and small or large intestine. Doctors rarely see this happen with standard radiation treatment, and it is not likely with pi meson radiation treatment.
2. I may have changes in blood cells. Tests are given every week or more often for this. I will be treated right away.
3. I may lose hair in the area being treated.
4. My skin may get red and peel in the treatment area.
5. I may have weakness in some parts of my body and not be able to move those parts. This problem does not happen very often in usual radiation treatments, so it is not expected to happen very often to patients receiving pi meson radiation.
6. I may have pain and swelling in the treatment area.
7. I may have diarrhea. Bleeding could happen with the diarrhea. I understand that these problems usually stop at the end of the treatment. I may be given medicine for these problems.
8. I may be sick at my stomach. This problem can be helped by medicine or by slowing the rate of radiation. Sometimes both methods are used to ease this problem.
9. I may have to pass my water more often. Sometimes I may have burning pain when I pass my water. These problems usually go away after the treatment is ended.
10. I understand that about 40% of men who are treated may not be able to produce children or have sex.

Signed: _____
Patient

Date: _____ Time: _____

C

PELVIC AND ABDOMINAL LESIONS, FEMALE PATIENTS

Possible Problems and Risks

1. I may get ulcers or other sores in my stomach and small or large intestine with pi meson radiation. Doctors rarely see this happen with usual radiation, so it is not likely to happen with pi meson radiation.
2. I may have changes in my blood cells. Tests will be done every week or more often for this. I will be treated right away.
3. I may lose my hair in the area being treated.
4. My skin may get red and peel in the treatment area.
5. I may have weakness in some parts of my body and not be able to move those parts. This problem does not happen very often in usual radiation treatment, so it is not expected to happen very often to patients receiving pi meson radiation.
6. I may have pain and swelling in the treatment area.
7. I may have diarrhea and some bleeding with the diarrhea. This problem can be treated quickly, and it usually goes away after the treatments are over.
8. I may be sick at my stomach. This problem can be helped by drugs or by slowing the rate of radiation. Sometimes both methods are used to ease this problem.
9. I may have to pass water more often. Sometimes I may have burning pain when I pass my water. Those problems usually go away after the treatment is ended.
10. I understand that my monthly periods may stop, and I may not be able to have children.
11. I may have a discharge from the vagina.

Signed: _____
Patient

Date: _____ Time: _____

HEAD AND NECK LESIONS

Possible Problems and Risks

1. No matter what type of radiation I am given, I might need an operation after the radiation which might make me lose my voice forever.
2. I may have weakness in some parts of my body and not be able to move those parts. This problem does not happen very often.
3. I may have unusual openings in my skin or other tissue. These openings might heal themselves, or I might need surgery to repair them.
4. I may have pain and swelling in the treatment area.
5. I may lose normal bone or tissue in the treatment area.
6. I may get cavities in my teeth.
7. I may get ulcers in my mouth and throat. These ulcers might go away or be permanent.
8. I may have sore throat and trouble swallowing.
9. I might have a cough.
10. I might have trouble breathing.
11. I may have changes in blood cells. Tests are given every week or more often for this. I will be treated right away.
12. I may have a fever.
13. I may have more chance of getting an infection.
14. Later, I may get cancer of the thyroid, but this problem does not happen very often.
15. My skin may get red and peel in the treatment area.
16. I might have much wetness or dryness near the top of my breathing tubes or food tubes.
17. I might lose my sense of taste. This loss usually does not last long.
18. I might lose hair in the treatment area.
19. I might get cataracts (clouding of the lenses in my eyes). This is not expected, but if it does happen it can be corrected by an operation.

Signed: _____
Patient

Date: _____ Time: _____

CHEST LESIONS

Possible Problems and Risks

1. My lungs may become red and scarred. The redness may go away or leave scars. The scars usually cause no problems that would harm me. Long-term problems were found in one out of 133 patients in one series of studies with usual radiation. I may have trouble breathing.
2. I may have weakness in some parts of my body and not be able to move those parts. This problem does not happen very often.
3. I may have unusual openings in my skin or other tissues. These openings might heal themselves, or I might need surgery to repair them.
4. I may have pain and swelling in the treatment area.
5. I might lose normal bone or muscle tissue in the treatment area.
6. I may have a sore throat and trouble swallowing.
7. I might have a cough.
8. I might have trouble breathing.
9. I may have changes in blood cells. Tests are given every week or more often for this. I will be treated right away.
10. I may have a fever.
11. I may have more chance of getting an infection.
12. Later, I may get cancer of the thyroid, but this problem does not happen very often.
13. My skin may get red and peel in the treatment area. Later, I might get skin cancer.
14. I might have much wetness or dryness near the top of my breathing tubes or food tubes.
15. I might lose hair in the treatment area.

Signed: _____
Patient

Date: _____ Time: _____

BRAIN LESIONS

Possible Problems and Risks

1. Patients with brain cancer often have some problems that are there before treatment. Treatments can stir up these problems for a time. Such problems are:
 - a. I may be sick at my stomach. This problem can be helped by drugs or by slowing the rate of radiation. Sometimes both methods are used to ease the problem.
 - b. I may have headaches, but these can be treated with medicine.
 - c. I may be drowsy, but this can be treated with medicine.
 - d. I may have double vision.

2. I may not feel well after the treatments. Some of the problems that might be caused by the treatments are:
 - a. Parts of my normal brain tissue might be destroyed. This could cause weakness in some parts of my body, and I may not be able to move those parts. I might also have trouble seeing, hearing, smelling, touching or tasting. I might also have trouble in thinking.
 - b. My skin may get red and peel in the treatment area. Later, I might get skin cancer.
 - c. I will lose my hair, but it will probably grow back after treatment.
 - d. I might get cataracts (clouding of the lenses in my eyes). This is not expected, but if it does happen it can be corrected by an operation.

Signed: _____
Patient

Date: _____ Time: _____

WOMEN OF CHILD-BEARING AGE

Possible Problems and Risks

Women of child-bearing age should understand that the pion treatments, like x-rays or other radiation, could cause changes that might result in birth defects in children born after treatment has been given. The chance of this happening is not known. Women who plan to have children at any time after they complete treatment should seek counseling from doctors who are qualified to help them understand the extent of this risk.

Signed: _____
Patient

Date: _____ Time: _____

#142-2

RADIATION THERAPY ONCOLOGY GROUP
RTOG 79-24

EVALUATION OF RADIOBIOLOGICAL EFFECTS OF
NEGATIVE PI MESONS ON MISCELLANEOUS METASTATIC LESIONS

Protocol for Human Radiobiology Studies of
Pi Meson Radiation Therapy at
University of New Mexico/Los Alamos Scientific Laboratory

Study Chairman: Steven E. Bush, M.D.
Phone: 505/277-6141

Activated: October 30, 1979
Current Edition: May 1, 1981

NOTE: Patients treated subsequent to
January 1, 1978 may be registered
retrospectively.

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Schema

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 - 2.0 Objectives
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RADIATION THERAPY ONCOLOGY GROUP

RTOG 79-24

EVALUATION OF RADIOBIOLOGICAL EFFECTS OF
NEGATIVE PI MESONS ON MISCELLANEOUS METASTATIC LESIONS

SCHEMA

Eligible Patients: Patients with metastatic lesions originating from biopsy-proven solid tumors, whose projected survival is at least three months

Treatment:

Non-randomized Negative Pi Meson Radiotherapy

Endpoints:

Tumor regression and time to recurrence
Evaluation of tissue tolerance for pion radiotherapy
Quality and length of survival
Adequacy of tumor localization, treatment planning,
and inhomogeneity correction

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1.0 INTRODUCTION

The rationale for pion radiotherapy is primarily related to two factors: (1) a different biological response in the stopping region of the pion beam from that seen in conventional radiation, and (2) the capability for localizing this differential response within the target volume, largely sparing normal surrounding tissues.

With high-linear-energy-transfer (high-LET) radiation (for example, neutrons, pions, and heavy ions), there is increased irreparable damage of critical molecules (i.e., double-strand breaks in DNA), as compared to the type of damage cause by low-LET radiation (e.g., x-rays, gamma rays of cobalt, electrons, and protons). In addition, cells exposed to low-LET radiation exhibit up to three times more resistance to injury if they are not well oxygenated. Thus, hypoxic cells, large numbers of which are usually present in tumors, are less sensitive to damage than are well oxygenated cells of the tumor and the surrounding normal tissue. The dense ionization of high-LET radiation may overcome the protective effect of hypoxia, killing those cells almost as effectively as well-oxygenated cells. Further, cells are more resistant to low-LET radiation in certain phases of the cell cycle than in others. High-LET radiation reduces differences in cellular sensitivity due to cell cycle variations.

Heavy charged particles, such as pions and heavy ions, distribute their dose with a Bragg peak, a region of intense radiation which can be located in the tumor volume.

Pions have the advantages of both high-LET and low-LET radiation, because they deposit low-LET radiation as they pass through tissue (plateau region), but produce a high-LET component in the stopping (tumor) region. Due to their negative charge, the stopping pions are absorbed by the positively charged nuclei of oxygen, carbon, and nitrogen atoms. This excess energy makes the nuclei unstable and they disintegrate, producing neutrons, protons, deuterons,

tritons, alpha particles, and heavy ions. These events increase the total dose in the pion stopping region and alter the biological effectiveness of the dose in that region because of the dense ionization produced mainly by the alpha particles, heavy ions, and neutrons.

Phase II trials are proposed to study the efficacy of pion radiotherapy in improving local control and, thus, potentially survival for patients with a variety of large solitary metastatic neoplasms, and to assess acute and chronic normal tissue injury associated with such treatment.

Patients with lesions amenable to treatment with conventional radiotherapy, surgery and/or chemotherapy with an anticipated five-year survival rate greater than approximately 40% would be excluded. Patients must be between 18 and 75 years of age and have a Karnofsky status of 60 or greater.

1.1 Summary of the Study-

This is a non-randomized pilot study to evaluate response to pion radiotherapy of miscellaneous metastatic lesions originating from any type of solid tumor. The study of local control as well as tissue tolerances will be the prime goal of this protocol. Additional valuable information will be gained regarding further refinement of techniques of treatment planning, patient set-up and immobilization, assessment of tissue inhomogeneities, and other technical aspects of pion therapy.

Patients previously treated with chemotherapy but not demonstrating objective response will be eligible provided they have not received previous radiotherapy to the area and have a life expectancy of at least three months.

2.0 OBJECTIVES

- 2.1 To evaluate tumor response to pion radiation.
- 2.2 To evaluate normal tissue response and tolerance to multi-fraction pion therapy.

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2.3 To evaluate important aspects of treatment planning and technical aspects of delivering the radiation (including inhomogeneity corrections) in an attempt to maximize the therapeutic ratio by minimizing the normal tissue volume to be irradiated.

3.0 ELIGIBILITY CRITERIA

3.1 Conditions of Eligibility.

The following conditions must be met before a patient can be admitted to the study:

- 3.1.1 Biopsy-proven malignancy.
- 3.1.2 Metastatic lesion originating from any solid tumor.
- 3.1.3 Patient age between 18 and 75.
- 3.1.4 Little or no chance of cure with conventional therapy.
- 3.1.5 Understanding by the patient of the provisions of the study and voluntary informed consent to participate in the study.
- 3.1.6 Karnofsky status \geq 60.

3.2 Conditions of Ineligibility.

- 3.2.1 Moderate to high chance of cure by other treatment modalities.
- 3.2.2 Previous radiotherapy to site.
- 3.2.3 Ongoing chemotherapy.
- 3.2.4 Life expectancy less than three months or Karnofsky status of less than 60.
- 3.2.5 Active uncontrollable infection in area of irradiation.
- 3.2.6 Medical, psychological or other contraindication to proposed treatment. Age $<$ 18 and $>$ 75 years.

4.0 PRETREATMENT EVALUATION

Pretreatment evaluation will be performed at the University of New Mexico Cancer Research and Treatment Center (CRTC) or by the referring physician at another institution, with findings verified and studies augmented as required by the CRTC study team. The evaluation will include:

C

- 4.1 Medical history.
- 4.2 Physical examination.
- 4.3 Laboratory tests.
 - 4.3.1 CBC (including differential)
 - 4.3.2 Platelet count
 - 4.3.3 Urinalysis
 - 4.3.4 Serum chemistry profile
 - 4.3.5 Others as indicated
- 4.4 Chest x-ray, tomograms, ultrasound, radionuclide studies, CT scans and others as indicated, particularly if tumor is in close proximity to bone.
- 4.5 Staging procedures as indicated.
- 4.6 An ophthalmologic examination to assess lens opacity (to be performed upon admission to the study).

5.0 ADMISSION TO STUDY

Any patient who meets the require eligibility and pretreatment evaluation criteria will be admitted to the protocol for pion radiotherapy at LAMPF. The following records will be generated by the study team and participating institutions for storage, retrieval and analysis.

1. Patient eligibility form.
2. Pretreatment evaluation form. This form, documenting the history and physical information, laboratory tests and special studies including surgery, will be submitted on those patients referred for treatment.
3. Study entrance form (patient name, address, referring institution, referring physician, etc.)
4. Patient consent form.

A study case number will be assigned to each patient by RTDG Headquarters.

6.0 TREATMENT

All patients will receive non-randomized pion therapy at the Clinton P. Anderson Meson Physics Facility (LAMPF) in Los Alamos, New Mexico, either alone or as a planned boost in conjunction with conventional radiotherapy. Pion doses are based upon previous experience with pion irradiation of various human tumors¹ and for representative sites are outlined below.

Current Treatment Policy

<u>Site</u>	<u>Maximum Dose (Peak Pion Rad)</u>	<u>Minimum Dose (Peak Pion Rad)</u>	<u>Fractions</u>	<u>Days</u>
Pelvis	4500	3600	36	50
Head & Neck*	4500	3600	36	50
Brain				
Whole	2750	2200	22	32
Cone-down	4500	3600	36	50
Pancreas**				
Whole	2400	1920	24	35
Cone-down	3840	3072	24	35

*Boost fields treated to 5000 peak pion cGy (rad) maximum

**Combined with planned external beam conventional therapy

Variations in total dose in the range of $\pm 10\%$ about the above doses will be explored to further evaluate tumor response and normal tissue tolerance. Doses in this range will be considered definitive and will be combined with other conventional therapy as outlined in Section 10.0 Additional Therapy, below.

Planned combinations of conventional radiation therapy with cone-down pion boost therapy will be applied in selected situations based upon previous experience regarding normal tissue tolerance in patients receiving pions alone. The estimated biological equivalent of combined pion and conventional treatment will not exceed that recognized as tolerance for pion or conventional therapy alone.

Treatment methods will be those developed previously for pion therapy with the fixed vertical beam at LAMPF with appropriate modifications and improvements consistent with improved techniques.² Single or multiple port therapy with or without cone-down therapy will be applied on an individualized basis to maximize normal tissue sparing and to accommodate particular difficulties with patient positioning or disease site.

Treatment planning will be performed by computerized calculation from CT data of necessary compensation for body and tumor contours and tissue inhomogeneities.³ Verification of treatment volumes will be accomplished by simulation using orthodiagraphic scanning⁴ and routine in vivo dosimetry.

7.0 ENDPOINTS

- 7.1 Tumor regression and time to recurrence.
- 7.2 Evaluation of tissue tolerances for pion radiotherapy.
- 7.3 Quality and length of survival.
- 7.4 Adequacy of tumor localization, treatment planning and inhomogeneity correction.

8.0 FOLLOW-UP SCHEDULE

8.1 Follow-Up Plan and Schedules.

The referring physician will be encouraged to see the patient in accordance with his customary schedule.

The patient will be seen at the Cancer Research and Treatment Center at one month after treatment, then every three months for 12 months counting from day 1, and semi-annually thereafter until death occurs or survival reaches five years. If the patient cannot return to the CRTC, arrangements will be made to have him examined at another hospital by his referring physician and preferably his radiotherapist and a report of this examination submitted to the CRTC.

8.2 Follow-Up Information.

The following information will be recorded on the follow-up forms at each visit:

- 8.2.1 Brief interval history related to disease.
- 8.2.2 Physical examination:
 - Weight, blood pressure
 - Temperature
 - Appropriate aspects of physical examination
 - Regression of palpable or visible tumor
- 8.2.3. Laboratory tests and routine x-rays; appropriate studies as indicated.
- 8.2.4 Specific diagnostic studies, or studies which gave the most reliable information regarding the initial extent of tumor will be repeated at periodic intervals.
- 8.2.5 Complications of treatment.
- 8.2.6 Recording and scoring of late reactions and pathologic studies by re-biopsy/autopsy as indicated.
- 8.2.7 Ophthalmologic exam to assess lens opacity (annually).

8.3 Study Parameters.

Parameters to be recorded throughout the study include:

- 8.3.1 Degree and time of regression and regrowth.
- 8.3.2 Assessment of acute radiation effects.
- 8.3.3 Assessment of long-term radiation effects.

CC
1.1.1

Summary of Study Parameters

	<u>Pretreatment</u>	<u>Follow-Up</u>
History and Physical	x	x
Performance Status (Karnofsky)	x	x
CBC, Differential, Platelet Count	x	x ^a
Chemistry Profile	x	x ^a
Urinalysis	x	
Diagnostic (radiographs, ultrasound, nuclear scans)	x ^a	x ^a
Staging/Localization Procedures	x ^a	
Ophthalmologic Exam	x	x ^b

a - As Indicated

b - Yearly

9.0 ADDITIONAL THERAPY

Subsequent therapy should proceed at the discretion of the patient's responsible physician. The patient or physician will notify the investigator of any treatment instituted that has not been prescribed by the investigator.

10.0 PATHOLOGY

10.1 Initial Surgical (Biopsy) Specimens.

Representative slides and copies of biopsy reports will be submitted to the study center and reviewed by the study pathologists. Copies of the reports from the study pathologists will be forwarded to the referring and/or follow-up physician.

10.2 Subsequent Surgical Specimens.

Any tissue surgically removed from anatomic sites will be examined by pathologists at the participating institution where surgery was performed. Appropriate microscopic slides and pathologic reports will be forwarded to the study center for review by the study pathologists.

10.3 Autopsies.

Autopsies are strongly urged on all study patients by pathologists at the participating institutions. Post-mortem

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studies should include a description of irradiated tissues and the character and extent of any persistent, recurrent or metastatic tumor. Autopsy reports and representative microscopic slides will be forwarded to the study center for review by the study pathologists.

11.0 FORMS.

Two copies of each study form must be submitted to RTOG Headquarters. Data will be recorded on standard forms to be supplied to participating institutions by RTOG Headquarters.

- a. Photocopy of patient consent form.
- b. Patient eligibility form.
- c. Pretreatment evaluation form.
- d. Study entrance form.
- e. Radiation treatment summary. A daily schedule of pion therapy will be prepared at LAMPF. This report will also include an end of treatment examination to include weight, pertinent general physical examination, performance status, current medications, and, if possible, an assessment of tumor response.
- f. Follow-up examination form.
- g. Pathology form.

12.0 PATIENT CONSENT AND PEER JUDGMENT

All institutional, Food and Drug Administration, and National Cancer Institute regulations requiring submission to the institutional human experimentation committee and the use of procedures for obtaining and recording informed consent will be followed. A patient may be removed from the study if the study is not in the best interest of the patient. A patient may withdraw voluntarily from the study at any time, as will be indicated in the consent form.

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13.0 REFERENCES

1. Kligerman, M., Bush, S., Kondo, M., Wilson, S., Smith A.R.: Results of Phase I/II trials of pion radiotherapy. In Proceedings of the Second Rome International Symposium on Biological Bases and Clinical Implications of Radioresistance, in press.
2. Kligerman, M.M., Hogstrom, K.R., Lane, R.B., Somers, J.: Prior immobilization and positioning for more efficient radiotherapy. Int J Radiat Oncol Biol Phys 2:1141-1144, 1977.
3. Hogstrom, K.R., Smith, A.R., Simon, S.L., Somers, J.W., Lane, R.G., Rosen, I.I., Kelsey, C.A., von Essen, C.F., Kligerman, M.M., Berardo, P.A., Zink, S.M.: Static pion beam treatment planning of deep seated tumors using computerized tomographic scans at LAMPF. Int J Radiat Oncol Biol Phys 5:875-886, 1979.
4. Tsujii, H., Bagshaw, M., Smith, A., von Essen, C., Mettler, F., Kligerman, M.: Localization of structures for pion radiotherapy by computerized tomography and orthodiagraphic projection. Int J Radiat Oncol Biol Phys 6:319-325, 1980.

APPENDIX I

KARNOFSKY PERFORMANCE STATUS

- 100 Normal; no complaints; no evidence of disease.
- 90 Able to carry on normal activity; minor signs or symptoms of disease.
- 80 Normal activity with effort; some sign or symptoms of disease.
- 70 Cares for self, unable to carry on normal activity or do active work.
- 60 Requires occasional assistance, but is able to care for most personal needs.
- 50 Requires considerable assistance and frequent medical care.
- 40 Disabled; requires special care and assistance.
- 30 Severely disabled; hospitalization is indicated, although death no imminent.
- 20 Very sick; hospitalization necessary; active support treatment is necessary.
- 10 Moribund; fatal process progressing rapidly.
- 0 Dead.

CS

APPENDIX II

PATIENT CONSENT FORM FOR PI MESON RADIATION THERAPY FOR
METASTATIC CANCER*

Patient's Name: _____

Address: _____

Hospital/Clinic: _____

Hospital/Clinic I.D. Number: _____

1. I, _____, agree to take part in a
Name of Patient
research study of pi meson radiation treatment for cancer that has spread. The pi meson radiation treatment will be given at the Clinton P. Anderson Meson Physics Facility in Los Alamos, New Mexico. Dr. Steven E. Bush and doctors he has chosen will do this study. Persons helping them will be supervised by a doctor at all times while treatment is being given.
2. The treatment to be given to me has been described to me by Dr. _____. It is as follows:
 - a. If I choose to be in the study and the physical examination and tests show that I am able to be in the study, I must agree to spend the needed time in Los Alamos for treatment. I must also agree to return to the University of New Mexico Cancer Research and Treatment Center for any check-ups and tests needed after the pi meson radiation treatments.
 - b. I will be given pi meson radiation treatments, usually five days a week, for about eight weeks.
 - c. Before treatment, I will receive standard tests and examinations. These tests will include x-ray pictures and scans so that the persons treating me can see what area should be treated.
 - d. Before treatment, I will be placed in the exact position that I will be in during treatment. This set-up is done in a room near the treatment room. X-ray pictures will be taken to see if the treatment planned for me is correct.

*Sample Consent Form submitted by the Study Chairman.

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- e. I will receive treatment in the same set-up position. There will be no pain or feeling from the pi meson beam during treatment. I will be alone in the treatment room, but persons treating me can see me on closed-circuit television. We will also be able to talk to each other through the microphone and speaker system. People will always be outside the treatment room and ready to help me.
- f. After the pi meson treatments end, I will receive standard medical tests to see what the treatments have done.
3. Dr. _____ has told me that I might not feel well after the pi meson radiation treatments. Complete information on problems and risks from pi meson treatment is not known. Tests with cells, animals, and patients have shown that pi meson radiation does not create problems much different from problems created by standard radiation treatments. Both pi meson and standard radiation could cause some or all of the following problems and risks: (Insert list for tumor site to be treated: _____). Attach signed list to consent form.
4. Dr. _____ has told me about the good things this research study might do for me and for other people.
- Pi meson treatment might make me feel better while I am being treated.
 - Pi meson treatment might shrink the tumor better than other treatments and improve chances for control of my disease.
5. Dr. _____ has told me about other treatments for me.
- Drug treatments.
 - Standard radiation.
 - Surgery.
6. Dr. _____ will answer any question I have during the treatment.
7. I know that the treatment could harm me. No one has said that it wouldn't. I can stop having treatment at any time I want to.
8. Dr. _____ is in charge of my treatment. He can change the treatment at any time, or stop it.
9. If my body is injured by the research treatment, more than or different from that explained above, I understand that any emergency medical care I need will be given to me at no cost, but I will not be paid any money. Payment for medical costs will not continue after the emergency treatment is finished.

10. I understand that by signing this paper, I am not giving up my legal rights. State laws exist which may help people who think they have been treated carelessly. For information, I can write or call the Risk Management Division, Room 24, Lamy Building, Santa Fe, New Mexico 87503.

Date: _____ Time: _____ Date: _____

Signed: _____ Witness: _____

Parent or Guardian when Indicated Witness: _____

cc: Patient

PELVIC AND ABDOMINAL LESIONS, MALE PATIENTS

Possible Problems and Risks

1. I may get ulcers and other sores in my stomach and small or large intestine. Doctors rarely see this happen with standard radiation treatment, and it is not likely with pi meson radiation treatment.
2. I may have changes in blood cells. Tests are given every week or more often for this. I will be treated right away.
3. I may lose hair in the area being treated.
4. My skin may get red and peel in the treatment area.
5. I may have weakness in some parts of my body and not be able to move those parts. This problem does not happen very often in usual radiation treatments, so it is not expected to happen very often to patients receiving pi meson radiation.
6. I may have pain and swelling in the treatment area.
7. I may have diarrhea. Bleeding could happen with the diarrhea. I understand that these problems usually stop at the end of the treatment. I may be given medicine for these problems.
8. I may be sick at my stomach. This problem can be helped by medicine or by slowing the rate of radiation. Sometimes both methods are used to ease this problem.
9. I may have to pass my water more often. Sometimes I may have burning pain when I pass my water. These problems usually go away after the treatment is ended.
10. I understand that about 40% of men who are treated may not be able to produce children or have sex.

Signed: _____
Patient

Date: _____ Time: _____

PELVIC AND ABDOMINAL LESIONS, FEMALE PATIENTS

Possible Problems and Risks

1. I may get ulcers or other sores in my stomach and small or large intestine with pi meson radiation. Doctors rarely see this happen with usual radiation, so it is not likely to happen with pi meson radiation.
2. I may have changes in my blood cells. Tests will be done every week or more often for this. I will be treated right away.
3. I may lose my hair in the area being treated.
4. My skin may get red and peel in the treatment area.
5. I may have weakness in some parts of my body and not be able to move those parts. This problem does not happen very often in usual radiation treatment, so it is not expected to happen very often to patients receiving pi meson radiation.
6. I may have pain and swelling in the treatment area.
7. I may have diarrhea and some bleeding with the diarrhea. This problem can be treated quickly, and it usually goes away after the treatments are over.
8. I may be sick at my stomach. This problem can be helped by drugs or by slowing the rate of radiation. Sometimes both methods are used to ease this problem.
9. I may have to pass water more often. Sometimes I may have burning pain when I pass my water. Those problems usually go away after the treatment is ended.
10. I understand that my monthly periods may stop, and I may not be able to have children.
11. I may have a discharge from the vagina.

Signed: _____
Patient

Date: _____ Time: _____

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HEAD AND NECK LESIONS

Possible Problems and Risks

1. No matter what type of radiation I am given, I might need an operation after the radiation which might make me lose my voice forever.
2. I may have weakness in some parts of my body and not be able to move those parts. This problem does not happen very often.
3. I may have unusual openings in my skin or other tissue. These openings might heal themselves, or I might need surgery to repair them.
4. I may have pain and swelling in the treatment area.
5. I may lose normal bone or tissue in the treatment area.
6. I may get cavities in my teeth.
7. I may get ulcers in my mouth and throat. These ulcers might go away or be permanent.
8. I may have sore throat and trouble swallowing.
9. I might have a cough.
10. I might have trouble breathing.
11. I may have changes in blood cells. Tests are given every week or more often for this. I will be treated right away.
12. I may have a fever.
13. I may have more chance of getting an infection.
14. Later, I may get cancer of the thyroid, but this problem does not happen very often.
15. My skin may get red and peel in the treatment area.
16. I might have much wetness or dryness near the top of my breathing tubes or food tubes.
17. I might lose my sense of taste. This loss usually does not last long.
18. I might lose hair in the treatment area.
19. I might get cataracts (clouding of the lenses in my eyes). This is not expected, but if it does happen it can be corrected by an operation.

C.

Signed: _____
Patient

Date: _____ Time: _____

CHEST LESIONS

Possible Problems and Risks

1. My lungs may become red and scarred. The redness may go away or leave scars. The scars usually cause no problems that would harm me. Long-term problems were found in one out of 133 patients in one series of studies with usual radiation. I may have trouble breathing.
2. I may have weakness in some parts of my body and not be able to move those parts. This problem does not happen very often.
3. I may have unusual openings in my skin or other tissues. These openings might heal themselves, or I might need surgery to repair them.
4. I may have pain and swelling in the treatment area.
5. I might lose normal bone or muscle tissue in the treatment area.
6. I may have a sore throat and trouble swallowing.
7. I might have a cough.
8. I might have trouble breathing.
9. I may have changes in blood cells. Tests are given every week or more often for this. I will be treated right away.
10. I may have a fever.
11. I may have more chance of getting an infection.
12. Later, I may get cancer of the thyroid, but this problem does not happen very often.
13. My skin may get red and peel in the treatment area. Later, I might get skin cancer.
14. I might have much wetness or dryness near the top of my breathing tubes or food tubes.
15. I might lose hair in the treatment area.

Signed: _____
Patient

Date: _____ Time: _____

BRAIN LESIONS

Possible Problems and Risks

1. Patients with brain cancer often have some problems that are there before treatment. Treatments can stir up these problems for a time. Such problems are:
 - a. I may be sick at my stomach. This problem can be helped by drugs or by slowing the rate of radiation. Sometimes both methods are used to ease the problem.
 - b. I may have headaches, but these can be treated with medicine.
 - c. I may be drowsy, but this can be treated with medicine.
 - d. I may have double vision.
2. I may not feel well after the treatments. Some of the problems that might be caused by the treatments are:
 - a. Parts of my normal brain tissue might be destroyed. This could cause weakness in some parts of my body, and I may not be able to move those parts. I might also have trouble seeing, hearing, smelling, touching or tasting. I might also have trouble in thinking.
 - b. My skin may get red and peel in the treatment area. Later, I might get skin cancer.
 - c. I will lose my hair, but it will probably grow back after treatment.
 - d. I might get cataracts (clouding of the lenses in my eyes). This is not expected, but if it does happen it can be corrected by an operation.

Signed: _____
Patient

Date: _____ Time: _____

WOMEN OF CHILD-BEARING AGE

Possible Problems and Risks

Women of child-bearing age should understand that the pion treatments, like x-rays or other radiation, could cause changes that might result in birth defects in children born after treatment has been given. The chance of this happening is not known. Women who plan to have children at any time after they complete treatment should seek counseling from doctors who are qualified to help them understand the extent of this risk.

Signed: _____
Patient

Date: _____ Time: _____

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