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Los Alamos Scientific Laboratory
DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

From Los Alamos
National Laboratory Archives

MANPOWER REPORT

Complete only if label missing

GRANT OR CONTRACT NUMBER CA-14052-05	BUDGET PERIOD (Same as progress report) 6-01-76/05-31-77
PRINCIPAL INVESTIGATOR OR PROGRAM DIRECTOR KLIGERMAN, MORTON M.	
GRANTEE OR CONTRACTOR INSTITUTION NAME UNIVERSITY OF NEW MEXICO, CRTC	
	714497

Please complete both parts of this report:

- Part I. All persons receiving any salary from the direct cost awarded for this grant or contract during budget period.
- Part II. All persons who performed some work during budget period on the research project for which no salary was received from this grant or contract.

Individual reports will be treated as confidential and will be used only in the form of statistical summaries. Names and Social Security numbers are necessary to avoid duplicate counting.

GENERAL INSTRUCTIONS

If data are not available on all questions, please supply as much information as is satisfactory.

Please use whole numbers. Do not use fractions, decimals or cents.

All information requested applies to the budget period specified above.

Please return one copy of the questionnaire and retain the other for your file. Division of Research Grants, National Institutes of Health, Westwood Building, Bethesda, Maryland 20014. For information on completion of form telephone (301) 251-2000.

REPOSITORY LANL/ARC

COLLECTION MP 20

BOX No. A-91-011

FOLDER 177-4



DEFINITIONS
(Part I and Part II)

PROFESSIONAL: Individuals who hold positions which normally: (1) require a baccalaureate, equivalent, or higher degree, and (2) are considered by the grantee institution as performing professional work. *Exclude all consultants.*

Faculty Status: All professional persons working on this grant or contract—including temporary, part-time and retired—who hold appointments designated as "faculty" by an institution of higher education.

Non-Faculty: All professional persons working on this grant or contract who do not hold appointments designated as "faculty" by an institution of higher education. This includes all non-faculty professional staff employed by non-academic institutions (independent hospitals, research institutes, nonprofit foundations, and private companies). Postdoctorals considered as primarily in a training status should be reported under "In Training Status."

In Training Status: Include only those individuals who, while working on a grant or contract, are considered to be in a predoctoral or postdoctoral training status. This includes graduate students registered in institutions of higher education for part-time study leading to an academic (PhD, ScD, MA, MS, MPH, or equivalent) or professional (MD, DDS, DVM, or equivalent) degree. Predoctorate students working on their dissertation should be entered in this section. Individuals who already have an academic or professional doctorate but are considered as being primarily in a training status should be included. Residents and interns should also be included except those serving on rotation as part of their regular medical training. Undergraduate students should be counted as "All Other Staff."

ALL OTHER STAFF: All other personnel working on this grant or contract. Include undergraduate students. *Exclude all consultants.*

SPECIFIC INSTRUCTIONS FOR PART I

- List in Items 1, 2, and 3 the names of all professional personnel who worked on activities supported by this grant or contract during the budget period specified who received any salary from the grant or contract.
- In Item 4, "All Other Staff," count all other personnel who received any salary from the grant or contract during the budget period specified. Give total number of persons in each of the four categories listed and estimate total manweeks and personnel costs.
- Exclude employer payments for Social Security and other fringe benefits from all amounts reported for salaries and personnel expenditures.
- Social Security Number (Items 1, 2, and 3, Column b):** If the individual does not have a Social Security Number, enter the month and day of birth. Example: 06-15 for June 15.
- Number of Weeks Worked (Items 1, 2, and 3, Column f):** Weeks worked during the budget period specified on activities supported by the grant or contract for which salary was received from grant or contract funds. Count each week regardless of number of hours worked. Do not report percent of effort.
- Estimated Total Manweeks (Item 4, Column r):** The total number of weeks all persons counted were paid for their work on the project. Reasonable estimates are acceptable. Part-time work should be computed on the basis of 40 hours a week or the accepted work week in the grantee institution if it is less than 40 hours.
- Total Personnel Expenditures (Item 5):** The amount given should be the sum of the professional salaries and the expenditures reported for the "all other staff." If continuation pages have been used, be sure to include all persons listed for a given professional category regardless of the page on which the name appears.

1091875

MP-D; sion
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 DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
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Check for label placement

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All information requested applies to the budget period specified above.

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DEFINITIONS
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1091876

PART I: PERSONNEL RECEIVING ANY SALARY FROM THIS GRANT CONTRACT DURING BUDGET PERIOD

READ INSTRUCTIONS BEFORE COMPLETING FORM. USE TYPEWRITER. USE CONTINUATION PAGES, IF NECESSARY

NAME (Last, first initial)	SOCIAL SECURITY NUMBER	YEAR OF BIRTH	SEX M OR F	HIGHEST DEGREE HELD CODE*	HOURS AND EARNINGS IN BUDGET PERIOD**			FDS CODE FOR PROJECT EMPLOYMENT	OTHER SOURCES OF INCOME WHILE ON PROJECT (Check more than one if appropriate)				
					NUMBER OF WEEKS WORKED	AVERAGE WEEKLY HOURS (Estimate)	TOTAL SALARY FROM PROJECT (DOLLARS ONLY)		NIH SUPPORT	TRAINING GRANT, FELLOWSHIP, OR CAREER AWARD	OTHER RESEARCH GRANT	RESEARCH CONTRACT	OTHER FEDERAL SUPPORT

Non-

1. PROFESSIONAL: FACULTY STATUS

Knapp, E. A.			M	5	8			S6					
Bradbury, J. N.			M	5	16			S6					
Amols, H. I.			M	5	26			S6					
Helland, J.			M	5	52			S6					
Paciotti, M.			M	5	52			S6					
Schillaci, M.			M	5	26			S6					
Berardo, P.			M	5	26			S6					

2. PROFESSIONAL: NON-FACULTY continued

Bush, E.			M	4	9			Q2					
Wing, J.			M	3	52			Q2					
Hutson, R. L.			M	5	52			S6					
Liska, D.			M	4	26			Q2					

3. PROFESSIONAL: IN TRAINING STATUS (Predoctorals and postdoctorals)

DEGREE SOUGHT CODE*
P

4. ALL OTHER STAFF RECEIVING ANY SALARY FROM THIS GRANT OR CONTRACT DURING THIS BUDGET PERIOD

	NUMBER OF PERSONS q	TOTAL MANWEEKS (estimate) r	TOTAL AMOUNT PAID FROM THIS GRANT OR CONTRACT - DOLLARS ONLY (estimate) s
CLINICAL SUPPORTING STAFF - those whose duties primarily involve patient care (orderlies, practical nurses, etc.) (2.)			
TECHNICAL - includes technicians, laboratory assistants, animal caretakers, etc. (3.)	4	52	
CLERICAL AND ADMINISTRATIVE STAFF (4.)	1	52	
OTHER STAFF (5.)			
TOTAL: ALL OTHER STAFF (1.)	5	260	

5. TOTAL SALARIES RECEIVED IN BUDGET PERIOD (Cols. h + s)
(Exclude employer payments for Social Security and fringe benefits)

\$ 246,287

NIH-1749
Rev. 3-74

* See CODE SHEET on Page 4.
** Exclude any weeks and hours worked for which no salary was received from this grant or contract. Report such time in Part II, column w.

1091877

PART II: PERSONNEL PERFORMING SOME PROJECT WORK DURING THIS GRANT OR CONTRACT BUDGET PERIOD FOR WHICH NO SALARY WAS RECEIVED

The purpose of this portion of the report form is to obtain information to help evaluate the contributions to NIH research programs by individuals who perform significant work on an NIH research project for which no salary is received from that NIH research grant or contract.

If no individuals performed unpaid work on this project as defined in the instructions below, please check box.

1. Exclude interns and residents working on this project on rotation as part of their regular medical training.
2. Column (t): Estimate the number of individuals in each occupational category given in the table below who contributed at least 80 hours of unpaid work on the research project during the budget period and received no salary from the grant or contract. Enter these numbers in Column (t). Exclude those individuals who contributed less than 80 hours of unpaid work. Note that individuals reported in Part I who also performed unsalaried work should be entered in Columns (v) and (w).
3. Column (u): For each of the individuals entered in Column (t) estimate the total number of unsalaried hours worked and divide by 40 hours (or the accepted work week in the grantee institution if it is less than 40 hours) to calculate manweeks. Add the number of manweeks for all individuals in a given occupational category and enter in Column (u).
4. Column (v): Estimate the number of individuals in each occupational category who received salary for work performed on the grant or contract but also performed *any amount* of work on the project without receiving salary from the grant or contract. Enter this number in Column (v).
5. Column (w): For all of the individuals entered in Column (v), estimate the total number of unsalaried hours worked. Convert to occupational category manweeks as described in paragraph 3 above and enter in Column (w).

OCCUPATIONAL CATEGORY	PERSONS NOT PAID BY THIS GRANT OR CONTRACT WHO WORKED AT LEAST 80 HOURS ON PROJECT		PERSONS REPORTED IN PART I WHO ALSO PERFORMED UNPAID WORK ON PROJECT	
	NUMBER OF PERSONS (t)	TOTAL UNPAID MANWEEKS (u)	NUMBER OF PERSONS (v)	TOTAL UNPAID MANWEEKS (w)
PROFESSIONAL STAFF:				
FACULTY STATUS				
(3.)				
NON-FACULTY	2	24		
(4.)				
Predoctoral in Training Status				
(6.)				
Postdoctoral in Training Status				
(7.)				
ALL OTHER STAFF:				
(8.)				
TOTAL	2	24		
(1.)				

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE APPLICATION FOR CONTINUATION GRANT	REVIEW GROUP	TYPE	PROGRAM	GRANT NUMBER (INSERT ON ALL PAGES)
	SRC	5	P01	CA14052-05
	TOTAL PROJECT PERIOD			
	FROM: 06/01/76		THROUGH: 05/31/79	
REQUESTED BUDGET PERIOD				
FROM: 06/01/77		THROUGH: 05/31/78		

TO BE VERIFIED BY APPLICANT. CHECK INFORMATION IN ITEMS 1 THROUGH 6. IF INCORRECT, FURNISH CORRECT INFORMATION IN ITEM 13.

1. TITLE	
PRECLINICAL STUDIES FOR PION RADIOTHERAPY	
2A. PRINCIPAL INVESTIGATOR OR PROGRAM DIRECTOR (Name and Address, Street, City, State, Zip Code)	4. APPLICANT ORGANIZATION (Name and Address, Street, City, State, Zip Code)
KLIGERMAN, MORTON M UNIVERSITY OF NEW MEXICO CANCER RES & TREATMENT CTR ALBUQUERQUE, N MEX 87131	CANCER RESEARCH & TREATMENT CTR UNIVERSITY OF NEW MEXICO ALBUQUERQUE, N MEX 87131
2B. DEGREE	2C. SOCIAL SECURITY NO.
MD	[REDACTED]
2D. DEPARTMENT, SERVICE, LABORATORY OR EQUIVALENT	5. PHS ACCOUNT NUMBER
CANCER RES & TREATMENT CENTER	1856000642A1
2E. MAJOR SUBDIVISION	6. TITLE AND ADDRESS OF OFFICIAL IN BUSINESS OFFICE OF APPLICANT ORGANIZATION
HEALTH SCIENCES CENTER	COMPTROLLER UNIVERSITY OF NEW MEXICO ALBUQUERQUE, N MEX 87131
3. ORGANIZATIONAL COMPONENT TO RECEIVE CREDIT FOR INSTITUTIONAL GRANT PURPOSES	
01 SCHOOL OF MEDICINE	

COMPLETE THE FOLLOWING (See Instructions)

7. RESEARCH INVOLVING HUMAN SUBJECTS (See Instructions)	8. INVENTION CERTIFICATION (See Instructions)																		
<input checked="" type="checkbox"/> NO <input type="checkbox"/> YES APPROVED: _____ DATE _____	<input checked="" type="checkbox"/> NO <input type="checkbox"/> YES - NOT PREVIOUSLY REPORTED <input type="checkbox"/> YES - PREVIOUSLY REPORTED																		
PERFORMANCE SITE(S)	TELEPHONE INFORMATION																		
Cancer Research and Treatment Center University of New Mexico Albuquerque, New Mexico 87131 Congressional District #1 Los Alamos Scientific Laboratory P. O. Box 1663 Los Alamos, New Mexico 87545 Congressional District #1	<table border="1"> <tr> <th>11A. PRINCIPAL INVESTIGATOR OR PROGRAM DIRECTOR (ITEM 2A)</th> <th>AREA CODE</th> <th>TELE. NO. & EXT.</th> </tr> <tr> <td></td> <td>505</td> <td>277-2151</td> </tr> <tr> <th>11B. NAME OF BUSINESS OFFICIAL (ITEM 6)</th> <td></td> <td></td> </tr> <tr> <td>Warren Baur</td> <td>505</td> <td>277-6264</td> </tr> <tr> <th>11C. NAME AND TITLE OF ADMINISTRATIVE OFFICIAL (ITEM 15B)</th> <td></td> <td></td> </tr> <tr> <td>Warren Baur Asst. Comptroller, Health Sciences</td> <td>505</td> <td>277-6264</td> </tr> </table>	11A. PRINCIPAL INVESTIGATOR OR PROGRAM DIRECTOR (ITEM 2A)	AREA CODE	TELE. NO. & EXT.		505	277-2151	11B. NAME OF BUSINESS OFFICIAL (ITEM 6)			Warren Baur	505	277-6264	11C. NAME AND TITLE OF ADMINISTRATIVE OFFICIAL (ITEM 15B)			Warren Baur Asst. Comptroller, Health Sciences	505	277-6264
11A. PRINCIPAL INVESTIGATOR OR PROGRAM DIRECTOR (ITEM 2A)	AREA CODE	TELE. NO. & EXT.																	
	505	277-2151																	
11B. NAME OF BUSINESS OFFICIAL (ITEM 6)																			
Warren Baur	505	277-6264																	
11C. NAME AND TITLE OF ADMINISTRATIVE OFFICIAL (ITEM 15B)																			
Warren Baur Asst. Comptroller, Health Sciences	505	277-6264																	
10. DIRECT COSTS REQUESTED FOR BUDGET PERIOD	12B. COUNTY OF APPLICANT ORGANIZATION SHOWN IN ITEM 4																		
\$1,002,684	Bernalillo																		
12A. CONGRESSIONAL DISTRICT OF APPLICANT ORGANIZATION SHOWN IN ITEM 4																			
Congressional District #1																			

13. USE THIS SPACE FOR CORRECTIONS TO ITEMS 1 THROUGH 6. INDICATE THE NUMBER(S) WHERE ANSWER(S) APPLY

3. 20 Cancer Research and Treatment Center

5. 726225

6. Asst. Comptroller, Health Sciences, University of New Mexico, Albuquerque, New Mexico 87131

14. CERTIFICATION AND ACCEPTANCE. WE, THE UNDERSIGNED, CERTIFY THAT THE STATEMENTS HEREIN ARE TRUE AND COMPLETE TO THE BEST OF OUR KNOWLEDGE AND ACCEPT, AS TO ANY GRANT AWARDED, THE OBLIGATION TO COMPLY WITH PUBLIC HEALTH SERVICE TERMS AND CONDITIONS IN EFFECT AT THE TIME OF THE AWARD.

SIGNATURES (Signatures required on original copy only. Use ink. "Per" signatures not acceptable.)	15A. PRINCIPAL INVESTIGATOR OR PROGRAM DIRECTOR	DATE
	15B. OFFICIAL SIGNING FOR APPLICANT ORGANIZATION	DATE
	<i>Warren Baur</i>	3/25/77

PHS 2590-1 OPTIONAL REV. 1-70

RETURN COMPLETED APPLICATION TO PHS AS SOON AS POSSIBLE:
NO LATER THAN 1 APRIL 1977

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CO.

SECTION II

SECTION II—BUDGET (USUALLY 12 MONTHS)	FROM 1 June 1977	TO 31 May 1978	GRANT NUMBER CA-14052-05
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A. ITEMIZE DIRECT COSTS REQUESTED FOR NEXT BUDGET PERIOD

PERSONNEL		TIME OR EFFORT %/MOS (c)	SALARY REQUESTED (d)	FRINGE BENEFITS (See Instructions) (e)	TOTAL (f)
NAME (Last, First, Initial) (a)	TITLE OF POSITION (b)				
See Attached	PRINCIPAL INVESTIGATOR				
Subtotals →			\$ 190,288	\$ 32,348	
(Indicate cost of each item listed below)				TOTAL (Columns (d) and (e)) →	\$ 222,636
CONSULTANT COSTS (See Instructions)					\$ 25,000
EQUIPMENT					
					\$ 39,000
SUPPLIES					
					\$ 59,331
TRAVEL	DOMESTIC				\$ 13,300
	FOREIGN				\$
PATIENT COSTS (See Instructions)					\$
ALTERATIONS AND RENOVATIONS					\$
Carry-forward from Year 4					\$ 75,000
OTHER EXPENSES (Itemize)					
Other Expenses		11,947			
Purchased Services		556,470			
					\$ 568,417
TOTAL DIRECT COST (Enter on Page 3, Item 10)					\$1,002,684

INDIRECT COST (See Instructions)	60.0 % SSW* ----- % TDC*	Date of DHEW Agreement: March 10, 1977	<input type="checkbox"/> Not Requested <input type="checkbox"/> Under negotiation with: off-site research
*If this is a special rate (e.g. off-site), explain.		For Los Alamos-based staff, rate applies, 38.0%	

1091881

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BIOLOGY LABORATORIES

SECTION II

SECTION II—BUDGET (USUALLY 12 MONTHS)	FROM 1 June 1977	THROUGH 31 May 1978	GRANT NUMBER CA-14052-05
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A. ITEMIZE DIRECT COSTS REQUESTED FOR NEXT BUDGET PERIOD

PERSONNEL NAME (Last, First, Initial) (a)	TITLE OF POSITION (b)	TIME OR EFFORT %/HRS. (c)	SALARY REQUESTED --	FRINGE BENEFITS (See Instructions) (e)	TOTAL (f)
Kligerman, M.M.	PRINCIPAL INVESTIGATOR	NA			
Yugas, J.M., Ph.D.	Assoc. Dir./Biology	60			
Li, Albert, Ph.D.	Cellular Biologist	75			
New Hire	Lab Chief	100			
New Hire	Mammalian Biologist	100			
Tarleton, A.	Cell Technician	100			
Azad, Mahmood	Animal Technician	50			
Rhiger, Thomas	Cell Technician	100			
*New Hire	Cell Technician	100			
*New Hire	Animal Technician	100			
Blaschak, C.	Secretary	60			
*Based in Los Alamos					
Subtotals			\$125,733	\$21,374	

(Indicate cost of each item listed below)

TOTAL (Columns (d) and (e))

\$ 147,107

CONSULTANT COSTS (See Instructions)

EQUIPMENT	Item	Cost	Item	Cost	Total
	Centrifuge	\$6,500	Rotor for ultracentrifuge	\$3,800	
	Dosimeters	600	Controlled Temp. Cell Exposure Chamber	1,400	
	Inverted Phase Microscope	\$6,000	Laboratory Microscope	2,000	
	Incubators (3)	6,000	Miscellaneous Laboratory equipment	600	\$ 29,000
	ph Meter	600			
	Analytic balance	1,500			

SUPPLIES	Item	Cost	Item	Cost	Total
	Mouse/Rat purchases	10,000	Fetal Calf Serum	\$7,500	
	Food/Bedding	5,000	Chemicals/Misc.	3,090	
	Isotopes	3,000			
	Plastics/media	10,000			
	Glassware	3,000			
	CO ₂	3,000			\$ 44,590

TRAVEL	Type	Description	Total
	DOMESTIC	Albuquerque/Los Alamos, 45 trips/year @ \$90/trip scientific meetings @ \$500/trip	\$ 5,000
	FOREIGN		\$

PATIENT COSTS (See Instructions)

ALTERATIONS AND REMOVATIONS	Total
Carry-forward from Year 4 (CRIC animal facility)	\$ 75,000

OTHER EXPENSES (Itemize)	Total
Xerox, communications, equipment maintenance	\$ 7,000

TOTAL DIRECT COST (Enter on Page 1, Item 10) \$ 307,697

INDIRECT COST (See Instructions)	_____ % SSW* _____ % TDC*	Date of DHEW Agreement: _____	<input type="checkbox"/> Not Requested <input type="checkbox"/> Under negotiation with: _____
*If this is a special rate (e.g. off-site), explain _____			

1091883

PURCHASED SERVICES - ASL SUBCONTRACT SECTION II

SECTION II—BUDGET (USUALLY 12 MONTHS) FROM 1 June 1977 THROUGH 31 May 1978 GRANT NUMBER CA-14052-05

A. ITEMIZE DIRECT COSTS REQUESTED FOR NEXT BUDGET PERIOD

PERSONNEL					
NAME (Last, First, Initial) (a)	TITLE OF POSITION (b)	TIME OR EFFORT %/HRS (c)	SALARY REQUESTED (d)	FRINGE BENEFITS (See Instructions) (e)	TOTAL (f)
Kligerman, M.M., M.D.	PRINCIPAL INVESTIGATOR	NA	NA		
Rosen, L., Ph.D.	Deputy Prin. Invest.	NA	(No salary requested)		
Bradbury, J., Ph.D.	Group Leader	15	(No salary requested)		
Bush, E.	Mechanical Engineer	25			
Helland, J., Ph.D.	Physicist	100			
Hutson, R., Ph.D.	Physicist	25			
Liska, D.	Engineer	50			
Paciotti, M., Ph.D.	Physicist	100			
Richman, C., Ph.D.	Physicist	100			
Schillaci, M., Ph.D.	Physicist	25			
Warner, R.	Asst. Division Ldr.	5	(No salary requested)		
Wing, J.	Engineer	100			
Blossom, J.	Electronics Tech.	100			
Cont. next page	Subtotals		\$	\$	

(Indicate cost of each item listed below) TOTAL (Columns (d) and (e)) \$ 256,100

CONSULTANT COSTS (See Instructions) \$

EQUIPMENT	Nuclear electronics and CAMAC modules	\$10,000	
	Dosimetry beam monitoring instrumentation	6,000	
	Channel control	11,000	
	Computer peripheral/interface equipment	9,000	
			\$ 38,600
			\$ 36,000

SUPPLIES	Electronic parts	10,000	
	Computer expendables	12,000	
	Control hardware	20,000	
	Dosimetry electronics/supplies	20,000	
	Clerical and other supplies	7,000	
			\$ 66,400
			\$ 69,000

TRAVEL	DOMESTIC	* Changes per Stephany Wilson 5-3-77 2FW	\$ 4,000
	FOREIGN		\$

PATIENT COSTS (See Instructions) \$

ALTERATIONS AND REMOVALS \$

OTHER EXPENSES (Itemize)
See next page
\$ 191,370

TOTAL DIRECT COST (Enter on Page 1, Item 10) \$ 556,470

INDIRECT COST (See Instructions) _____ % S&W* _____ % TDC* Date of DHEW Agreement: _____ Not Requested Under negotiation with: _____

*If this is a special rate (e.g. off-site), explain.

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Personnel (Continued)

Chavez, A.	Programmer	50
Helm, C.	Data Analyst	50
George, C.	Electronics Technician	100
Rivera, O.	Electronics Technician	100
New Hire	Electronics Technician	50

Other Expenses

Computer facility charges	\$2,000
Electronics and instrumentation maintenance and repair	8,600
Communications	5,000
ADP equipment maintenance/leases	2,000
Construction of beam hardware	9,000
Contractual services	7,000
Animal housing and care	10,000
Indirect costs @ 57.7% of personnel costs	147,770
Total Other Expense	\$191,370

SECTION II—BUDGET (Continued)

Grant Number

5-P01-CA-14052-05

B. Supplemental information regarding ITEMS in the proposed budget for the next period which require explanation or justification. (See instructions)

1. Personnel:

Personnel costs are based on current year plus 7 percent. The biology budget reflects the consolidation of this activity at the UNM Cancer Research and Treatment Center, with the Los Alamos Scientific Laboratory providing only short-term animal care and housing support (see "other expense" for LASL subcontract). This consolidation will enable us to operate with greater efficiency in accomplishing the biology tasks. The budget also reflects our experience during the past year that the overall funding level for the biology effort was inadequate. This estimate more closely corresponds with our experience for the past year, and our anticipated requirements with a relatively continuous operating schedule for the coming year.

2. Consultants:

Consultant expenses are the same as for the past year, and cover the consulting services of the Committee on Human Trials of Pion Radiotherapy, as well as other scientific consults and visiting scientists.

3. Equipment:

The equipment budget is based on our projected needs and the recommendations of the NCI review team.

4. Supplies, Travel, and Other Expense:

Items in these categories reflect our past experience, the recommendations of the NCI review team, and a projected 7 percent increase for the coming year. The biology component for Health Division of the Los Alamos Scientific Laboratory has been reduced to a charge for short-term animal care (\$10,000), included in the "other expense" category of the LASL subcontract budget.

5. Alterations and Renovations:

A carry-over of \$75,000 awarded in Year 4 for animal housing renovations at the UNM CRTC is requested. We anticipate being able to accomplish this task during the coming year, and housing is needed, as UNM has assumed all long-term animal housing requirements for this project.

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SECTION III

SECTION III—FISCAL DATA FOR
CURRENT BUDGET PERIOD
(USUALLY 12 MONTHS)

FROM

THROUGH

AWARD NUMBER

1 June 1976

31 May 1977

5-P01-CA-14052-05

The following pertains to your CURRENT PHS budget. Do not include cost sharing funds. This information in conjunction with that provided on Page 2 will be used in determining the amount of support for the NEXT budget period.

A. BUDGET CATEGORIES		CURRENT BUDGET (As approved by awarding unit) (1)	ACTUAL EXPENDITURES THRU	ESTIMATED ADDITIONAL EXPENDITURES AND OBLIGATIONS FOR REMAINDER OF CURRENT BUDGET PERIOD (3)	TOTAL ESTIMATED EXPENDITURES AND OBLIGATIONS (Col. 2 plus Col. 3) (4)	ESTIMATED UNOBLIGATED BALANCE (Subtract Col. 4 from Col. 3) (5)
			(Insert Date) (2)			
Personnel (Salaries)		159,397	107,415	51,982	159,397	0
Fringe Benefits		27,098	12,948	14,150	27,098	0
Consultant Costs		25,000	1,542	23,458	25,000	0
Equipment		35,900	32,845	3,055	35,900	0
Supplies		42,600	39,920	2,680	42,600	0
TRAVEL	Domestic	14,539	12,770	1,769	14,539	0
	Foreign					
Patient Costs						
Alterations and Renovations		75,000				75,000
Other		2,064	529	1,535	2,064	0
Other Purchased Services		602,540	297,798	282,142	579,940	22,600
Total Direct Costs		984,138	505,767	380,771	886,538	97,600
Indirect Costs (If included in award)						
TOTALS →		\$984,138	\$505,767	\$380,771	\$886,538	\$97,600

Use space below to:

B. List all items of equipment purchased or expected to be purchased during this budget period which have a unit cost of \$1000 or more.

C. Explain any significant balance or deficit shown in any category of Column 5.

D. List all other research support for Principal Investigator by source, project title, and annual amount.

B. Roller apparatus, cell production	\$1,167
Lyophilizer apparatus	3,453
Monroe programmable calculator	2,791
Stereomicroscope and camera system	2,741
Bioguard cabinet and hood	3,541
Incubator	2,304
Patient dosimetry equipment	3,320
Keithley multimeter and calibration equipment	2,509

TOTAL

\$21,826

C. \$75,000 A&R funds for animal facility renovation for CRTC requested for carry-over into Year 5.
\$18,400 personnel costs and \$4,200 indirect costs to be returned to NCI from LASL subcontract, due to transfer of mammalian biologist and technician from project.

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- D. NCI-5-P01-CA-16127-03: Clinical Studies of Pion Radiotherapy, \$1,460,692 (current year), \$943,029 estimated for Year 4 (beginning 1 May 1977).
- NCI-1-R01-CA-20379-01: Radiation Therapy Oncology Group Clinical Investigations, \$25,272 (current year).
- NCI-1-P30-CA-21074-01: Cancer Center Support (Core) Grant, \$511,953 estimated for Year 1 (beginning 1 May 1977).

SECTION IV

APPLICANT: REPEAT GRANT NUMBER SHOWN ON PAGE 1 →		GRANT NUMBER	
SECTION IV—SUMMARY PROGRESS REPORT		5-P01-CA-14052-05	
PRINCIPAL INVESTIGATOR OR PROGRAM DIRECTOR (Last, First, Initial)		PERIOD COVERED BY THIS REPORT	
Kligerman, H.M.		FROM	THROUGH
NAME OF ORGANIZATION		1 June 1976	31 May 1977
Cancer Research and Treatment Center, UNM			
TITLE (Repeat title shown in Item 1 on first page)			
Preclinical Studies for Pion Radiotherapy			

1. List publications: (a) published and not previously reported; (b) in press. Provide five reprints if not previously submitted.
2. List all additions and deletions in professional personnel and any changes in effort.
3. Progress Report. (See Instructions)

See Attached

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1. PUBLICATIONS

- *Amols, H.I.; Bradbury, J.; 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. Submitted to Physics in Medicine and Biology.
- Amols, H.I.; Awschalom, M.; Bradbury, J.; Boyd, T.J.; Bush, E.; Coulson, L.; Dicello, J.F.; Faulkner, R.; Jameson, R.A.; Johnson, S.; Knapp, E.A.; Smith, A.; Stovall, J.; Swenson, D.A.; and Theus, R.: Fast neutron dosimetry and ion linear accelerators. Workshop on Physical Data for Neutron Dosimetry, Rijswijk, The Netherlands. Los Alamos, New Mexico: Los Alamos Scientific Laboratory Report No. UR-76-1007, 1976.
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- *Amols, H.I.; Liska, D.J.; and Halbig, J.: The use of a dynamic range-shifter for modifying the depth dose distributions of negative pions. Submitted to Medical Physics.
- Barnes, J.E. and Hutson, R.L.: Techniques for visualizing pion treatment ports at LAMPF. Los Alamos, New Mexico: Los Alamos Scientific Laboratory, Informal Report UC-48, December 1974.
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- Kligerman, M.M.: Meson radiobiology and therapy. Atomikernenergie 27: 165-169, 1976.
- Kligerman, M.M.: Pion radiation therapy. Proceedings, International Particle Radiation Therapy Workshop. Chicago: American College of Radiology, pp. 404-412, 1976.
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*Publications during Grant Year 4, Copy Attached.

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Kligerman, M.M.; Knapp, E.A.; and Petersen, D.F.: Biomedical program leading to therapeutic trials at Los Alamos. Cancer 36: 1675-1680, 1975.

Kligerman, M.M.; West, G.; Dicello, J.F.; Sternhagen, C.J.; Barnes, J.E.; Loeffler, K.; Dobrowolski, F.; Davis, H.T.; Bradbury, J.N.; Lane, T.F.; Petersen, D.F.; and Knapp, E.A.: Initial comparative response to peak pions and x-rays of normal skin and underlying tissue surrounding superficial metastatic nodules. American Journal of Roentgenology 126: 261-267, 1976.

*Kligerman, M.M.; Smith, A.; Yuhas, J.M.; Wilson, S.; Sternhagen, C.J.; Helland, J.A.; and Sala, J.M.: The relative biological effectiveness of pions in the acute response of human skin. International Journal of Radiation Oncology, Biology and Physics, in press.

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*Liska, D.J.: Pi meson range-shifter for clinical therapy. Review of Scientific Instruments 48: 52-57, 1977.

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*Smith, A.R.; Rosen, I.; Lane, R.G.; Kelsey, C.A.; Amols, H.I.; Dicello, J.; Berardo, P.A.; Helland, J.; Bradbury, J.; Knapp, E.A.; and Paciotti, M.A.: Dosimetry of pion therapy beams. Submitted to Medical Physics.

*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. J.J. Broerse, ed. Luxembourg: Commission of the European Communities, EUR 5629C, 1976.

Todd, P.; Shonk, C.R.; West, G.; Kligerman, M.M.; and Dicello, J.F.: Spatial distribution of effects of negative pions on cultured human cells. Radiology 116: 179-181, 1975.

*Publications during Grant Year 4, Copy Attached.

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2. PROFESSIONAL PERSONNEL CHANGES

a. University of New Mexico:

New Hires:

Albert Li, Ph.D., Research Associate
Andrew Martinez, Ph.D., Research Associate
Michael Yurconic, Lab Chief
Kenneth Hogstrom, Ph.D., Physicist

(Both Dr. Martinez and Mr. Yurconic have left the project.
Replacements are being sought.)

b. Los Alamos Scientific Laboratory:

J. N. Bradbury, Ph.D., promoted to Group Leader, MP-3, Medium
Energy Physics Division.

Leo Gomez, Ph.D., mammalian biologist, has transferred to another
unit within LASL. A replacement (to be based at UNM) is
being sought.

3. SUMMARY PROGRESS REPORT

a. Objectives

(1) Overall Objectives

The primary objective of this project is to provide a broad base of
information on the expected responses of both normal and tumor tissues following
exposure to negative pi mesons (pions), such that clinical trials of pion radio-
therapy for patients with extensive cancer (which may include regional metastases)
can be designed most effectively. Subobjectives are:

(a) Continue to develop the pion channel and associated
hardware and to understand the physical characteristics of the beam, to achieve
prescribed dose distributions in a treatment volume of arbitrary size and location,
with minimum damage to surrounding normal tissue.

(b) Continue to develop, test, and apply methods of pion dosimetry
essential to the radiobiology experiments, which will logically carry over into
the early pilot trials and subsequent clinical trials of pion radiotherapy.

(c) Continue to employ appropriate quantitative cellular
radiobiology techniques to establish the relative biological effectiveness (RBE),
oxygen enhancement ratio (OER), and effects of dose fractionation of pions.

(d) Continue to observe in appropriate experimental animals

early and late responses and radiopathology of normal and tumor tissues exposed to various segments of the pion beam to assess acute effects and delayed sequelae as a function of dose and exposure conditions.

(e) Perform such radiobiological and physics experiments as may be necessary after the start of clinical trials.

(2) Goals for Current Year

(a) Physics. To improve reliability and safety of the pion operating channel, to develop larger static and range-shifted beams for pion radiotherapy, to improve dosimetry/microdosimetry systems, to improve the pion treatment planning code, and to design and test a prototype patient immobilization, alignment, and transport system.

(b) Biology. To expand studies with single cells and multicellular tumor spheroids (MTS) exposed to x-rays or pions; to continue characterizing the biological responses of newly developed tunes; to develop a predictive model correlating beam composition with biological response; and to continue to study the response of slowly dividing critical tissues to pions and x-rays.

b. Current Studies

This report describes studies conducted by personnel of the University of New Mexico Cancer Research and Treatment Center (CRTC) and the Los Alamos Scientific Laboratory (LASL) at the Los Alamos Meson Physics Facility (LAMPF), during Grant Year 4 (1 June 1976-31 May 1977).

(1) Physics

The total physics effort is directed toward obtaining answers needed for initiation of clinical trials, with basic projects goal-oriented toward obtaining specific information needed for clinical applications of the pion beam. The pion biomedical channel at LAMPF was reactivated in April 1976, and was operating at 100 microamps of current by August 1976. The accelerator current was elevated to 150 microamps in February 1977, and is planned to be escalated to 300 microamps by October 1977 and to design intensity of 1000 microamps (1 milliamp) by the fall of 1979.

(a) Channel Operation and Control System Development. Major accomplishments during the past year relate to improved reliability and efficiency. Hardware improvements include a new pion production target, the addition of water cooling, modification of the target controller, installation of a gas distribution and monitoring system, and improvements in hardware for regulating slits and wedges. Considerable software development was also instituted to improve personnel safety and to check out equipment.

(b) Channel Tuning/Static Beam Development. Static beams were developed for radiobiology and radiotherapy. Those for clinical use included:

- 1) A 4 cm diameter beam matched in three dimensions to a 100 kVp x-ray beam for use in comparative studies with tumor nodules at and near the skin.
- 2) A 5 x 5 x 5 cm beam for use with lesions near or deep to the surface of the skin.
- 3) A beam with transverse dimensions of 8 x 10 cm, for use with the dynamic range shifter (to regulate the beam in depth), for deeper tumors.

The channel tuning system was improved to spread the pion beam more uniformly in the transverse dimensions, and to produce the sharpest possible fall-off at depth, at some sacrifice in dose rate. Until a scanning couch system can be installed and tested, beams will continue to be static in the transverse dimensions.

The channel momentum has been raised to its limit, providing a beam of nearly 30 cm range in water, to be used for deep-seated tumors (27 cm when used with the range-shifter). Beam tuning parameters are measured and recorded for input into the computerized treatment planning code.

(c) Range-Shifter/Dynamic Beam Development. A prototype range-shifter was fabricated and installed to regulate the pion stopping region in depth. Computer-controlled sweep functions and dosimetric measurements were also implemented. Range-shifted beams have been used in dosimetry and radiobiology experiments and in patient treatment.

Four basic beams have been developed for use with the range-shifter, with spacing of the beam momenta chosen so that the entire range of depths from 0 to 27 cm can be obtained by adding polyethylene absorbers to shift the peak to shallower depths. The narrow peaks of the basic beams are spread with the range-shifter to achieve larger treatment volumes, varying the width of the peak up to a maximum of 15 cm. A new range-shifter is now being built which will spread the peak up to a maximum of 28 cm.

(d) Dosimetry. Dose distributions for the available static and dynamic beams have been obtained by use of thimble-chamber dosimeters. Because conversion from ionization to absorbed dose in the pion beam is extremely difficult, primarily due to complex secondary charged particle fluence in the chamber wall, experiments are now being designed to obtain absorbed dose with a calorimeter. In the interim, approximations of absorbed dose have been made, using standard calculational techniques, with modifications as indicated by Monte Carlo calculations of secondary particle effects. The present estimates of pion absorbed dose have a minimum uncertainty of 10%, and may be in error by as much as 20%, depending upon the applicability of the Bragg-Gray theory for the heavy, short-range recoils produced in pion reactions.

A computer-controlled dosimetry collection system has been installed, which links a three-dimensional scanner with the channel control computer and output peripherals. Software has been written to control, calibrate, and test the hardware; acquire dosimetry data; and analyze data from previous scans.

(e) Microdosimetry. Measurements of dose per particle and energy per ion pair, previously obtained only from theoretical estimates, have now been obtained, along with measurements of beam fluence. A system has been developed to measure the pion flux by use of activation techniques, reproducible to about $\pm 3\%$. W values for pions have been calculated for an ionization chamber filled with air, nitrogen, argon, methane-based tissue-equivalent gas, and propane-based tissue equivalent gas. Two new techniques have been developed and tested to obtain microdosimetric spectra at high average beam intensities. Monte Carlo programs have been written for generating microdosimetric spectra corresponding to the experimental data, taking into account straggling, distribution of path lengths in the detector, and gas multiplication.

Silicon detector microdosimetry work included implementation of a technique for handling the high fluxes of pions required for therapy. Studies were conducted of radiotherapy and radiobiology beams to determine the relative magnitude of three linear energy transfer (LET) components: low LET, consisting of passing pions, muons, and electrons; medium LET, consisting of protons, deuterons, and tritons; and high LET, consisting of alpha particles, helium ions and recoils.

(f) In-Vivo Dosimetry. Preliminary measurements have been made using 12 silicon diode dosimeters on loan from the M.D. Anderson Hospital and Tumor Institute Physics Department. The results indicate that the diode may be less sensitive to a non-neutron beam, but the tests will be repeated to determine a future course of action. A group of silicon diodes and a reader have been purchased. Initial calibration experiments are underway.

(g) Effect of Inhomogeneities on Dose Distribution. Changes in dose arising from inhomogeneities being located upstream in the pion beam and hence shifting the distribution of stopping pions downstream have been investigated. A variety of bolus materials have been tested to correct for these changes, with paraffin now appearing most advantageous.

(h) Patient Immobilization, Alignment, and Transfer Systems. A prototype system for patient immobilization, alignment, and transfer has been implemented so that patients can be made ready for treatment outside of the treatment room. The system consists of two movable carts, a whole-body immobilization cast, ancillary casts, and bolus individualized to each patient; a collimator holder and collimators; and alignment lasers (matched in the staging area and treatment room). Use of the system has reduced loss of beam time due to patient set-up from about 20 minutes to about 4 minutes (3 minutes for transferring patients in and out of the room, and 1 minute for patient set-up under the beam). The system is now being modified for use with the permanent treatment couch and simulator couch, scheduled to be delivered soon.

(i) Computerized Treatment Planning. Improved physical models for calculating dose distributions and software improvements for upgraded clinical utility have been incorporated into the treatment planning program PIPLAN. PIPLAN is now used for a variety of detailed dosimetry, microdosimetry, and radiobiology studies and experimental investigations. Detailed comparisons between PIPLAN and the Oak Ridge Monte Carlo code, PION-1, are being made so that PIPLAN can be further improved.

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(j) Patient Treatment Software System. Patient treatment monitoring and record-keeping software has been installed and is being refined. Work has begun on linking the ultrasound unit with the treatment planning computer, so that inhomogeneity data can be directly input to the computer.

(k) Clinical Evaluation of Pion Visualization. Methods of visualizing the pion treatment field, for confirmation of treatment planning and delivery hardware configuration, are being investigated. Problems being explored are inherent spatial resolution, effects of inhomogeneities, and technique sensitivity. Pion-induced gamma and beta activity are being evaluated.

(2) Biology

(a) Cellular Biology. Effort has been directed toward an understanding of the mechanism of action of an idealized small volume tune and preliminary, but continuing, studies on the relative biological effectiveness (RBE) of large volume tunes being used for patient treatment. Studies have been conducted with a 2 x 2 x 2 cm biology tune, and 5 x 5 x 5 cm and 8 x 10 x 8 cm patient tunes, with approximate dose rates of 20, 10-12, and 3 rads per minute, respectively, at 100 microamps of current in the main accelerator channel.

The CHO and Line 1 lung carcinomas have been studied in monolayer. Studies of relative survival have indicated a shift to the left in the survival curve of 120-140 rads, but no change in the slope of the curve. This is significant in that CHO and Line 1 lung carcinomas are quite different in their sensitivity to radiation; yet, the shift was of approximately the same size in number of rads. This would suggest that tissues with a small shoulder (such as tumors) would recover relatively less efficiently than tissues with large shoulders (such as the normal tissues) during pion treatment, i.e., a constant number of rads equals a greater fraction of the shoulder region of the cell line with a small shoulder.

Fractionation studies with cells have also shown that pions allow far less recovery than x-rays, which is consistent with a reduction in the size of the shoulder. Studies with a larger volume tune indicate the same effect in the distal region of the peak, but less so in the proximal region. This is with a tune, which has a flat physical dose across depth, but not a flat distribution of stopping pions or high-LET particles.

A technique has recently been developed at the UNM/CRTC which allows the simplified production of multicellular tumor spheroids (MTS) which possess the following characteristics of in vivo tumors: intimate cell/cell contacts, well-developed hypoxic regions, and altered cell cycle distributions. This system has been used to study effects of pions on tumors, since the present beam intensity restricts the quantity of data that can be derived from in vivo tumor studies with animals.

A variety of techniques have been developed to study the growth, behavior, and responses of MTS to therapy; for pion exposures the most adequate are delay in growth and "cure." The growth delay studies with Line 1 MTS indicate a no-response region between 0 and 400 rads of x-rays, followed by a rapidly ascending relationship between dose and delay. Above a dose of 1000 rads, the relationship lessens, reflecting reduced efficiency in injury to the

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more radiation resistant hypoxic fraction. With pions, the shoulder region for Line 1 MTS is completely eradicated, and the RBE is dose dependent, declining with increasing dose. At about 1000 rads, the RBE again rises, reflecting more efficient injury to the hypoxic fraction, in comparison with x-rays.

In the "cure" experiments, the ability of MTS to grow out when placed on standard petri dishes is measured. Approximately 1.7 times as many x-ray rads as pion rads are required to yield a 50% "cure" for Line 1 spheroids.

(b) Mammalian Biology. X-ray data for rat colon acute effects (ulceration, colitis cystica profunda, and mucosal atypia) and late effects (muscular hypertrophy, vascular sclerosis, and fibrosis) are complete. Pion irradiations are completed but animals are only now being sacrificed.

In spinal cord studies, initial signs of hind limb reflex, loss and paralysis are just beginning to show and no estimate of RBE is yet available. Testicular injury studies show no apparent differences between pions and x-rays in terms of weight loss, but this appears to be a function of the assay system used, as spermatogenic colony forming unit assays showed an RBE of 1.5 for peak pions as compared with x-rays.

c. Significance

At present, a large number of patients with large solid tumors fail to respond to even the most rigorous therapeutic methods. Heavy charged particles offer a means of depositing a relatively high dose of radiation within the tumor volume while sparing surrounding normal tissues, which theoretically could result in higher cure rates. Because of their unique properties, pions appear to be the most advantageous of these particles for treatment of large volumes, although protons and heavy ions are also under investigation. The biomedical pion channel at LAMPF is the first such facility in the world capable of producing pions in sufficient quantities for medical testing, although other facilities are expected to be operational in two to five years for clinical use. The technology developed for use of the pion channel at LAMPF will logically be transferable to other pion installations as they come on-line. In addition, much of the effort directed at localizing the tumor volume and body inhomogeneities, computerized treatment planning, treatment optimization, and improved patient immobilization will improve technology available in conventional radiation therapy at treatment centers throughout the nation.

The preclinical biology studies are essential to avoid the possibility that the complexity of pion interactions with living tissues could result in untoward and totally unexpected injury to normal living tissues in patients. Secondly, the biological studies help to ensure that pions are tested under conditions that maximize tumor injury and minimize normal tissue injury, thus ensuring an accurate evaluation of any changes in therapeutic ratio with pion radiation. It has now been shown that the use of pion radiation results in diminished recovery during a fractionation exposure pattern as compared to x-rays, indicating that the potential for a therapeutic gain exists, beyond the expected reduction in protection of tumor cells by hypoxia or cycle kinetics. The progression of these studies should make it possible to guarantee patient safety while providing a definitive test of the practical clinical applications of pions.

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d. Research Goals For Year 5

Research goals for Year 5 are summarized as follows:

(1) Physics

(a) To continue to improve the channel operating and control system by increasing its reliability, safety, and efficiency, through installation of additional updated computer software and peripheral equipment, installation of optical shaft encoders to all moving hardware, and replacement of electronic controllers with microprocessors for critical hardware items.

(b) To increase beam-development capability by:

1) Development of a fan tune that is achromatic with respect to position and momentum, uniform over the depth dimension of the stopping region, narrow in the couch scanning direction, and that has the highest possible dose rate.

2) Design and application of new field flattening techniques and application of those techniques to new beams, in particular the fan beam.

3) Development of improved magnet current selection and optimization techniques for providing required therapy beams.

4) Improving understanding of the properties of the channel and beams in terms of changes in momentum, flux rate, contamination, momentum spread, and other optical properties.

(c) To complete and install a new range-shifter that will spread the peak region up to 18 cm in the dimension of beam penetration (the present model is useful for spread peaks of 12 cm or less), and to coordinate the range-shifter functions with the scanning treatment couch system, variable-jaw collimators, treatment planning codes, and other hardware and software.

(d) To continue to measure lineal energy and LET distributions of beams required for radiobiology and radiotherapy, for correlation with experimental results and theoretical calculations.

(e) To evaluate a number of in vivo dosimeters in an effort to determine those best suited for experimental verification of treatment planning, including intracavitary ionization chambers, silicon diode dosimeters, thermoluminescent dosimeters, and activation reaction dosimeters (to monitor high LET dose).

(f) To continue to refine the computerized treatment planning code by incorporating new experimental data for pion-nuclear cross-sections and pion-star secondary distributions in various tissue, upgrading biological models of effective dose, incorporating improved beam emittance data, adding new hardware correlation data (for range-shifter, scanning couch system, simulator, and other equipment), and coordinating output format with treatment planning evaluation requirements.

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(g) To improve treatment planning and inhomogeneity localization and compensation techniques, and to continue to improve the patient immobilization, alignment, and transfer systems (including installation and testing of the scanning treatment couch and pion simulator systems, already ordered).

(h) To continue to investigate methods of visualization of the pion stopping region for verification of treatment planning parameters.

(2) Biology

(a) To compare the pion-induced reduction in shoulder width with cell lines with small, intermediate, and large shoulders.

(b) To compare reductions in shoulder width noted in (a) with the extent of pion-induced inhibition of two-fraction recovery.

(c) To compare the effects of proximal, intermediate, and distal portions of the larger tunes (~1 liter) on two-fraction recovery in both monolayers and multicellular tumor spheroids (MTS).

(d) To develop and employ means of studying five or more treatment fractions in both monolayers and MTS systems.

(e) To compare the physical beam composition of various tunes with their biological effect in the hope of developing a predictive model.

(f) To expand our studies on the relationship between dose size and RBE in the monolayer and MTS systems.

(g) To continue our studies on the radiation (pion and x-ray) response of the colon, spinal cord and kidney, and to initiate studies on the heart, lung and brain.

(h) To continue to use somatic cell mutagenesis as the most precise biological endpoint for comparison with mutagenesis.

e. Principal Investigator Assurance

The undersigned agrees to accept responsibility for the scientific and technical conduct of the project and for the provision of required progress reports if a grant is awarded as a result of this application.

76 March 77
Date

M. M. Kligerman
Principal Investigator

C.

Kligerman, M.M.

5-P01-CA-14052-05

ATTACHMENT A

DETAILED PROGRESS REPORT

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DETAILED PROGRESS REPORT

1. OBJECTIVESa. Overall Objectives

The primary objective of this project is to provide a broad base of information on the expected responses of both normal and tumor tissues following exposure to negative pi mesons (pions), such that clinical trials of pion radiotherapy for patients with extensive cancer (which may include regional metastases) can be designed most effectively. Subobjectives are:

(1) Continue to develop the pion channel and associated hardware and to understand the physical characteristics of the beam, to achieve prescribed dose distributions in a treatment volume of arbitrary size and location, with minimum damage to surrounding normal tissue.

(2) Continue to develop, test, and apply methods of pion dosimetry essential to the radiobiology experiments, which will logically carry over into the early pilot trials and subsequent clinic trials of pion radiotherapy.

(3) Continue to employ appropriate quantitative cellular radiobiology techniques to establish the relative biological effectiveness (RBE), oxygen enhancement ratio (OER), and effects of dose fractionation of pions.

(4) Continue to observe in appropriate experimental animals early and late responses and radiopathology of normal and tumor tissues exposed to various segments of the pion beam to assess acute effects and delayed sequelae as a function of dose and exposure conditions.

(5) Perform such radiobiological and physics experiments as may be necessary after the start of clinical trials.

b. Goals for Current Year(1) Physics

(a) To improve reliability and safety of the channel operating system.

(b) To develop larger static and range-shifted beams for pion radiotherapy, which would provide maximum dose rate within the required uniformity and penumbra constraints.

(c) To install, test and place into use a prototype range-shifter for adjusting depth-dose distributions for specific shapes.

(d) To refine and improve dosimetry systems, to develop computerized dosimetry data collection systems, and to provide dosimetry required for pion biology and radiotherapy studies.

(e) To measure distributions of lineal energy and LET to obtain data required for interpreting experimental data, for extrapolation/interpolation to new beams (to reduce the total number of required measurements), and for incorporation into treatment planning models.

(f) To improve the pion treatment planning code, particularly through incorporation of an improved pion beam model.

(g) To design and test a prototype patient immobilization, alignment, and transport system, to minimize loss of valuable beam time and maximize the number of patients who can be treated at LAMPF.

(2) Biology. To expand our studies with single cells and multicellular tumor spheroids (MTS) to include multiple fractionations; to investigate reoxygenation in MTS exposed to x-rays or pions; to continue characterizing the biological responses of newly developed tumors; to develop a predictive model correlating beam composition with biological response; and to continue to study the response of slowly dividing critical tissues to pions and x-rays.

2. CURRENT STUDIES

This section describes studies conducted by personnel of the University of New Mexico Cancer Research and Treatment Center (CRTC) and the Los Alamos Scientific Laboratory (LASL) at the Los Alamos Meson Physics Facility (LAMPF), during Grant Year 4 (1 June 1976-31 May 1977). Because of the time between submission of the competing renewal application (August 1975) and the deadline for this application (April 1977), work performed during the last nine months of Year 3 of the grant period was not reported in CA-14052 applications. It was reported, however, as background in the renewal application submitted in June 1976 for 2-P01-CA-16127-04 (Clinical Studies of Pion Radiotherapy) and will not be repeated here.

a. Physics

The total physics effort is an integrated part of the preclinical program designed to obtain answers needed for the initiation of clinical trials. The basic projects being undertaken are goal-oriented toward obtaining specific information needed for clinical applications of the pion beam.

The pion biomedical channel at LAMPF was reactivated in April 1976, after a 15-month shutdown for major refitting of the main accelerator and installation of shielding and remote-handling systems for high-intensity operations. The main proton accelerator current was reactivated at 10 microamps for initial studies to compare operations prior to shutdown with those after shutdown. The current was then escalated at intervals until 100 microamps were achieved in August 1976. This level was maintained until February 1977, when the current was escalated to 150 microamps. Operation at 300 microamps is planned to start in October 1977, and 500 microamps are expected on or before the fall of 1978. Operation at the full design intensity of 1000 microamps (1 milliamp) is planned in 1979.

(1) Channel Operation and Control System Development

The biomedical channel was used for clinical, biology, and physics research. Major accomplishments in this area during the past year relate to improved reliability and efficiency. Some of the hardware was replaced or rebuilt, and new hardware was added to improve efficiency. Considerable software was rewritten to make it more efficient.

The pion production target was redesigned for greater reliability. Water cooling was added so the target could withstand the increased heat that results from the higher intensity proton beams. A target-cooling water controller was design-

and built. The target controller was modified for increased reliability, including a more reliable target interlock system, a more positive indication that the target is out, and added safety switches to turn off the target mechanism if the target is moved out of range. Software was written and the controller was modified to allow the user to make target scans to determine the vertical extent and shape of the main proton beam (which can affect the pion beam characteristics).

A gas distribution and monitoring system was installed. This system is being used for dosimetry, beam diagnostic equipment, and beam monitoring chambers.

The magnet cables were modified to avoid overheating at junctions. The mechanical shunt controller was replaced with a far more reliable electronic controller. This required design and fabrication of a DC-to-DC voltage converter with isolated grounds, since the shunt usually operates up to 100 volts above normal ground level.

Two sets of slits were installed at the intermediate pion-beam focal position. The entire control system for these slits was designed and built. This slit control system facilitates the moving of the slits locally, remotely in a manual mode at two different locations, and remotely with the computer. Considerable software had to be developed to move the slits without hitting the various momentum shaping wedges that might be inserted between the jaws, to calibrate the jaw motion, and to monitor the positions of the slit jaws.

To make it easier for users to change the wedge at the intermediate focus, a remotely controlled wedge changer was designed, built and installed. With this system any one of three wedges can be inserted in the proton beam, either manually or by computer. Software was written to accommodate this system. A hardware monitor was added to the prototype range-shifter system to detect malfunctions. Considerable computer work was done to develop range-shifter functions that would yield pion depth dose distributions required for specific patient treatments.

A large effort was devoted to rewriting the overall control software safety for greater safety and efficiency. This program cycles and sets the magnets, opens all four pairs of slit jaws to predetermined settings, inserts the appropriate wedge, and prepares the channel for the insertion of the production target.

The system has been improved in several other ways. A hardware debugging module was built and connected to the computer Unibus; this module aids in locating and correcting both hardware and software bugs in the system. The magnetic tape units were replaced by later models to improve reliability. A cache memory was added to the computer to increase its speed. The computer operating system was recently replaced by the latest version, which greatly improved the stability of the system.

(2) Channel Tuning/Static Beam Development

Static beams have been developed for radiobiology and radiotherapy. For tests comparing effects of 100 kVp x-rays with those of pions on tumor nodules in the skin and the surrounding normal tissues, a 4 cm diameter field with a maximum dose rate, consistent with requirements of physical dose uniformity, was developed. Scattering materials were inserted into the pion beam after the last quadrupole magnet in an effort to more uniformly distribute the Gaussian-like profiles of the beam. This method did not prove successful. The most effective method was one of retuning the channel so that the beam slightly diverged in both planes. Collimation then produced the sharpest possible edges and provided acceptable uniformity at some

sacrifice in dose rate. The beam shaping and collimation were done with the attenuator collimator cone shown in Figure 1. This brass nose cone was designed to completely attenuate pions outside the desired treatment volume. The peak of the pion depth dose distribution was placed at the desired depth by adjusting the thickness of the polyethylene absorber.

For the treatment of skin nodules, the wedge degrader at the momentum dispersion plane was used to compress a 7% Δ p/p rms momentum spread into a 1.5% Δ p/p rms width. The depth-dose distribution was shaped by detuning the entrance triplet so that the momentum spread was close to 2% Δ p/p rms. In this way, the pion depth-dose distribution was tailored to match the 100 kVp x-ray depth-dose distributio

Figure 2 shows the beam geometry for the treatment of skin nodules. The left side of the graph shows the central axis depth distribution of the ionization resulting from 165 MeV/c pions ($E = 76.5$ MeV) incident upon a 4 cm diameter attenuator collimator cone. The polyethylene absorber thickness was adjusted so that the end of the nose plug (skin surface) was at a point 0.5 cm past the maximum of the Bragg peak. This region of the peak is the region of highest linear energy transfer (LET) resulting from the heavy particle components of the pion capture reaction. A typical beam profile taken along the y-axis at $z=0$ is shown on the right side of Figure 2.

These scans were measured in water. The correct thickness of polyethylene needed to place the peak at the desired place was calculated, then verified, by ion chamber measurements.

Figure 3 shows typical central axis depth distributions for static beams designed to treat larger (up to 5 x 5 x 5 cm) tumors lying at shallow depths below the skin surface. The beam tune and collimator for these beams were the same as for the skin nodule beam but a different wedge degrader was used at the momentum focus of the channel, changing the momentum spread from approximately 1.7% Δ p/p rms to 4.5% Δ p/p rms. The larger momentum spread produced an extended peak by spreading the stopping pions over a greater distance. The channel tuning system records trajectories at the position of the wedge, as well as at the exit of the channel. Thus, the momentum spread from any shape wedge can be calculated by simulating the effect of the trajectories passing through the wedge. This permitted the design of the wedge producing 4.5% Δ p/p rms momentum spread. In addition, the shape of the distribution was controlled to significantly sharpen the fall-off on the downstream edge of the beam. The distribution at the left of Figure 3 is the widest spread resulting from this particular wedge degrader. To achieve narrower peaks for smaller lesions, such as shown on the right of Figure 3, momentum dispersion slits were adjusted to obtain peak dimensions consistent with the size of the tumor to be treated. The beam profiles of these beams were much the same as the profile shown in Figure 2.

For treatment of larger tumors, a beam of approximate transverse dimensions of 8 x 10 cm was developed. The channel was again tuned so that the beam diverged slightly in each plane, providing optimum conditions for collimation and field uniformity. To obtain improved dose rate, dose uniformity in depth, and flexibility in depth adjustments, the dynamic range-shifter rather than wedge shaping was used for z dimensions of up to 8 cm (see subsection (3)). The momentum spread was made as small as possible, to provide the sharpest fall-off on the downstream edge. The use of the range-shifter is the first step toward a dynamic beam system. However, until a scanning couch system can be installed and tested, beams will continue to be static in the transverse dimensions.

1091906 The channel momentum has been raised to its limit, providing a beam of

nearly 30 cm range in water, to be used for deep-seated tumors. The range-shifter has a minimum thickness of 3 cm reducing maximum penetration to approximately 27 cm.

The beam tuning instrumentation provides total information about each beam to be used in PIPLAN, the treatment planning code. The system measures particle type, particle momentum, and position and angle at the treatment location. The tuning system acquires complete distributions of these parameters, particle by particle, in the form of a history tape for each tune. The complexities of the pion beams are thus represented as input to PIPLAN without approximation.

(3) Range-Shifter/Dynamic Beam Development

Fabrication of the prototype range-shifter was completed (Figure 4), and work was initiated to use this device under beam conditions. Calculations were performed to determine the periodic piston motion (denoted as range-shifter sweep functions) required to produce various depth dose distributions needed for biological and clinical experiments. Different sweep functions were tailored to produce flat physical dose and shaped physical dose for a variety of different tunes. Isodose regions up to 10 cm in depth were obtained in these initial experiments.

The range-shifter is a hydraulically actuated, fluid-filled piston, which can be programmed to provide a computer-controlled, time-dependent thickness to perform the necessary beam shaping for therapy. The variable thickness fluid column is placed in the pion beam, and alters the range of the pions so as to produce any desired stopping distribution (and hence depth dose distribution). The piston and associated actuator units are neatly packaged in a cylindrical module (92 cm in diameter, and 33 cm thick) which can easily be positioned above a patient in a clinical situation. A second range-shifter is now being designed which will have less than half the volume of the present model, yet enable treatment of larger fields.

The hydraulic actuators require command signals of 0-10 volts DC to vary the thickness of the fluid column. This signal is provided either by an M6800 microprocessor (dedicated to the range-shifter) or by the PDP-11/45 computer via CAMAC interfacing. Although the 11/45 is more versatile than the M6800, it operates in a time sharing mode with other users. Techniques have been developed to run various sweep functions by means of either of these systems. Communication between the 11/45 and the M6800 is also possible by punched paper tape.

A control module with switch selectable sweep functions (i.e., depth dose curves), sweep intervals, and control type was installed for use in patient treatments. Hardware and software were also developed to enable accurate dosimetric measurements with the range shifter in the beam.

Four basic beams have been developed for use with the range-shifter in the treatment of deep seated tumors; the central axis depth profiles for these beams are shown in Figure 5. These curves have been normalized to 100% at the maximum peak dose. The spacing of the beam momenta was chosen such that the entire range of depths from 0 to 27 cm could be obtained by adding polyethylene absorbers in the beam to shift the peak of each beam to shallower depths. These curves were measured underneath the range-shifter, which has an equivalent water thickness of approximately 3.0 g/cm^2 at its minimum position. Thus, the range in water for these beams is 3.0 cm more than shown in Figure 5.

The narrow peaks of these beams are spread with the range-shifter to achieve larger treatment volumes. The range-shifter can be programmed to produce

peaks varying in dimension from the width of the static peaks shown in Figure 5 to widths up to 15 cm. Figure 6 shows a typical spread peak produced by the range-shifter. This peak is spread over 8 cm, and the physical dose is flat within 5% over the entire peak. The range-shifter produces these distributions by varying the column of fluid in the beam path so as to superimpose a large number of the static peaks over the desired width.

It was observed in biology and clinical tests that greater biological effect was obtained in the distal portion of the 5 x 5 x 5 cm static beam. In the clinical tests, these observations occurred early enough for the radiotherapists to attempt to achieve a more uniform biological effect by stepping the extended peak across the tumor volume and adjusting the tumor dose for each application. With the range-shifted beam, an effort was made to achieve greater uniformity from the outset by sloping the physical dose in depth, as shown in Figure 7. The slope was calculated on the basis of available biological data. However, the result was not sufficient, and the beam was again stepped across the tumor volume, with the dose adjusted for each application. A series of experiments to explore this problem is now underway, including development and testing of a new range-shifter function which more uniformly distributes pion stars across the peak region.

Treatment cones such as the one in Figure 1 are not practical for the large volume beam tunes. Currently, collimators made from a low melting point alloy (Cerrobend) are being tested. The advantage of this alloy is that it is dense ($\rho = 9.4 \text{ g/cm}^3$) and can be easily formed into collimators of highly irregular shapes. Calculations were made to determine the correct thickness of the alloy required to completely stop the pions from each beam tune. These calculations weighed the pion stopping power for the components in the alloy (50.0% bismuth, 26.7% lead, 13.3% tin and 10.0% cadmium). The calculations were then verified by experiment and a comparison of calculation versus experimental data is shown in Figure 8.

The collimation effect of the alloy collimators on the pion beam is exemplified in Figure 9 which shows a typical x-profile of the beam taken in the center of an 8 cm spread peak underneath a 9 x 7 cm elliptical collimator 3 cm thick. The collimators are most effective when placed at the surface of the phantom with the range-shifter directly above and in physical contact with the upper collimator surface.

The shape of the beam profiles varies considerably with depth in phantom. At the surface ($z=0$) directly under the collimator the plateau profile is very flat with almost perpendicular fall-off on the edges. In the peak region the profiles diminish in flatness as the depth increases as shown in Figure 10. At the 80% level the distal peak profile is 6.4 cm wide compared to a width of 7.8 cm at the same level for the profile taken in the proximal peak. The profile shapes also change depending on which beam tune is used, being flatter and sharper for the beams which have shallower penetration (less multiple scattering). In the near future scanning pion beams will be developed which will have much sharper edges and higher dose rates than the beams presented in this report.

A typical isoionization distribution for the 170 MeV/c pion 8 cm spread peak is shown in Figure 11. This beam is composed of 81.7% pions, 6.6% muons, and 11.7% electrons.

(4) Dosimetry

The pion dose distributions described in subsections (2) and (3) above have been given in terms of ionization produced in the thimble chamber, because the conversion from ionization to absorbed dose in the pion beam is a complicated problem. This is primarily due to the complex secondary charged particle fluence generated in

the chamber wall. Pion interactions in the wall material produce electrons, protons, deuterons, tritons, alpha particles and heavy recoils, which in turn produce ionization in the tissue-equivalent gas volume. To give a complete physical characterization of the energy deposition in the gas it is necessary to know accurately the fluence and energy spectra of all the secondary charged particles. These data are not available at this time. However, experiments are being designed which will provide this information.

Presently, it is assumed that the thimble ion chamber acts as a Bragg-Gray cavity in the pion beam and the dose in muscle is calculated using the relation

$$D = \frac{100 Q (W/e) S}{MK} \text{ rad,} \quad (1)$$

where D is the absorbed dose, Q is the ionization charge in coulombs, W is the energy in joules required to produce an ion pair in the gas volume, e is the electron charge, S is the average mass-stopping-power ratio for the secondary charged particles in the chamber wall relative to the chamber gas, M is the mass of gas in Kg, and K is a kerma correction required to convert the dose in the chamber wall to dose in muscle.

For the Bragg-Gray relation to be valid, the range of secondary particles must be large compared to the dimensions of the gas volume. This restriction can be relaxed if the wall material and gas are matched such that the atomic composition of the wall and gas are nearly the same and there are no density effects. Complete matching would require that the interaction cross-sections and the mass stopping power be identical for the wall and gas. Even when the atomic compositions of the gas and wall are identical, a correction for the density effect has to be made in practice.

The gas volume (-0.1cc) cannot be reduced for absorbed dose measurements in the pion beam because the rather low beam intensities (3-15 rads/min) would not give signal responses large enough for reliable measurement. As the beam intensities are increased it will be practical to use chambers having smaller gas volumes. Whether or not the wall and gas are sufficiently matched to apply the Bragg-Gray principle must be verified by experiment. The greatest problem lies with the heavy recoils, which produce significant biological effect, and whose ranges extend only about 20 microns in tissue with an average of about 8 microns. When Equation 1 is used to calculate the absorbed dose, the mass of gas is determined by exposing the chamber to cobalt-60 radiation that has been calibrated independently by a chamber whose correction factor is traceable to the National Bureau of Standards. The cobalt-60 values of the Bragg-Gray parameters are used in the mass determination. The W values are weighed according to the components of the secondary charged particle fluence and the constituents of the compound gas. The average value of S must be obtained by integrating over the charged particle energy spectra and weighing according to the gas components and the wall materials. The detailed information required for these calculations is not well known for the pion beams. Therefore, certain assumptions have been made for the pion absorbed dose calculations.

From Monte Carlo calculations for 175 MeV/c pions in tissue (1), internuclear cascade model calculations for 180 MeV/c pions in carbon (2), and silicon diode measurements for 168 MeV/c pions in lucite (3), estimates have been made of the fraction of the absorbed dose contributed from each class of secondary particles and their average energies. These are given in Table 1 for the peak region. It has been assumed that all singly charged heavy particles are protons and all heavier particles are alpha particles. The average energies of particles are measured by silicon detectors; these energies are sufficiently high to transport the particles in

the tissue-equivalent gas more than ten times the average distance traversed by particles in crossing the 0.1 cc ionization chamber, but a significant fraction of heavier particles is known to have much lower energies.

The W values for the charged particle components in Table 1 were measured values taken from the literature. The mass stopping powers were calculated using standard formulas. The kerma correction, K, which transforms the absorbed dose from the tissue-equivalent plastic chamber wall to absorbed dose in muscle was deduced from measured data and calculations. The calculated parameters are given Table 2. These values are currently being used to calculate pion absorbed dose in muscle.

At present it is not possible to present pion dosimetry in terms of absorbed dose distributions because of the great variance in the charged particle fluence in the plateau and in the peak. It is expected that the charged particle fluence will vary considerably across the spread peaks and also be dependent upon the width of the peak. Very detailed measurements must be made in all regions of the beam before complete absorbed dose distributions can be calculated.

The present statement of pion absorbed dose has a minimum uncertainty of 10% and, in fact, may be in error by as much as 20%, depending upon the applicability of the Bragg-Gray theory for the heavy, short-range, recoils produced in pion reactions.

A computer-controlled dosimetry data collection system has been installed which uses the PDP 11/45 computer connected to the necessary dosimetry hardware through a CAMAC interface system. A three-dimensional scanner which moves an ionization chamber through the beam and electrometers for the ionization chamber and monitor chambers are controlled and monitored by the computer. A Tektronix 4010 graphics terminal is used for interactive control and data display. Hardcopy output is obtained via a Versatek electrostatic plotter/printer.

The existing software can be divided by function into three groups of programs. The first group of programs can be used to control, calibrate, and test the hardware. The user can test the scanner limits, move the scanner to any position within the limits, calibrate the analog position signals, check the present scanner position, monitor the scanner position during scanning, or test the scanner interface. The second group of programs is used for dosimetry data acquisition. The user can select one-, two-, or three-dimensional scans with a variety of options, and can change the scan parameters during scanning. The third group of programs allows the user to analyze the data from previous scans. Data from different scans may be compared or combined. Any scans may be reproduced with any desired normalization. Two- and three-dimensional scans may be displayed in a variety of formats. All the software is activated through a button panel and is user oriented, requiring no computer experience of the user.

(5) Microdosimetry

(a) Conventional Microdosimetry, Pion Fluence, and Pion W-Values.

Dose per particle and energy per ion pair (W-values) for pions have been obtained previously only from theoretical estimates. Measurements of both quantities, along with the beam fluence, were performed at the biomedical channel at LAMPF during the current grant year.

A system has been developed to measure the pion flux by use of activation techniques. Disks of plastic scintillator are placed in the beam and

irradiated for several minutes. After the irradiation, an off-line measurement is made to determine the amount of β^+ activity from ^{11}C produced in the plastic. Cross-sections (4) for the reaction $^{12}\text{C}(\pi^-, \pi^0)^{11}\text{C}$ are then used to determine absolute fluences. An initial check on the relative precision of the method showed it to be reproducible to about $\pm 3\%$. This value could be improved if necessary.

W-values were determined in the following manner. A parallel plate ionization chamber, 2.5 cm in diameter, was sandwiched between two disks of plastic scintillator of the same diameter. The total charge produced in the gas volume of the chamber during irradiation was measured, and the total fluence through the gas was determined by the technique described in the previous paragraph. Data were obtained with the chamber filled with air, nitrogen, argon, methane-based tissue-equivalent gas, and propane-based tissue-equivalent gas. Preliminary W-values for these gases for 78 ± 2 MeV negative pions are 35.8 ± 0.7 , 36.2 ± 0.7 , 27.5 ± 0.6 , 35.1 ± 0.8 , and 28.1 ± 0.4 eV per ion pair, respectively. Only the relative uncertainties are given. The absolute uncertainties include uncertainties in incident energy of the pions, stopping powers, and activation cross-sections. These W-values also include contributions from delta-rays from the walls of the ion chamber. It is not yet known to what extent this effect could alter the values given. The fraction of the total charge in the ion chamber produced by delta rays from the walls has been calculated analytically. Preliminary results are shown in Figure 12.

Since the last report, two new techniques have been developed to obtain microdosimetric spectra at high average beam intensities, and data have been acquired using both methods. The high intensity of the biomedical beam (typically about 10^6 pions/sec/cm² average) necessitates using a programmed low intensity pulse (every tenth pulse) for counting experiments. Even with these low intensity pulses, pile-up is still a problem. For this reason, and to collect data at the maximum possible count rate, a pile-up rejection system was developed. This system has a typical resolution of less than 200 nsec, the present limitation being the response time of the detector itself. This system, along with continued development of low noise, fast-recovery preamplifiers and linear energy transfer (LET) chambers capable of having the bias voltage pulsed in coincidence with the 1-in-10 pulse, has allowed data acquisition with beams of high average intensity. To check the reliability of the new methods data have been taken in the plateau and Bragg region of various beams. The agreement with data reported in a previous progress report is generally satisfactory, although differences have been observed below lineal energies of 1 keV/ μm .

Monte Carlo programs have been written for generating microdosimetric spectra corresponding to the experimental data. The calculations take into account straggling, the distribution of path lengths in the detector, and gas multiplication. The effects of delta rays are now being incorporated. The program requires as input the energy spectrum for each particle type. A comparison is shown in Figure 13 of the calculated spectrum for 168 MeV/c negative pions and experimental data. It is believed that the response of the detector to monoenergetic particles can now be accurately calculated. Calculations are now being performed that include the scattered pions, secondary protons, and heavier particles, and results should be available soon.

(b) Silicon Detector Microdosimetry. The work of the past year was directed toward developing a technique for handling in a silicon detector the high fluxes of pions required for therapy. The LET analysis of a pulse requires several

microseconds in the system, and a second pulse must not enter during this period of analysis. In the electronic technique finally adopted, the 1 in 10 low intensity beam is used for the LET measurements of the incoming pions. For the star products the counting rate is low so the full intensity beam was used. The monitor can count with either beam. The LAMPF gate generator is used to gate all of the scalars, the analyzer, and the oscilloscopes with either beam.

Three different beams have been characterized with this technique, two patient beams and a radiobiology beam. The first beam studied was the 5 x 5 x 5 cm beam produced by a collimator-attenuator unit. For this beam, Figure 14 shows the analysis of three basic LET components: low LET, consisting of passing pions, muons, and electrons; medium LET, consisting of protons, deuterons and tritons; and high LET, consisting of alpha particles, helium ions and recoils. Figure 15 compares the shape of the total dose measured with an ionization chamber and with that measured with the silicon detector, as obtained by adding the doses of the LET components. The agreement of the total dose distribution of the silicon detector with the ionization chamber is apparent. This beam was used with a patient having melanoma lesions deep to the skin surface and it was observed by the radiotherapists that the distal portion of the tumor became softer and smaller much earlier than the proximal portion. This may be due to the relatively large component of high LET dose in the distal region.

Figures 16 and 17 are the same data for a beam 8 x 10 x 8 cm with the range-shifter. This beam was intended to be uniform in physical dose over a depth of 8 cm, and is being used for radiobiologic studies.

Figures 18 and 19 are the equivalent data for an 8 x 10 x 8 cm beam made by the range-shifter for patient treatment and correspond to Figure 7.

(6) In-Vivo Dosimetry

Preliminary measurements have been made using 12 silicon diode dosimeters on loan from the M. D. Anderson Hospital and Tumor Institute Physics Department. These diodes were exposed to a clinical pion beam at dose levels comparable to those used in treating patients. The following properties were exhibited:

(a) Diode response is correlated to dose via the same relation found to hold for fast neutron beams (5):

$$D = K \ln (V_f/V_i) \quad (2)$$

Where D is the dose in rads, K is the response constant, V_f is the diode forward voltage for 25 ma current after irradiation, and V_i is the diode forward voltage for 20 ma current prior to irradiation. The fits to the data are seen in Figure 20.

(b) The diode response K, varies with position in the pion beam as seen in Figure 20. Note that diode sensitivity increases in and on the back edge of the peak where neutron and high-LET dose is at maximum.

(c) The response constant K is approximately four times greater than that in a fast neutron beam, which indicates that the diode might be less sensitive to non-neutron dose.

These results have prompted a more intense effort, with immediate plans to repeat these measurements at several depths in both the narrow and range-shifter broadened beams. Because of a smearing effect, it can be predicted that the diode sensitivity should be reasonably constant across the broad peak.

(7) Effect of Inhomogeneities on Dose Distribution

Two problems are being studied concerning inhomogeneities in pion beams: the interface effect and the distal effect. The interface effect consists of the changes in dose near the interfaces of inhomogeneities, which are caused by the densities of the interfacing tissues and by changes in secondary particle emission. Dosimetry, microdosimetry, and radiobiology experiments are presently being designed to study these effects. The distal effect is defined as the changes in dose arising from inhomogeneities being located upstream in the pion beam and hence shifting the distribution of stopping pions downstream. Experimental results are reported below on this effect.

To correct for the distal effect of inhomogeneities, bolus material is used. Paraffin appears to be a good material, having a stopping power relative to water of .92, and it has been used in all inhomogeneity experiments. A dental alginate (stopping power relative to water of 1.10) was used with one series of patients. However, it has the disadvantages of being less tissue equivalent than paraffin, deteriorating with time and hence leaving no permanent record, and requiring considerable care to prevent dehydration. A practical molding system for paraffin has been developed, so that it can now be used as bolus material for patients.

Two types of bolus must be constructed for patient treatment. The first is contour bolus, which simply corrects for contours in the skin by producing a planar surface perpendicular to the incident beam. The second, compensating bolus, corrects for inhomogeneities in the patient and partly shapes the treatment volume. Figure 21 illustrates how these bolus components appear in a typical treatment situation.

Inhomogeneity experiments have been performed with a clinical beam. This beam has a momentum of 163 MeV/c ($\sigma = 1.8\%$) which produces a depth dose peak at approximately 17.5 cm. A parallel beam, it is approximately 11 cm wide at the 80% level in x and y, and approximately 18 cm wide at the 50% level in x and y. Such a beam is easily collimated using 3.5 cm thick Cerrobend collimators. Collimation and geometry used for these measurements closely resemble a clinical setup. Although pion peaks in patient beams are normally broadened by the dynamic range-shifter, the results here are from only the narrow static beam, so that the effects of inhomogeneities can be more easily observed.

Teflon and air inhomogeneities in a water phantom have been chosen for an approximation of bone and lung. Teflon has a stopping power relative to water of 1.81.

A recent calculation emphasizes the change in pion peak dose rate with the presence of inhomogeneities. This effect is seen in Figure 22 where the incident pion beam passes through an 11 x 9 cm elliptical collimator and an 8 x 4 x 4 cm Teflon block is placed along the beam axis 1 cm below the water surface. Note the forward shift of the pion peak, due to the Teflon causing the direct beam to equivalently pass through an additional 3.25 cm water $[(1.81 - 1.0) \times 4 = 3.24]$. By shifting back the peak under Teflon by 3.25 cm, it is easily seen that the peak dose under Teflon is a few percent less than the peak dose with no Teflon.

This decrease occurs because there are fewer secondary interactions in the peak, since pions which do not pass through the Teflon stop at a deeper depth. Likewise when these pions do stop, they contribute additional dose to the rear of the central peak as seen in Figure 22. These effects are significantly less than those of Hamm *et al.* (6), because the inhomogeneity in this example is a factor of two greater in transverse direction, thus decreasing the second particle effect.

The ability to compensate for the Teflon inhomogeneity using a parallel beam bolus correction is shown in Figures 23 and 24. The bolus is 3.5 cm paraffin (3.24/.92) with an 8 x 4 cm rectangular hole directly above the Teflon. In Figure 23, the depth dose peak is almost identical to that with no inhomogeneity. In Figure 24 transverse profiles across the peak show how the bolus restores the original beam profile. The slight discrepancy is a result of the paraffin bolus being cut to 3.7 cm thickness rather than 3.5 cm.

Similar results for air inhomogeneities are seen in Figure 25. Note that 3 cm from the edge of the inhomogeneity in cases A and C, the depth dose curves are influenced little by the stopping pion distribution. In contrast, under the edge of the inhomogeneity in Case B, there is maximum distortion in the peak. Again the bolus sufficiently corrects for the inhomogeneity across the peak. However, the bolus was 2 mm too thick, over-shifting the peak.

One practical aspect of the inhomogeneity experiment is the concept of using quantitative pion radiography to deduce bolus construction from inhomogeneity attenuation. In Figure 26 the dose image behind a Teflon inhomogeneity suggests this possibility. The dashed line is the required response. However, the effect of secondaries washes away such resolution, indicating that a positive pion rather than a negative pion beam would be required. A positive pion beam has a lower high LET dose, and thus the advantages of a lower equivalent dose to the patient and a decreased variation in film response. This method might be beneficial in the head and neck region, where treatments are often bilateral, since a symmetry plane is required perpendicular to the treatment beam.

The above results show that paraffin bolus can be used to correct for inhomogeneities, provided information about the inhomogeneities is available. A study of the ability of computerized axial tomography (CAT) scanner data to provide such information should begin by the summer of 1977. A first-order correlation between electron density and the pion stopping power of tissue-like material relative to water should prove helpful in data analysis.

A strong dependence of dose upon the stopping pion distribution accentuates the need for completion of the treatment planning code PIPLAN (subsection (9)), so that the dose can be accurately predicted for other stopping pions which do not stop in a plane perpendicular to the incident beam. Future experiments will be designed for comparisons to PIPLAN calculations, particularly for converging beams where the problems of inhomogeneities and compensating bolus become more complex. One long-term goal of the project is to treat with a fan beam (highly convergent in a plane perpendicular to the beam plane), to increase the dose rate and improve treatment planning.

(8) Patient Immobilization, Alignment, and Transfer Systems

Pion irradiation of patients with portals up to 8 x 10 x 8 cm began in November 1976, for treatment of large lesions extending several centimeters in depth.

These treatments constituted a significant departure from previous pion patient irradiations for several reasons. First, a collimator, rather than a treatment applicator, was used to define the beam. Second, a range-shifter was utilized to spread the pion stopping region in depth. Third, bolus was used to present a flat surface to the pion beam. Fourth, a shaping bolus was used to take into account variations in tumor depth in the same treatment field. Fifth, compensating bolus was used to overcome differences in stopping power of inhomogeneities in the treatment volume. Finally, it was now necessary to use a whole-body immobilization and repositioning device to ensure proper patient positioning for each treatment session. All of these factors combined to make patient set-up a time-consuming procedure. Because of the extended treatment time and the desire to optimize treatment room utilization, a technique of prior immobilization and positioning (PIP), planned from the project inception, was instituted.

A prototype patient immobilization, repositioning and transfer module has been developed, which has a base of expanded polystyrene foam such as used in building insulation. This is the same material used in making individualized secondary field blocks by the hotwire cutting technique. Two different sizes are used, 2' x 10' x 2" thick and 2' x 4' x 3" thick. The thinner sheet provides a foundation upon which the thicker sheet is mounted. Constructing the basic repositioning unit is quite simple. With the patient lying on the thick sheet in the appropriate treatment position, the patient's contour is traced directly to the foam with a wax pencil. This outline is cut out using a band saw or small hand saw and the sheet is placed on the thin foundation sheet. The patient then positions himself in the cutout and minor changes or modifications are made to the cutout. Once a good fit is obtained, the position of the cutout on the foundation is marked and the patient is removed from the unit.

The cutout is then placed on the foundation sheet again as marked, and lead bricks are used to hold it firmly in place. One to 2" diameter holes are drilled through both sheets of foam about every 16" to 20" around the patient's contour. Two-component liquid polyurethane which expands and hardens to low density foam when combined is then mixed and poured into the holes. It expands and fills the holes with a strong hard foam permanently binding together the patient cutout and the foundation sheet.

For conventional radiotherapy treatments, the repositioning unit may be made for anterior and posterior treatments when necessary, as in the case of extended field treatments for Hodgkin's disease. The basic unit also may be modified by cutting the foam to hold an electron cone in the proper orientation. Finally, a conventional plaster of paris head cast may be fitted to the basic whole-body repositioning system for treatments of the head and neck. The advantages of this system, which is composed almost entirely of foam, are: (a) it is lightweight, and (2) fluoroscopic and radiographic procedures performed with the patient in this immobilization device are of excellent quality.

Casts used with pion therapy patients have proved to be quite good with some modifications required. Because the dose rate for an 8 x 10 x 8 cm field was approximately 3 rads per minute with 100 microamps of beam current, a typical 100-150 rad treatment would require the patient to be in the immobilization device for approximately one hour (occasionally split by a brief rest period). Thin foam rubber padding was added to increase patient comfort and proved to be quite adequate.

More extensive use of the liquid polyurethane foam is being explored to make the cast more closely conform to the patient's contour, thereby providing more uniform support.

Alignment lasers were installed in the pion treatment area and in the staging area, so that patient alignment could be quickly and accurately reproduced. Two different arrangements of laser beams are used to produce visible crosshair patterns. Both arrangements utilize the same principle of refraction of light by a cylindrical lens to convert a laser spot into a line. The lens is a 3 mm diameter quartz rod supported by aluminum holders which are attached to the laser case to position the quartz rod in the laser beam and to hold a front-surface mirror in front of the rod. Light enters the quartz rod perpendicular to the longitudinal axis of the rod and refracts, producing a beam of 1 mm width and 17° divergence.

Two such assemblies are mounted in the treatment room to give orthogonal lines which intersect at the vertical axis of the pion beam. This yields two visible axes for precise patient alignment in the horizontal plane. A third laser, without the refracting lens, is used as a vertical height reference.

In the patient staging area, where there is no overhead obstruction from beam hardware, only one laser is required. The laser beam is passed through a beam splitter and then reflected onto two quartz rods which are fixed perpendicular to each other. The resulting cross pattern is used for horizontal alignment of the treatment couch, collimators, and bolus relative to the patient.

Treatment couches for the pion treatment and simulator rooms, which will require scanning motion under the pion beam, have been ordered with delivery and installation expected by the summer of 1977. To implement the PIP system prior to installation of those couches, two identical stretchers were purchased and modified, to accept patient immobilization modules and collimator holders and to allow localization radiography.

The tables as purchased have variable height and tilt, but an inadequate top which would not provide the features listed above. New tops were constructed of two flat plywood slabs, 1.25 cm thick, 82 cm wide, 200 cm long, and separated by a 2.5 cm gap. This opening allows insertion of x-ray film cassettes for diagnostic imaging. Flat aluminum rails were attached along each side of these tops. These rails, approximately 5.5 cm wide and spanning the length of the couch, provide a straight, flat surface to which the collimator holders are attached. The collimator holders rest on brackets with Teflon bearings which slide easily along the couch rails. Floor brakes have been obtained which will be installed on each of the couches. These will replace the manufacturer's wheel locks, which have proven inadequate. When the permanent treatment couches are delivered and installation is complete, these temporary tables will be reconverted to patient transport stretchers.

Two identical collimator holders have been mounted on the temporary treatment tables. The requirements for these devices included the following:

(a) Variable positioning was needed along three linear axes, i.e., vertical height above the treatment volume and x-y (horizontal) positioning relative to the alignment of the patient.

(b) A limited amount of rotational adjustment was needed for treatments in which the tumor location and surrounding anatomy require inclination of the treatment couch out of the horizontal plane. In these cases, the collimator must be

rotated relative to the couch, to maintain collimation perpendicular to the beam.

(c) Rotation about the vertical axis was required to align asymmetrical collimators.

(d) All positioning needed to be precisely reproducible.

(e) The collimator holder needed to be strong enough to ensure patient safety with the 10 to 25 kg collimators required.

(f) The holder needed to be compatible with the temporary treatment table.

The collimator holders were designed and fabricated incorporating the five degrees of freedom required to meet individual patient needs. Vertical translation is allowed in 1.25 cm increments over a range of 42 cm. Translations in the horizontal plane are continuously variable and have ranges of 40 cm and 150 cm. Rotation about the vertical axis is continuous over 360° , and rotation about the axes of the horizontal plane proceeds in 2° increments over ranges of $\pm 20^\circ$.

The devices were fabricated from aluminum plate and stainless steel rods with steel fasteners, resulting in strong, lightweight holders which have tested safe under a load of three times the average collimator weight. The net weight of one holder is 15.7 kg, which can easily be placed on the treatment couch by two people. Ball bushings and Teflon bearings ensure quick, easy adjustment for x-y positioning and facilitate patient entry to and exit from the treatment couch. Thumbscrews are used as locks for all translational motion.

As constructed and modified, these collimator holders have performed their required functions during patient treatment. They require a minimal amount of time and effort for adjustment, thus contributing to optimal patient setup.

With all these components assembled, it was possible to implement the PIP system. On the day prior to the first treatment, the patients were brought individually to the treatment room and set up in their immobilization casts under the treatment beam, using the laser alignment system. The patient was marked appropriately for beam direction and field size, the height of the table was recorded, and the height of the collimator support assembly above the table top was recorded.

With this information the patient could then be set up and positioned in the staging room external to the treatment room. After the first patient was set up and treatment begun, the procedure could be done quite carefully for the next patient, without losing valuable beam time. When the treatment was completed, the patient in the treatment room was wheeled out on his treatment table, while the second patient, already immobilized and prepared for treatment, was wheeled into the treatment room on a second table. The actual positioning of the patient under the treatment beam required only about one minute, and the total time spent in the exchange of patients averaged about 4 to 5 minutes.

(9) Computerized Treatment Planning

The computer program PIPLAN was the primary focus of treatment planning development during the past year. This involved both improving physical models for calculating dose distributions and upgrading clinical utility.

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Coding was completed to convert anatomy contour data into a three-dimensional density matrix to interface with the BUCKET dose-model program and to eventually accept CAT-scan data. To obtain high resolution within memory limitations, densities are converted into 4-bit density codes representing 16 different tissues and treatment devices. The codes are packed 15 per word, producing 0.25 cm resolution in a 10 x 10 x 20 cm volume with only 8000 words of memory. This feature is general to allow a different number of densities or a different computer word length.

PIPLAN was modified to predict dose distributions for static beams and the dose model BUCKET was installed. The comparison of dose distributions calculated from BUCKET with the simplest experiments in water phantoms is good. However, when collimators, range-shifter and inhomogeneities are added, the agreement between calculation and experiment deteriorates considerably. To trace the source of these difficulties, systematic comparisons with the Oak Ridge Monte-Carlo code, PION-1, have been made starting with the simplest configuration—a pencil beam in a water phantom. As a result of these comparative studies, improvements in both codes have been made, most notably in pion ionization and in-flight interactions. Theoretical calculations by Carl Werntz of Catholic University have provided inelastic and absorption cross-sections for pions not available experimentally. The multiple scattering algorithm has been improved to more accurately deal with air gaps. Modifications to the pion stopping distribution calculation have been made, giving a more accurate description of the high-LET dose. Fine tuning of the physical approximations employed in BUCKET, resulting from comparisons with PION-1 as well as experimental dosimetry, will continue until the fundamental accuracy of the code is assured.

Because both PIPLAN and BUCKET are large codes, it was necessary to "overlay" sections of PIPLAN as part of the BUCKET installation. This step also further modularizes PIPLAN consistent with the final clinical version. Many non-clinical features of BUCKET were also adopted. Thus, PIPLAN is now also used for a variety of detailed dosimetry, microdosimetry, and radiobiology studies and experimental investigations.

New collimator and bolus models have also been installed in PIPLAN. The main feature of these models is that they enable the code to design devices that can be easily fabricated using methods presently available in a clinical setting. A range-shifter model has been installed in PIPLAN, using as a predefined function the amount of range attenuation as a function of time. This function is generated independently for a particular beam tune by specifying the final depth-dose distribution desired. To accommodate patient set-up, additional geometry has been installed to definitively locate the patient and treatment volume in the beam channel and to independently move the peak dose distribution relative to the treatment volume. (This is analogous to specifying the source-skin distance in x-ray therapy and using variable energy x-rays during treatment).

A remote graphics terminal, a plotter, and an acoustical modem were obtained to implement the interactive capability of PIPLAN. While the PDP-11/45 computer at the treatment facility will be used for input and data manipulation, the LASL Central Computing Facility (CCF) will be used for calculations. However, the CCF has been continually changing both machine and operating-system configurations, as well as changing algorithms. This has caused a deliberate delay in implementation of the interactive mode until about June 1977, when the CCF will complete much of its conversion to an improved time-sharing system. Postponing this commitment has avoided the duplication of converting from more than one system to another and allowed other requirements to be developed instead.

For patient treatment configurations, PIPLAN has been used to calculate various dose and particle distributions in a water phantom. The results agree well with both macro- and microdosimetry measurements. Such calculations are of value in interpreting clinical results with patients. An earlier version of PIPLAN was used as part of the first intercomparison of treatment planning using various types of high LET radiation. Four typical deep-seated tumors were treatment-planned independently for each type of radiation.

(10) Patient Treatment Software System

The biomedical pion patient treatment software performs a monitoring function prior to and during patient treatment. Prior to the treatment, the operator enters patient information such as name, portal identification, treatment day and fraction number. Hardware safety interlocks are checked and continuously monitored during treatment. Presently, the software has the channel operator verify that the range-shifter is running the proper function for each treatment. This check is backed during treatment by a hardware "range-shifter dead" alarm. A treatment status display is generated by the software during treatment, showing dose rate and estimated time to completion of treatment. This display is distributed throughout the Biomedical Facility via closed circuit television for the information of physicians and staff. Dynamic channel parameters such as time-of-day, dose rate, dose delivered, and hardware status are sampled periodically and saved in such a manner as to allow accurate determination of dose delivered in the event of severe hardware/software failure. At the completion of the treatment, this information, along with patient specifics, is produced as a treatment summary for inclusion in the patient's record.

Improvements to be implemented in the near future include a patient treatment file that can be created in advance of actual treatment to include, along with patient data, the channel tune necessary for each treatment, the range-shifter function for same, and treatment data such as prescribed dose and minimum acceptable dose rate. Control functions will be included to allow the proper channel tune to be set up and verified. The range-shifter will come under computer control of the function followed, and two separate processors will monitor and verify that the function is properly executed. Cumulative records of pion irradiations will be kept for each patient, and facilities for transmitting the records to the UNM-CRTC are being evaluated.

An extension of these applications and development of new applications in preparation for Phase III trials include: (1) computer monitoring of Clinac-18 treatments at the CRTC, (2) sonic tablet input to the computer of patient treatment planning data, and (3) direct ultrasound scan data input to the computer for treatment planning and possible diagnostic analysis. Computer monitoring of Clinac-18 treatments may be extended to include patient record-keeping and eventually statistical analysis of the total patient population. An additional application, indirectly related to patient treatment, may be the automation of dosimetry hardware, specifically the SHM three-dimensional isodose scanner.

At this time, all the hardware required for the above applications has been ordered and, with the exception of the sonic tablet, received. Until recently, computer system problems prevented work on the hardware interfacing. Those problems have been resolved and work on these applications may now begin. Preliminary work on the ultrasound application has been done, and involved the identification of the signal lines to be read by the computer.

(11) Clinical Evaluation of Pion Visualiziation

Pion beams have an advantage over conventional treatment beams in that the patient is slightly radioactive following treatment, which allows the possibility of gamma radiographic imaging. An evaluation of pion visualization from a clinical viewpoint is planned, based upon the results of researchers at LANPF (7,8). The benefits from pion visualization would be the confirmation of treatment planning and localization.

The first problem to be investigated is inherent tomographic resolution based on the estimated activity in a patient for a typical pion irradiation. Computer simulations should delineate the resolution which could be expected for various detector arrangements. The second problem is to investigate the effects of inhomogeneities. Positive beta imaging has the advantage that inhomogeneity attenuation can be measured (9). Assuming that the study of these two problems indicates visualization is still practical, additional experiments must be performed to relate dose to beta activity for various tissues. The final and most perplexing problem is that of diffusion rates, which not only lower the count rate but may also smear the activity.

All but the diffusion problem can be studied by computer simulation and measurements with a simple solid or Rando phantom. However, the diffusion problem can be answered only by measurements in vivo. Although the resolution presented in previous beta imaging papers (9,10), coupled with the above problems, makes pion visualization appear difficult, the potential clinical benefit is so great as to warrant evaluation.

b. Biology

(1) Cellular Biology

The cellular biology effort during the past year has been directed toward development of an understanding of the mechanism of action of an idealized small volume tune and preliminary, but continuing, studies on the biological effectiveness of large volume tunes presently being used for patient treatment.

Three different tunes or depth dose distributions have been studied within the past year:

(a) The 2 x 2 x 2 biology tune which yields a dose rate of approximately 20 rads per minute at 100 microamps of proton current (Figure 27).

(b) The 5 x 5 x 5 tune which yields a dose rate of approximately 10-12 rads per minute (Figure 3).

(c) The 8 x 10 x 8 tune which yields a dose rate of approximately 3 rads per minute (Figure 6).

The composition of tunes (b) and (c) in terms of the various LET components is provided in subsection (a-5) of this progress report. The LET composition of the 2 x 2 x 2 biology tune is proportionally the same as for the 5 x 5 x 5 tune.

As the treatment volume is increased the relative proportion of the higher LET components declines as does the peak-to-plateau ratio. For these reasons

the biological effectiveness is expected to decline as the treatment volume increases, and therefore all baseline studies are initially conducted with the 2 x 2 x 2 tune. Certain of these studies have been or will be repeated with the larger tunes as experience dictates.

(a) Monolayer Studies. Two cell lines have been used for the assay of the response of single cells in culture to the pion beams. These have been CHO cells (sublines K₁ and C₁₆) and the Line 1 lung carcinoma. Due to the limited volume which can be irradiated at a single time and an unwillingness to introduce artifacts via trypsinization after exposure, an assay system was developed in which 10⁶ cells were placed in liquid media in a 15 cc test tube filled with varying amounts of agar and liquid media. The depths of the agar in the tube regulated the position of the cells within the depth dose profile, thereby allowing study of a range of positions within any profile. The tubes were immersed in water during the exposure so as to provide maximum scatter.

Figure 28 is a plot of the relative survival of CHO cells which were exposed to peak pions (a depth of 1.8 centimeters) from the 2 x 2 x 2 biology tune as compared to results with x-rays. No differences could be detected in the slope of the survival curves between pions and x-rays, but the pion curve was shifted by approximately 120 rads to the left, i.e., the width of the shoulder for the cell survival curve was reduced by 120 rads. Figure 29 is a plot of the relative cell survival for Line 1 carcinoma cells which were irradiated under the same conditions. This cell line, which is more resistant than the CHO cells both in terms of the width of the shoulder and the slope of the survival curve, showed a response similar to that of the CHO cells. Pions were no more effective than x-rays in terms of the slope of the survival curve, but the width of the shoulder on the survival curve was reduced by 140 rads (Figure 29).

This raises an interesting point regarding the potential applicability of negative pi mesons in radiotherapy. Table 3 summarizes the survival curve characteristics for the two cell lines. In this table the cell line with the small shoulder (CHO) and the cell line with the large shoulder (Line 1) both show a reduction in the size of the shoulder by approximately 120-140 rads. This would suggest that tissues with a small shoulder (such as tumors) would recover relatively less efficiently than tissues with large shoulders (such as the normal tissues) during pion treatment, i.e., a constant number of rads equals a greater fraction of the shoulder region of the cell line with a small shoulder. Verification of this potential advantage of pions is presently being tested in vivo and is discussed further below.

At present the cells can be kept in the exposure tubes for up to 16 hours with only minimal clumping, thereby allowing the performance of fractionation studies. Table 4 summarizes the results of such an investigation and demonstrates quite clearly that two fractions of 150 rads of pions with a 2-hour recovery period between allows far less recovery than is observed with x-rays which are similarly fractionated. This relative lack of recovery in the pion-treated groups is consistent with a reduction of the size of the shoulder (Figures 28-30), i.e., the shoulder is reflective of the accumulation of sublethal injury and, therefore, indicative of the amount of injury which might recover between exposures.

Single cell survival curves have been determined for CHO cells at depths of 0, 2, 4, 7 and 8 cm along the 8 cm z axis of the 8 x 10 x 8 tuna (0 = lead

edge of the peak). The resultant single cell survival data are shown in Figure 30, in which, again, no significant differences could be detected in the slopes of the survival curves at any depth, nor could any differences be detected in shoulder width among positions 0, 2 and 4 or between positions 7 and 8. The pattern is consistent, however, with that given above, in that the major effect of the pion exposure has been to reduce the width of the shoulder region. Again, this would predict that recovery between exposures would be less pronounced in the pion treated groups. Table 5 is a comparison of pions and x-rays in terms of amount of recovery between two 150-rad fractions separated by 16 hours. The proximal portions of the peak (positions 0, 2 and 4) show moderate recovery between the two 150-rad exposures (relative to x-rays), while the distal positions (7 and 8 cm) show barely detectable recovery between the two exposures. In summary, all three tumors tested have been characterized by a reduction in the shoulder width. This is consistent with the fractionation studies which have indicated less recovery between exposures, at either 2- or 16-hour recovery intervals.

(b) Multicellular Tumor Spheroids (MTS). Due to limitations on the volume that can be irradiated with the smaller tumors and the need to study a number of positions in depth with the larger tumors, it has not been possible at the present beam intensity to study in vivo tumors. However, a technique has recently been developed at the UNM/CRTC which allows the simplified production of multicellular tumor spheroids (MTS) which possess the following characteristics of in vivo tumors: intimate cell/cell contacts, well-developed hypoxic regions, and altered cell cycle distributions. This system has been used in all biological program attempts to study the effects of pions on tumors.

The method for producing these MTS involves underlaying petri dishes with a mixture of 0.5% agar in complete medium. A single cell suspension of the tumor cells is then laid over the agar and within 3-14 days (depending on the specific tumor type) multicellular tumor spheroids, such as those shown in Figure 31, develop. These MTS grow unattached over the surface of the agar and can be studied over a size range of 100 μm through 2-3 mm. Included in Figure 31 are sections through these MTS which range in size from 280 μm through 840 μm . As the MTS increase in size, a nondividing hypoxic fraction develops beneath the dividing capsule, and at the largest sizes a necrotic central region is observed. These MTS, therefore, parallel the in vivo problem in an everted sense, since in vivo oxygen diffuses radially from a central source whereas in the spheroid it diffuses centripetally from an exterior source. A wide variety of MTS have been produced from tumors representing three species and four different etiologies (spontaneous, radiation-induced, chemically induced, and virus-induced), and these will eventually provide a battery of tumors to be tested with the pion beam. Among the MTS developed, evidence has been found of variability both in the depth of the dividing shell and the cycle kinetics of those cells which are in cycle.

A variety of techniques have been developed to study the growth, behavior, and responses of these MTS to therapy. For the purposes of studying pion exposures, the most adequate are delay in growth and "cure." Figure 32 is a plot of the growth of Line 1 carcinoma MTS which has been exposed at the size of 280 μm to graded doses of x-rays. These growth curves are similar to the inhibition of growth observed with in vivo mouse tumors, such as those used in the Tomlinson assay (10). Laboratory studies at the UNM/CRTC have established that delay in growth to a given size can provide an adequate dose response curve for pions and x-rays and that the size selected for the cut-off point does not affect the overall shape of the curve. Figure 33 is a plot of the radiation-induced delays in growth to a size of

720 μ m for Line 1 MTS which were exposed to peak pions (2 x 2 x 2 biology tune) or x-rays at a diameter of 280 μ m. The x-ray groups are characterized by a no-response region between 0 and 400 rads of x-rays, followed by a rapidly ascending relationship between dose and delay. Extension of these studies to larger doses (Figure 34, taken from a study on drug alterations of radiation resistance) shows a lesser relationship at doses above 1000 rads which is a reflection of injury to the more radiation resistant hypoxic fraction. Of greater interest to the present study is the complete eradication of the shoulder region in the Line 1 MTS exposed to peak pions from the 2 x 2 x 2 biology tune. In this study, the relative biological effectiveness (RBE) is dose dependent and declines with increasing dose.

A second assay system is presently being used with these MTS which involves determination of whether the MTS are able to grow out when placed on standard petri dishes. Table 6 summarizes the radiation doses (pions and x-rays) required to yield a 50% cure (no outgrowth) for Line 1 carcinoma MTS. In this comparison approximately 1.7 times as many x-ray rads as pion rads are required to "cure" a spheroid.

To summarize, from the Line 1 MTS studies which have been performed with the 2 x 2 x 2 biology tune, the RBE can be calculated as a function of the pion dose used. Figure 35 is a plot of these data and shows that the RBE declines rapidly as the dose is raised between 100 and 400 rads and then rises again in the area of 1000 rads of pions. The initiation of decline is interpreted as the result of a declining importance of shoulder reduction as the total dose is increased, and the rise of the RBE at the higher dose levels is interpreted as a reflection of the increasing importance of the hypoxic cell fraction.

Figure 36 is a plot of delay in regrowth versus dose for Line 1 MTS exposed to x-rays, peak pions from the 2 x 2 x 2 tune, pions from the proximal region of the 8 x 10 x 8 tune (depths of 0, 2 and 4 cm) and pions from the distal region of the 8 x 10 x 8 tune (depths of 6, 7 and 8 cm). In this comparison, it is clear that the two regions of the 8 x 10 x 8 tune fall intermediate in effect between x-rays and 2 x 2 x 2 peak pions, and that the distal portion of the 8 x 10 x 8 peak is more effective than the proximal portion.

Fractionation studies, under the same conditions are presently in progress.

(2) Mammalian Biology

(a) Radiation Responses of the Colon. During the past year Sprague-Dawley rats have been exposed to doses of 2000-10,000 rads of x-rays or negative pions (in the peak region of the 2 x 2 x 2 biology tune) and killed four months later for the analysis of radiation-induced ulceration, colitis cystica profunda, mucosal atypia, fibrosis, vascular sclerosis and muscle hypertrophy. The x-ray experiments are complete and have been analyzed, and at the time of writing the pion exposed animals are being killed.

Within each treatment group (four to six rats) the six endpoints were assigned a numerical grading which was then averaged within the group. Tables 7-9 give the average responses for the rats exposed to graded doses of x-rays in 1, 2, 5 or 10 fractions for the three early epithelial lesions: ulceration, colitis cystica profunda, and mucosal atypia. As was indicated in earlier reports these

three epithelial lesions are already declining by the time of sacrifice, four months, and, therefore, the dose response curves were at best marginally informative. Tables 10-12 present the raw data for the three support structure endpoints: muscular hypertrophy, vascular sclerosis and fibrosis. The data for these late-occurring and progressive lesions were more adequate and were subjected to an analysis of the effects of total dose size and fractionation.

Through use of multiple regression techniques, both dose size and number of fractions have been taken into account, according to the formula

$$D_G = D_X \times F^Y \quad (3)$$

where D_G = the dose required to produce a given grade of response, D_X equals the nominal standard dose, F = the number of fractions and Y = the recovery constant. As shown in Table 10 the recovery constant for hypertrophy induced by x-ray injury is approximately .3 for the milder grades but declines to .24 at the higher grades. Although these differences are not large they suggest that recovery from x-ray injury for this endpoint declines with increasing dose size. Table 11 shows a similar pattern for the fibrosis data in that the recovery constant Y declines from .41 at the mildest grade of injury through .32 at the most severe injury grade. Table 12 for the sclerosis data again shows the same pattern with the recovery constant declining from .41 at the mildest grade through .35 at the most severe grade.

Considering these late-occurring injury data in total (Tables 10-12), recovery appears not as a constant fraction of the dose size, but rather as declining with increasing dose size. The analysis of pion radiation effects for these same endpoints should be available soon.

(b) Spinal Cord. A preliminary study of the spinal cord responses to pion radiation was initiated in August 1976. At the time the available dose rate was 3 rads per minute (the 2 x 2 x 2 biology tune had not yet been developed), and, therefore, a single dose study was conducted comparing x-rays and pions. Pion doses of 933 rads through 1733 rads were delivered to the lumbar spinal cord and compared with doses of 1400-3000 rads of x-rays. At the time of writing initial signs of hind limb reflex, loss and paralysis are just beginning to show and no estimate of the RBE is available.

(c) Testicular Colony Forming Units. As reported earlier in progress reports, there appear to be no differences between pions and x-rays in terms of weight loss. This apparently is a function of the assay system in which a large stromal component affects the shape of the curve. When similar studies were performed using spermatogenic colony forming units (11), an RBE of 1.5 was apparent for peak pions from the 2 x 2 x 2 biology tune.

(3) Summary. The biology studies conducted during the past year have indicated that the major effect of pions in the peak region is to reduce the width of the shoulder, thereby resulting in diminished recovery during a fractionated exposure pattern. These studies are currently being repeated and expanded.

3. SIGNIFICANCE

At present, a large number of patients with large solid tumors fail to respond to even the most rigorous therapeutic methods. Heavy charged particles offer a means

of depositing a relatively high dose of radiation within the tumor volume while sparing surrounding normal tissues, which theoretically could result in higher cure rates. Because of their unique properties, pions appear to be the most advantageous of these particles for treatment of large volumes, although protons and heavy ions are also under investigation. The biomedical pion channel at LAMPF is the first such facility in the world capable of producing pions in sufficient quantities for medical testing, although other facilities are expected to be operational in two to five years for clinical use. The technology developed for use of the pion channel at LAMPF will logically be transferable to other pion installations as they come on-line. In addition, much of the effort directed at localizing the tumor volume and body inhomogeneities, computerized treatment planning, treatment optimization, and improved patient immobilization will improve technology available in conventional radiation therapy at treatment centers throughout the nation.

The preclinical biology studies are essential to avoid the possibility that the complexity of pion interactions with living tissues could result in untoward and totally unexpected injury to normal living tissues in patients. Secondly, the biological studies help to ensure that pions are tested under conditions that maximize tumor injury and minimize normal tissue injury, thus ensuring an accurate evaluation of any changes in therapeutic ratio with pion radiation. It has now been shown that the use of pion radiation results in diminished recovery during a fractionation exposure pattern as compared to x-rays, indicating that the potential for a therapeutic gain exists, beyond the expected reduction in protection of tumor cells by hypoxia or cycle kinetics. The progression of these studies should make it possible to guarantee patient safety while providing a definitive test of the practical clinical applications of pions.

4. RESEARCH GOALS FOR YEAR 5

Research goals for Year 5 are summarized as follows:

a. Physics

(1) To continue to improve the channel operating and control system by increasing its reliability, safety, and efficiency, through installation of additional updated computer and peripheral equipment, installation of optical shaft encoders to all moving hardware, and replacement of electronic controllers with microprocessors for critical hardware items.

(2) To improve beam development capability by:

(a) Development of a fan tune that is achromatic with respect to position and momentum, uniform over the depth dimension of the stopping region, narrow in the couch scanning direction, and has the highest available dose rate.

(b) Design and application of new field flattening techniques and application of those techniques to new beams, in particular the fan beam.

(c) Development of improved magnet current selection and optimization techniques, for providing required therapy beams.

(d) Improving understanding of the properties of the channel and beams in terms of changes in momentum, flux rate, contamination, momentum spread, and other optical properties.

(3) To complete and install a new range-shifter that will spread the peak region up to 18 cm in the dimension of beam penetration (the present model is useful for spread peaks of 12 cm or less), and to coordinate the range-shifter functions with the scanning treatment couch system, variable-jaw collimators, treatment planning codes, and other hardware and software.

(4) To continue to measure lineal energy and LET distributions of beams required for radiobiology and radiotherapy, for correlation with experimental results and theoretical calculations.

(5) To evaluate a number of in vivo dosimeters in an effort to determine those best suited for experimental verification of treatment planning, including intracavitary ionization chambers, silicon diode dosimeters, thermoluminescent dosimeters, and activation reaction dosimeters (to monitor high LET dose).

(6) To continue to refine the computerized treatment planning code by incorporating new experimental data for pion-nuclear cross-sections and pion-star secondary distributions in various tissue, upgrading biological models of effective dose, incorporating improved beam emittance data, adding new hardware correlation data (for range-shifter, scanning couch system, simulator, and other equipment), and coordinating output format with treatment planning evaluation requirements.

(7) To improve treatment planning and inhomogeneity localization and compensation techniques, and to continue to improve the patient immobilization, alignment, and transfer systems (including installation and testing of the scanning treatment couch and pion simulator systems, already ordered).

(8) To continue to investigate methods of visualization of the pion stopping region for verification of treatment planning parameters.

b. Biology

(1) To compare the pion-induced reduction in shoulder width with cell lines with small, intermediate, and large shoulders.

(2) To compare reductions in shoulder width noted in (1) with the extent of pion-induced inhibition of two-fraction recovery.

(3) To compare the effects of proximal, intermediate and distal portions of the larger tunes (~1 liter) on two-fraction recovery in both monolayers and multicellular tumor spheroids (MTS).

(4) To develop and employ means of studying five or more treatment fractions in both monolayer and MTS systems.

(5) To compare the physical beam composition of various tunes with their biological effect in the hope of developing a predictive model.

(6) To expand studies on the relationship between dose size and RBE in the monolayer and MTS systems.

(7) To continue studies on the radiation (pion and x-ray) response of the colon, spinal cord and kidney, and to initiate studies on the heart, lung and brain.

(8) To continue to use somatic cell mutagenesis as the most precise biological endpoint for comparison with mutagenesis.

5. ADMINISTRATIVE/OPERATIONAL CHANGES

Dr. James N. Bradbury has been appointed Group Leader, MP-3, Medium Energy Physics Division, LASL, and is leading the effort of that division in the pion biomedical studies. Dr. E. A. Knapp, former group leader, is now concentrating on accelerator technology development (particularly design of a small pion generator for medical use), and is available to this project for consultation on technical matters.

Dr. Kenneth Hogstrom has been appointed a biomedical physicist at the UNM/CRTC, but is based full-time in Los Alamos. He has been supported on CA-16127-03, but his support is being shifted to this grant for Year 5. He was formerly with the TAMVEC project of the M.D. Anderson Hospital and Tumor Institute (see his c.v. under Attachment C). Dr. Alfred R. Smith, biomedical physicist at the UNM/CRTC, is being based at Los Alamos, effective April 1977. Dr. Albert Li has joined the project as a cellular biologist (see also Attachment C for c.v.), and Dr. Leo Gomez, mammalian biologist, has left the project. A replacement is being sought for him.

As noted by the principal investigator last year, the biology funding level is insufficient for the job to be accomplished if rapid clinical progress is to be realized. It was necessary during Year 4 to reprogram resources to biology, via institutional and NCI prior approval mechanisms. Accordingly, it is proposed for the coming year that all biology resources be consolidated at the UNM/CRTC, with support provided by LASL Health Division only in short-term animal care and housing. It is also proposed that certain UNM technical staff be based in Los Alamos, as noted in the budget for Year 5.

CC

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TABLE 1

ASSUMED SECONDARY CHARGED PARTICLES
FROM TISSUE-EQUIVALENT PLASTIC

Peak	<u>Particle</u>	<u>Dose</u>	<u>E(Avc)</u>
	Electrons	35	10.0 MeV
	Protons	38	3.0 MeV
	Alpha Particles	27	3.5 MeV

TABLE 2

PION DOSIMETRY PARAMETERS FOR
 TISSUE-EQUIVALENT PLASTIC AND TISSUE-EQUIVALENT GAS

	<u>Peak</u>
W/e	30.1 ± 3%
$\frac{W}{Sg}$	1.006 ± 10%
K	1.09 ± 4%

TABLE 3

PION AND X-RAY

SURVIVAL CURVE PARAMETERS

FOR CHO AND LINE 1 CELLS

		<u>X</u>	<u>P</u>	<u>Δ</u>
D ₀ (rads)	CHO	136 ± 10	138 ± 9	+ 2
	Line 1	204 ± 13	205 ± 13	+ 1
D _q (rads)	CHO	182 ± 14	62 ± 7	- 120
	Line 1	242 ± 21	100 ± 11	- 142

TABLE 4

2-HOUR FRACTIONATION EXPERIMENT (5 x 5 x 5 CM. BEAM)

CHO

Depth (cm)	Relative Plating Efficiency			Survival Ratio*
	300 rads	2 x 150 rads		
1	28%	29%		1.00
3	34%	39%		1.14
4	34%	40%		1.17
5	23%	27%		1.17
X-ray	34%	50%		1.47

*
Ratio of 2 x 150/300

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TABLE 5

16-HOUR FRACTIONATION EXPERIMENT (8 x 10 x 8 CM BEAM)

ClHO

Depth (cm)	Relative Plating Efficiency		Survival Ratio*
	300 rads	2 x 150 rads	
0	25%	>760%	30.40
2	36%	188%	5.22
4	15%	173%	11.50
7	26%	23%	.90
8	19%	30%	1.60
X-ray	53%	191%	3.60

*
Ratio of 2 x 150/300

TABLE 6

EFFECTS OF PIONS (2 x 2 x 2 BIOLOGY TUNE)
AND X-RAYS ON MTS GROWTH *

<u>Type of Radiation</u>	<u>Dose (rads)</u>	<u>Percent Cured**</u>	<u>TCD₅₀</u>
Peak Pions	0	0	
	400	0	
	800	7	
	1200	80	1035 ± 68
	1600	100	
	2000	100	
X-rays	0	0	
	400	0	
	800	0	
	1200	11	
	1600	33	1701 ± 97
	2000	100	

* 280 μMTS; growth measured within two weeks after plating on standard tissue culture plates.

** Number of MTS per dose point ranged from 11 to 19.

TABLE 7

ULCERATION DATA, RAT COLON
X-IRRADIATION EXPERIMENT

Dose (rads)	<u>Number of Fractions</u>				
	<u>1</u>	<u>2</u>	<u>5</u>	<u>10</u>	
2000	0	0			
3000	0.5 ± 0.34	0			
3500			0		
4000	1.16 ± 0.74	0		0	
5000	1.66 ± 0.91	3.33 ± 1.49	0		
6000				0	
6500			1.5 ± 1.5		
8000			1.16 ± 1.16		
10,000					1.5 ± 0.96
		Control = 0			

TABLE 8

COLITIS CYSTICA PROFUNDA DATA, RAT COLON

X-IRRADIATION EXPERIMENT

Number of Fractions

Dose (rads)	<u>Number of Fractions</u>				
	<u>1</u>	<u>2</u>	<u>5</u>	<u>10</u>	
2000	0	0			
3000	3.0 ± 0.89	0.67 ± 0.67			
3500			0		
4000	1.16 ± 0.65	1.25 ± 1.25		0	
5000	1.83 ± 0.91	5.0 ± 1.14	0		
6000					0.25 ± 0.25
6500			1.67 ± 1.08		
8000			4.0 ± 0.93		2.5 ± 1.44
10,000					2.17 ± 1.11

Controls = 0

TABLE 9

ATYPIA DATA, RAT COLON
X-IRRADIATION EXPERIMENT

Dose (rads)	<u>Number of Fractions</u>				
	<u>1</u>	<u>2</u>	<u>5</u>	<u>10</u>	
2000	2.5 ± 0.22	1.25 ± 0.25			
3000		2.60 ± 0.50			
3500	4.83 ± 0.70		2.33 ± 0.33		
4000	4.83 ± 0.30	4.50 ± 0.28			1.80 ± 0.20
5000	4.83 ± 0.16	4.50 ± 0.22	3.25 ± 0.25		
6000					3.0 ± 0.40
6500			5.0 ± 0.44		
8000			5.16 ± 0.47		4.25 ± 0.25
10,000					4.5 ± 0.22

Controls = 0.62 ± 0.18

TABLE 10

HYPERTROPHY DATA, RAT COLON
X-IRRADIATION EXPERIMENT

	<u>Grade</u>		
	<u>1</u>	<u>2</u>	<u>3</u>
1F	2797	4333	5869
2F	4008	5407	6806
5F	5311	7110	8908
10F	5537	7701	9866

$$D_G = D_X F^Y$$

<u>Grade</u>	<u>D_X</u>	<u>Y</u>	<u>R</u>
1	3023	.298	.956
2	4455	.256	.986
3	5874	.235	.994

TABLE 11

FIBROSIS DATA, RAT COLON
X-IRRADIATION EXPERIMENT

Number of Fractions	Doses Required to Induce Fibrosis Grade					
	<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>6</u>
1	1575	2146	2718	3289	3861	4432
2	2687	3245	3811	4372	4934	5496
5	3122	3979	4835	5692	6549	7406
10	1100	2707	4315	5923	7531	9138

$$D_G = D_X F^Y$$

Grade	$\frac{D_X}{Y}$	$\frac{R}{Y}$
1	1724	.924
2	2269	.963
3	2812	.984
4	3350	.995
5	3887	.999
6	4422	.999

(~10 Fraction)

TABLE 12

SCLEROSIS DATA, RAT COLON

X-IRRADIATION EXPERIMENT

Doses Required to Induce Sclerosis Grade

<u>Number of Fractions</u>	<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>
1	1320	1960	2600	3230	3870
2	2280	2790	3310	3820	4330
5	3370	4160	4960	5760	6560
10	3350	4580	5800	7030	8260

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$$D_G = D_X F^Y$$

<u>Grade</u>	<u>D_X</u>	<u>Y</u>	<u>R</u>
1	1510	.41	.93
2	2068	.38	.98
3	2617	.36	.99
4	3149	.35	.99
5	3685	.35	.99

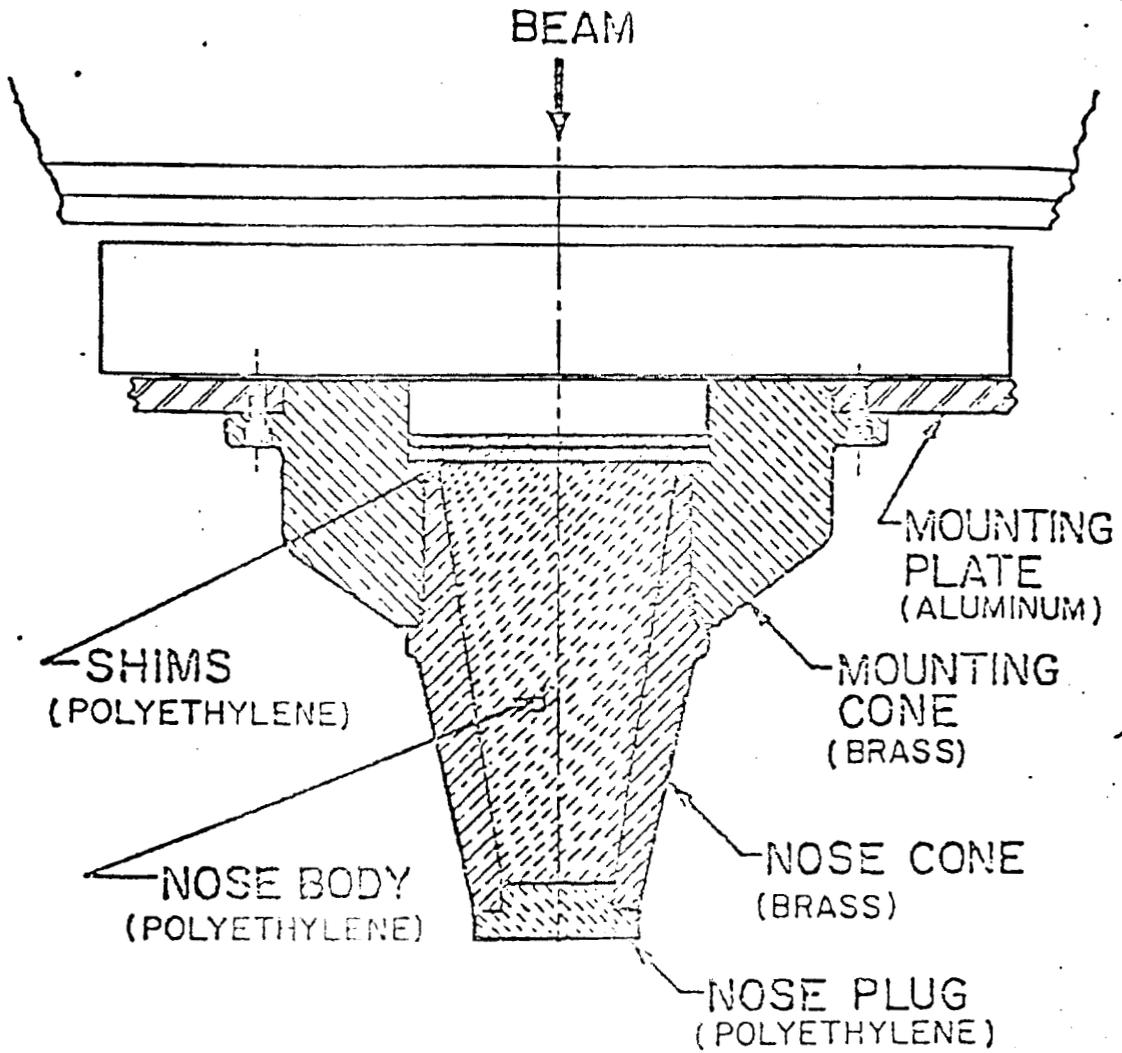


Figure 1. Attenuator-collimator treatment cone for skin nodules and superficial tumors.

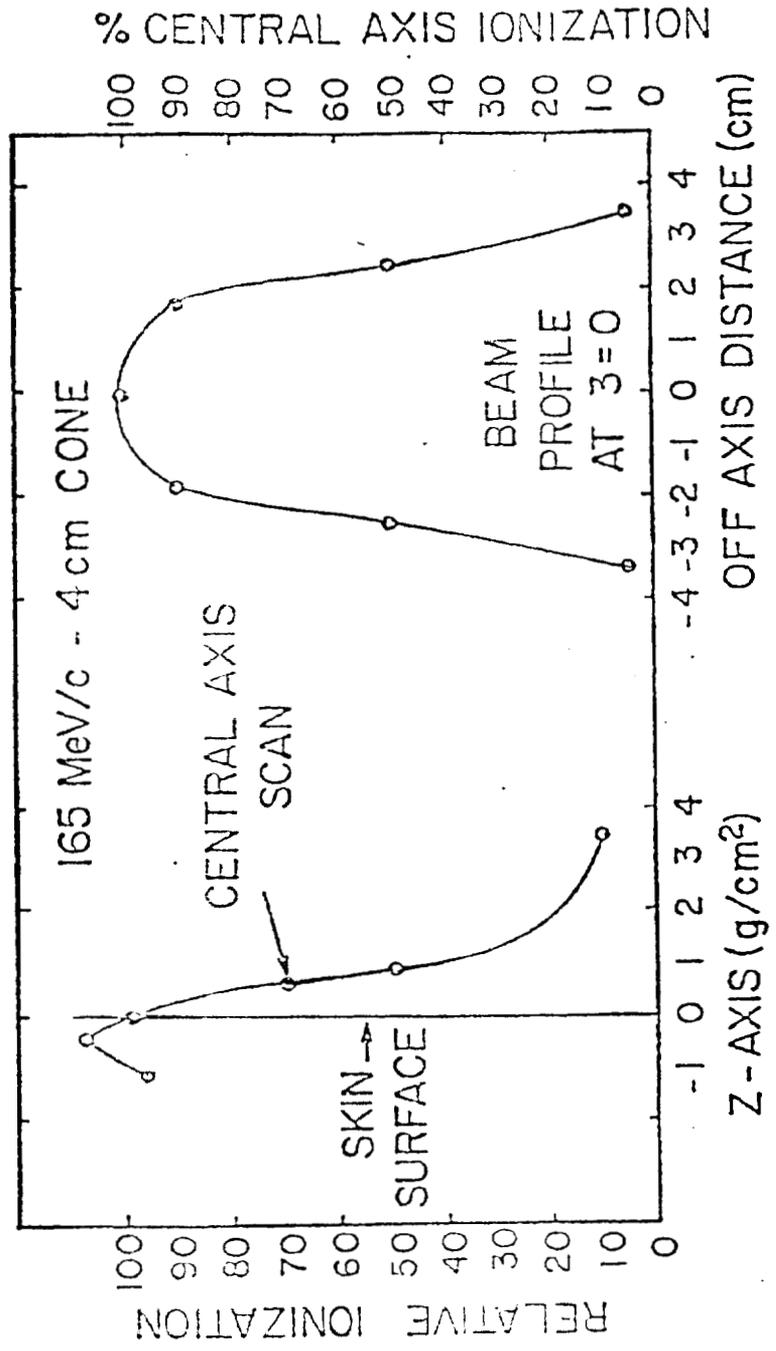


Figure 2. Central axis distribution for skin nodule beam; $z = 0$ is at skin surface (left). Typical beam profile taken at $z = 0$ (right).

LASL BIOMEDICAL RANGE SHIFTER

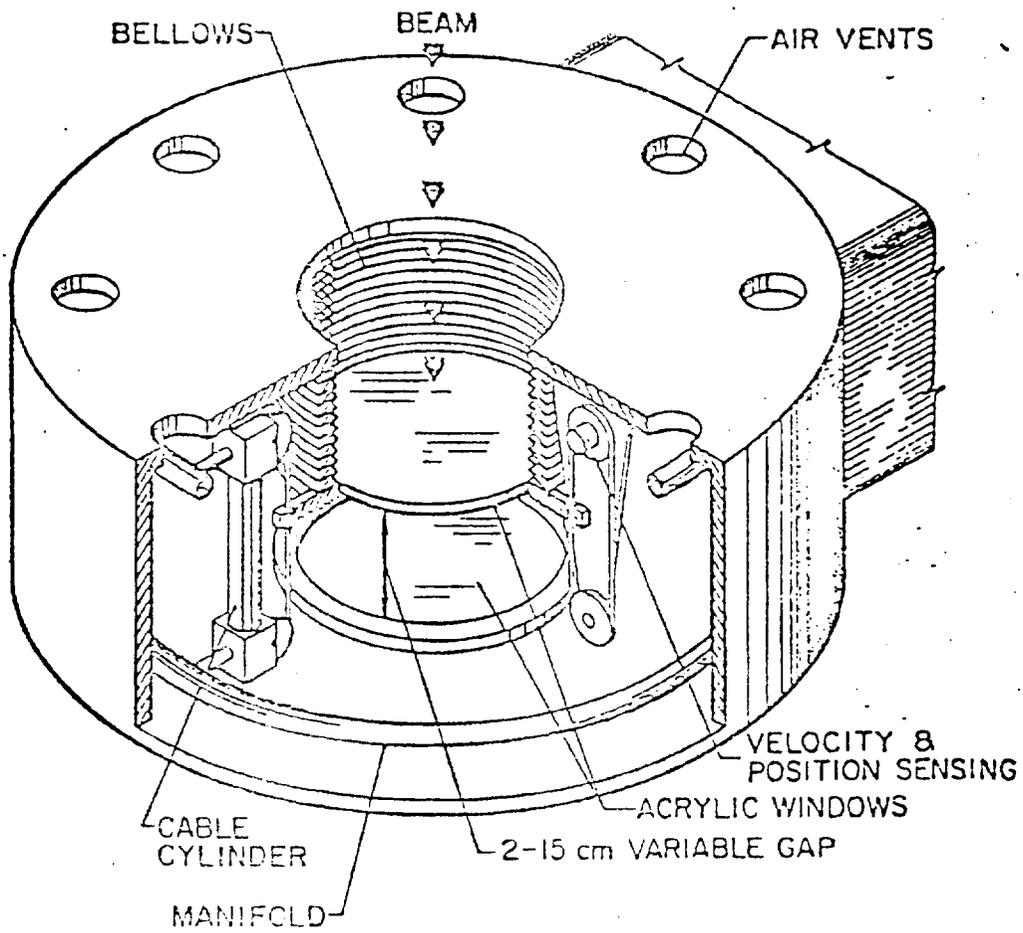


Figure 4. The dynamic range-shifter used to spread in depth the Bragg peak of pion beams.

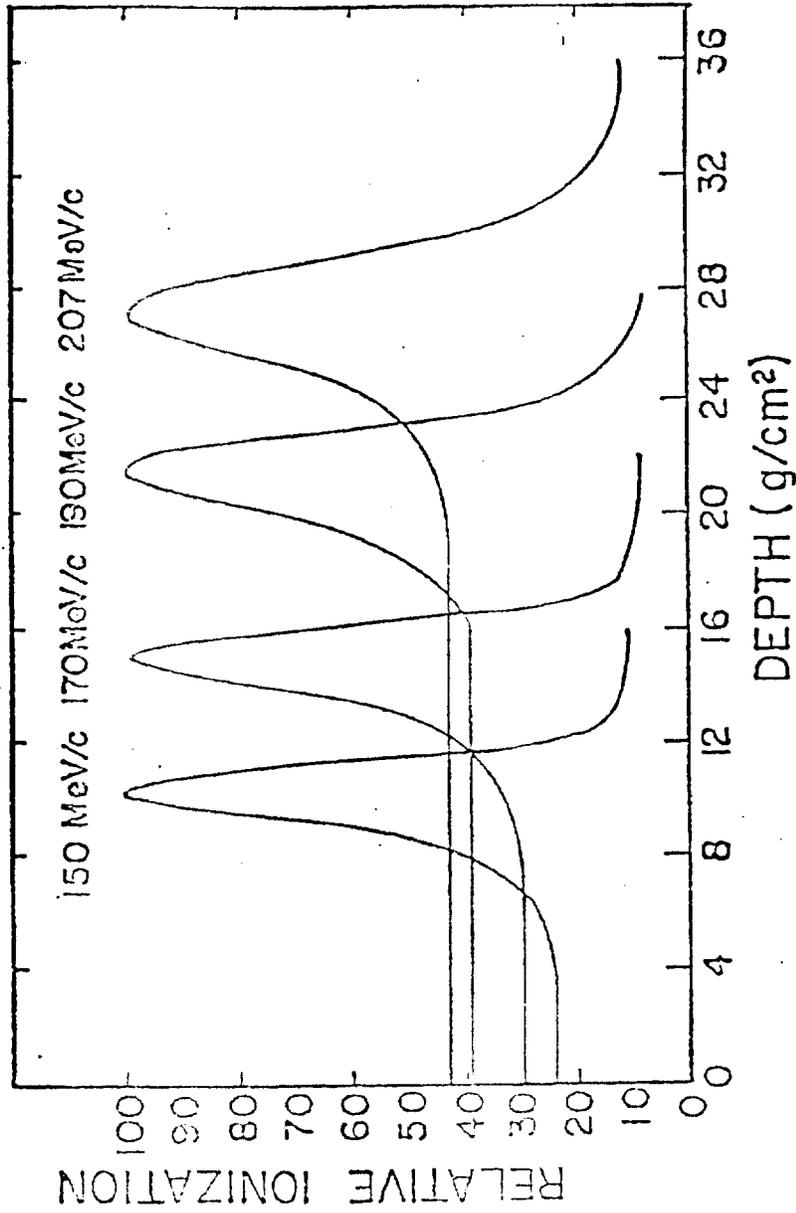


Figure 5. Central axis depth profiles for basic beams used to treat deep-seated tumors.

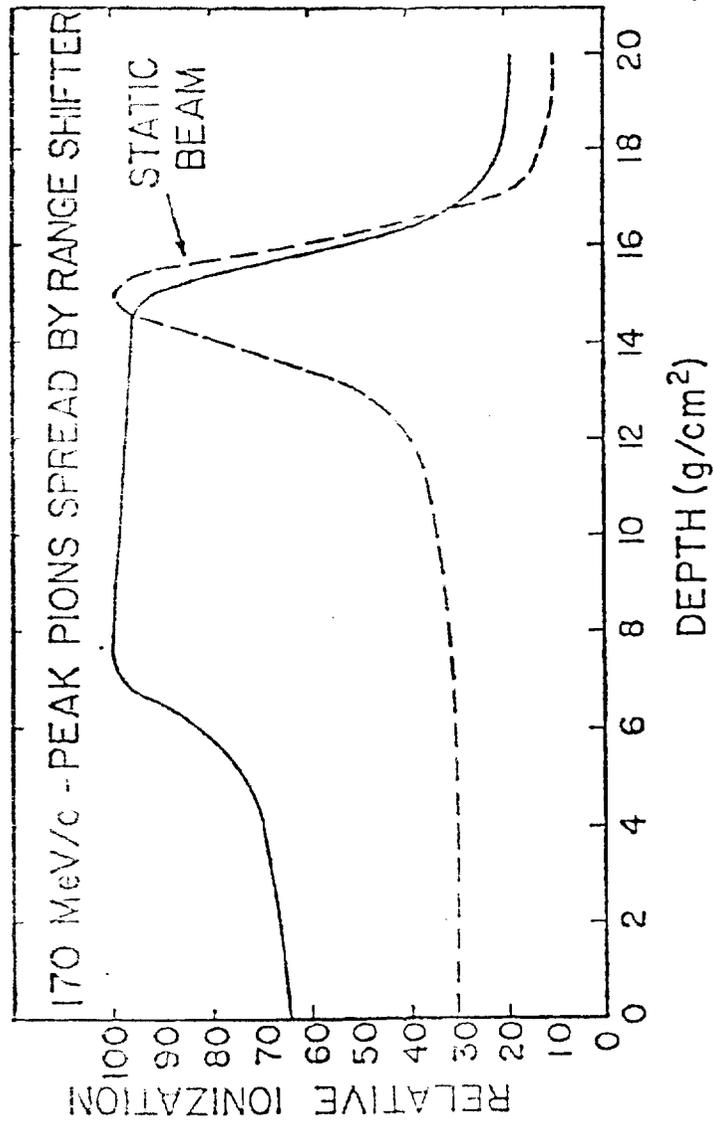


Figure 6. Example of a Bragg peak (slashed line) spread to 8 cm (solid line) by use of the range-shifter.

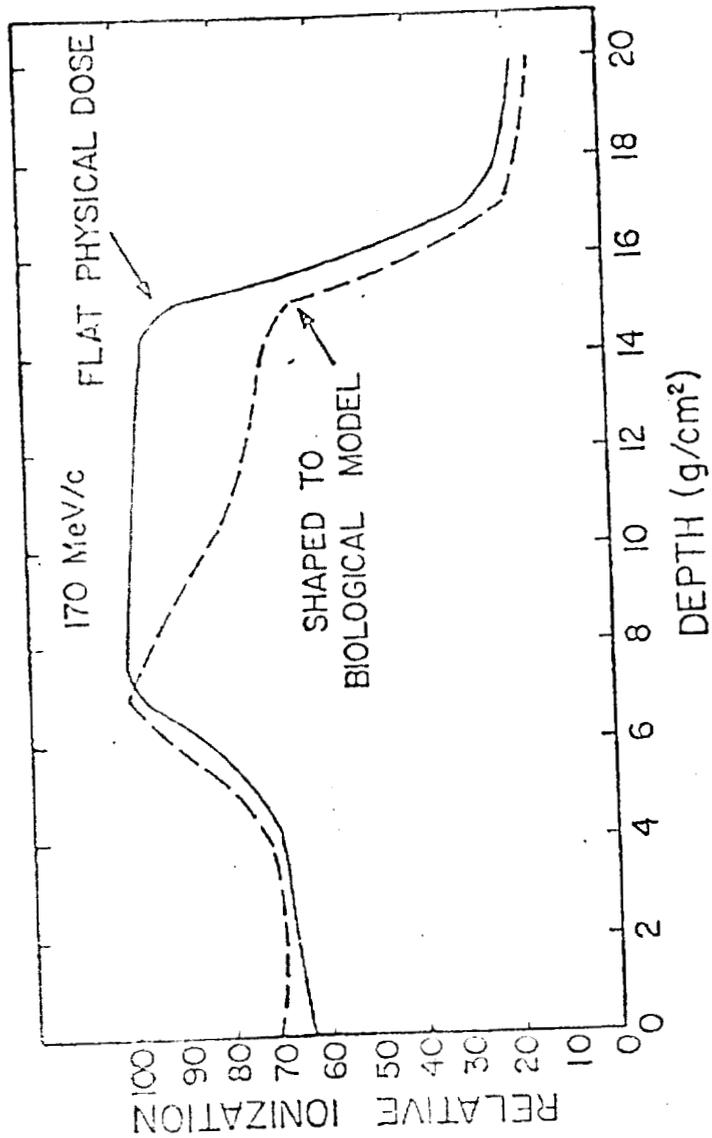


Figure 7. Example of a spread peak (solid line) shaped to attempt to compensate for increased biological effectiveness in distal region (dashed line).

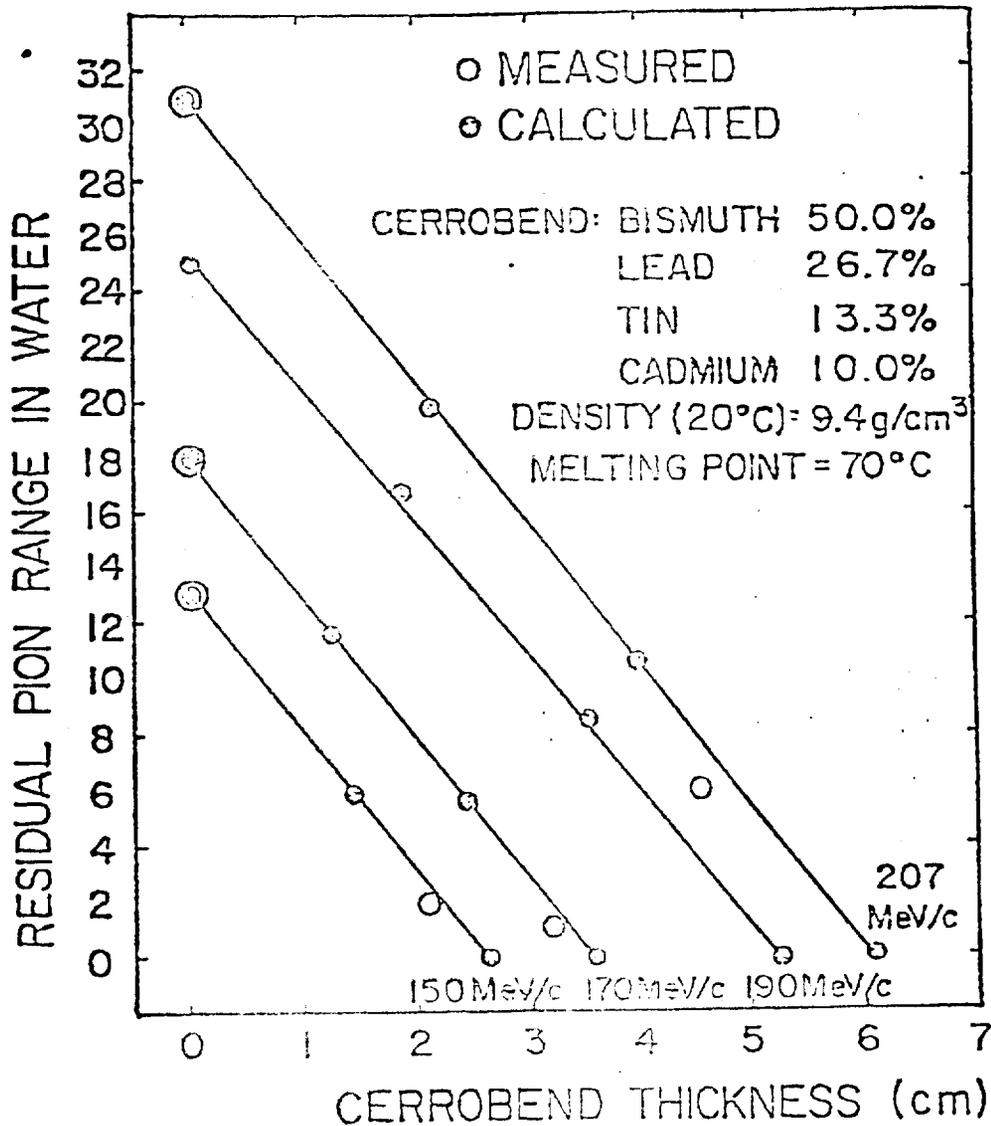


Figure 8. Calculated (closed circles) and measured (open circles) residual pion range in water versus thickness of alloy used for collimation.

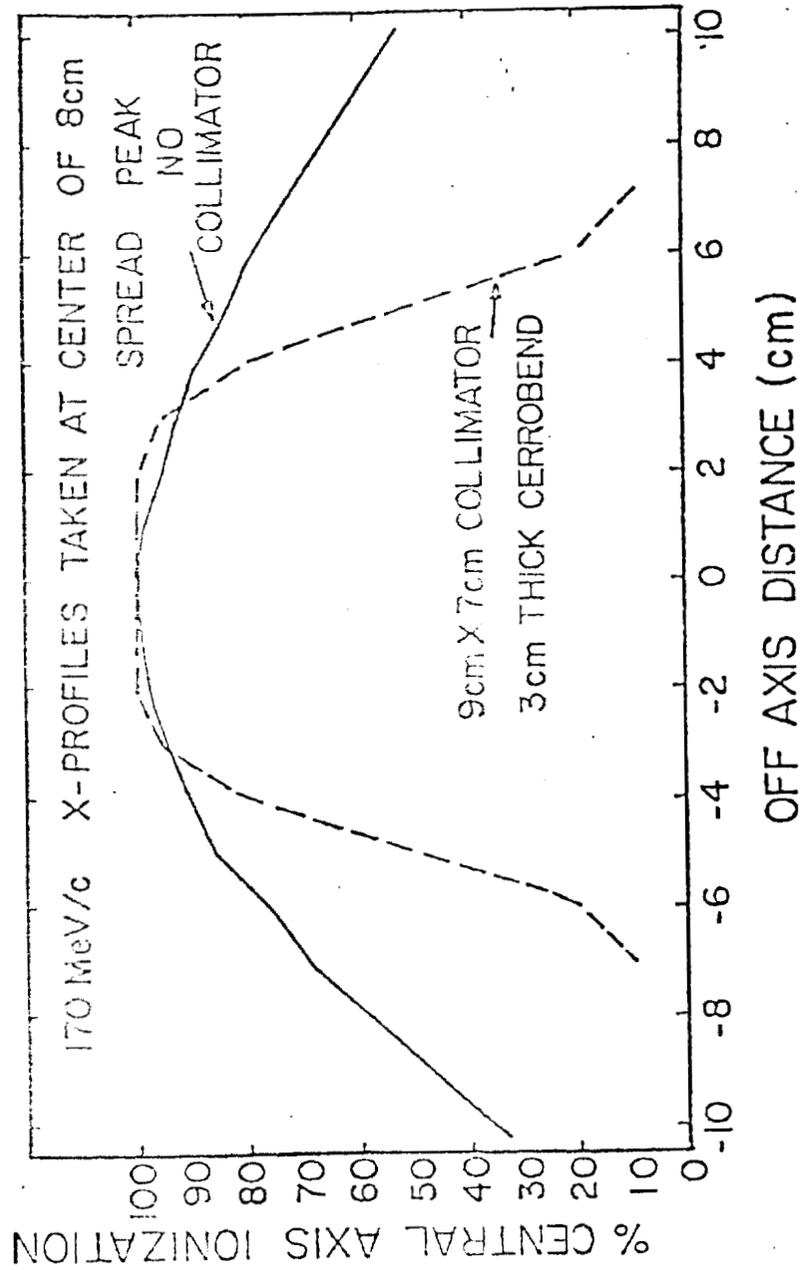


Figure 9. Example of uncollimated (solid line) beam profile and profile of collimated beam (dashed line) using alloy (cerrobend).

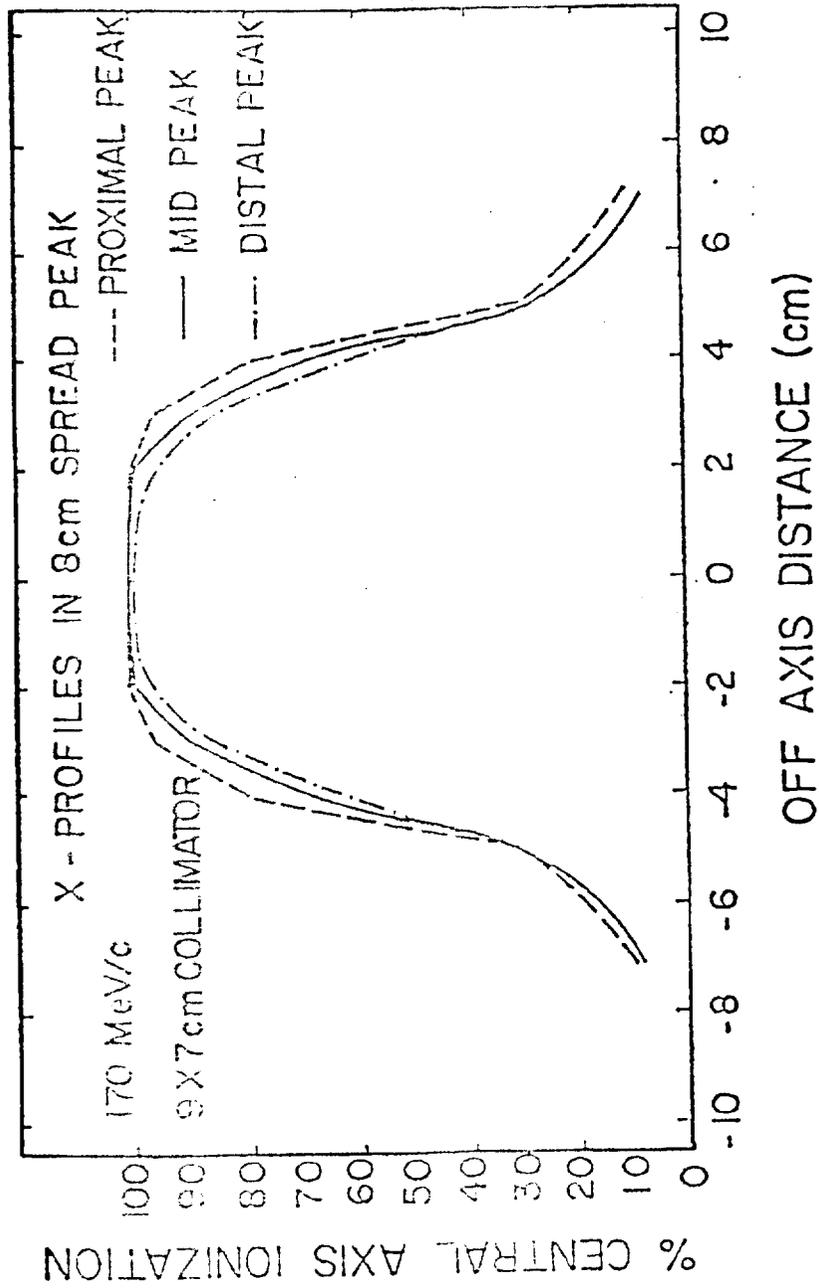


Figure 10. Beam profiles of collimated pion beam taken in the proximal peak (dashed line), mid peak (solid line), and distal peak (dash-dot line), of an 8 cm spread peak.

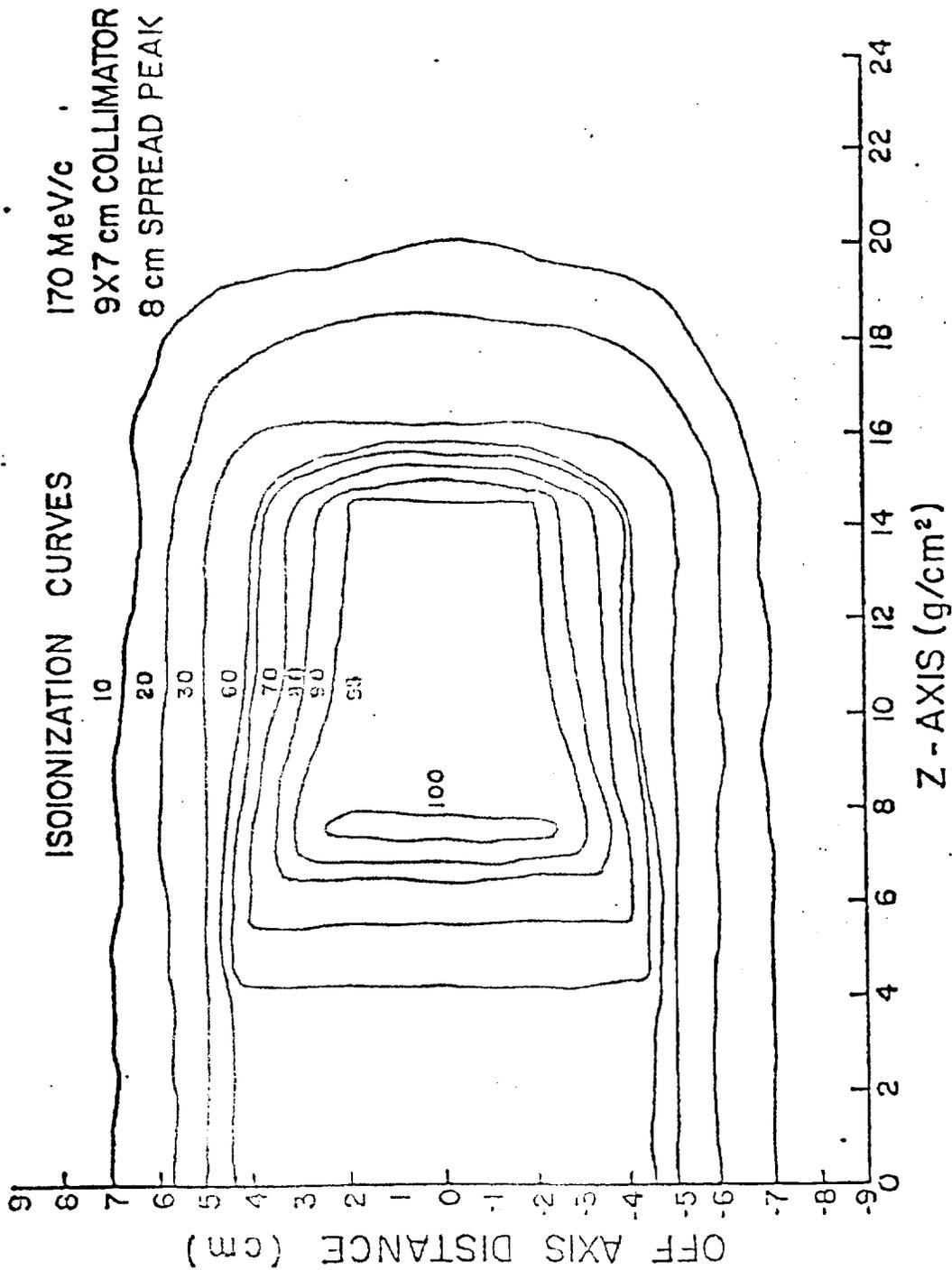


Figure 11. Isoionization distribution of 170 MeV/c collimated pion beam with peak spread to 8 cm.

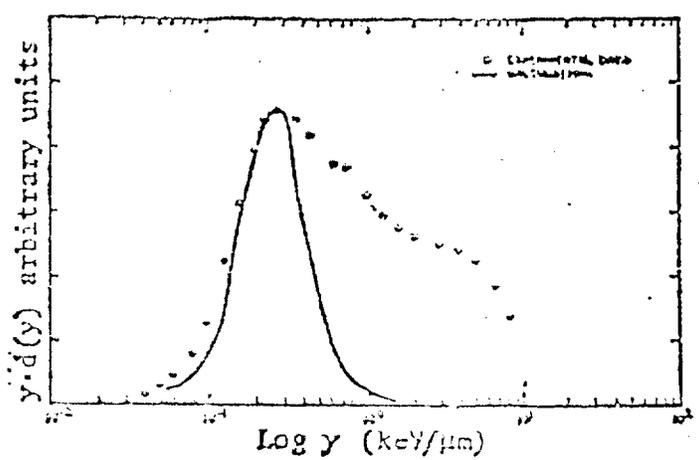


Figure 12. Preliminary results, energy per ion pair (W-values) for pions.

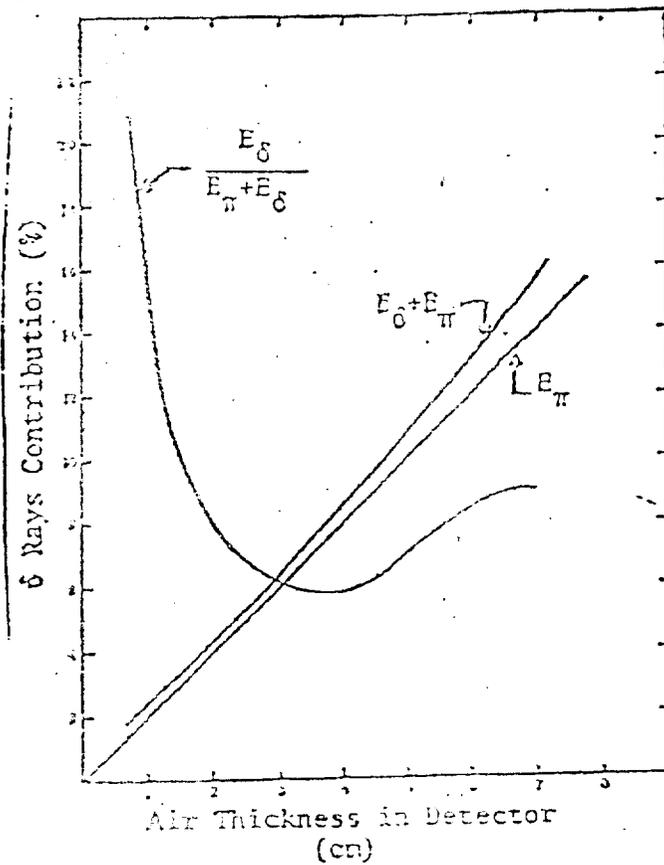


Figure 13. Comparison of calculated and measured pion energy spectra.

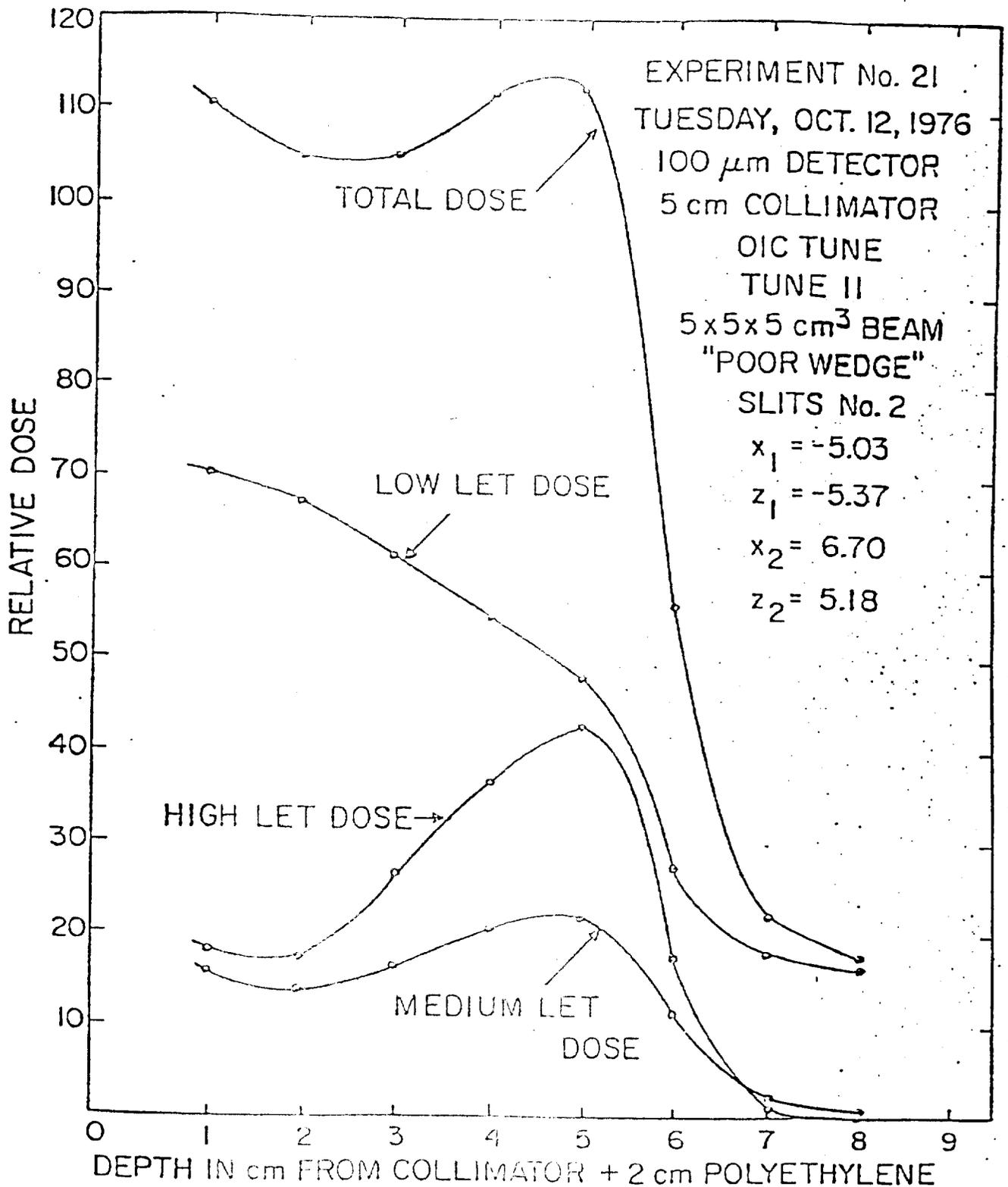


Figure 14. LET component analysis,
5 x 5 x 5 cm beam.

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00133396.079

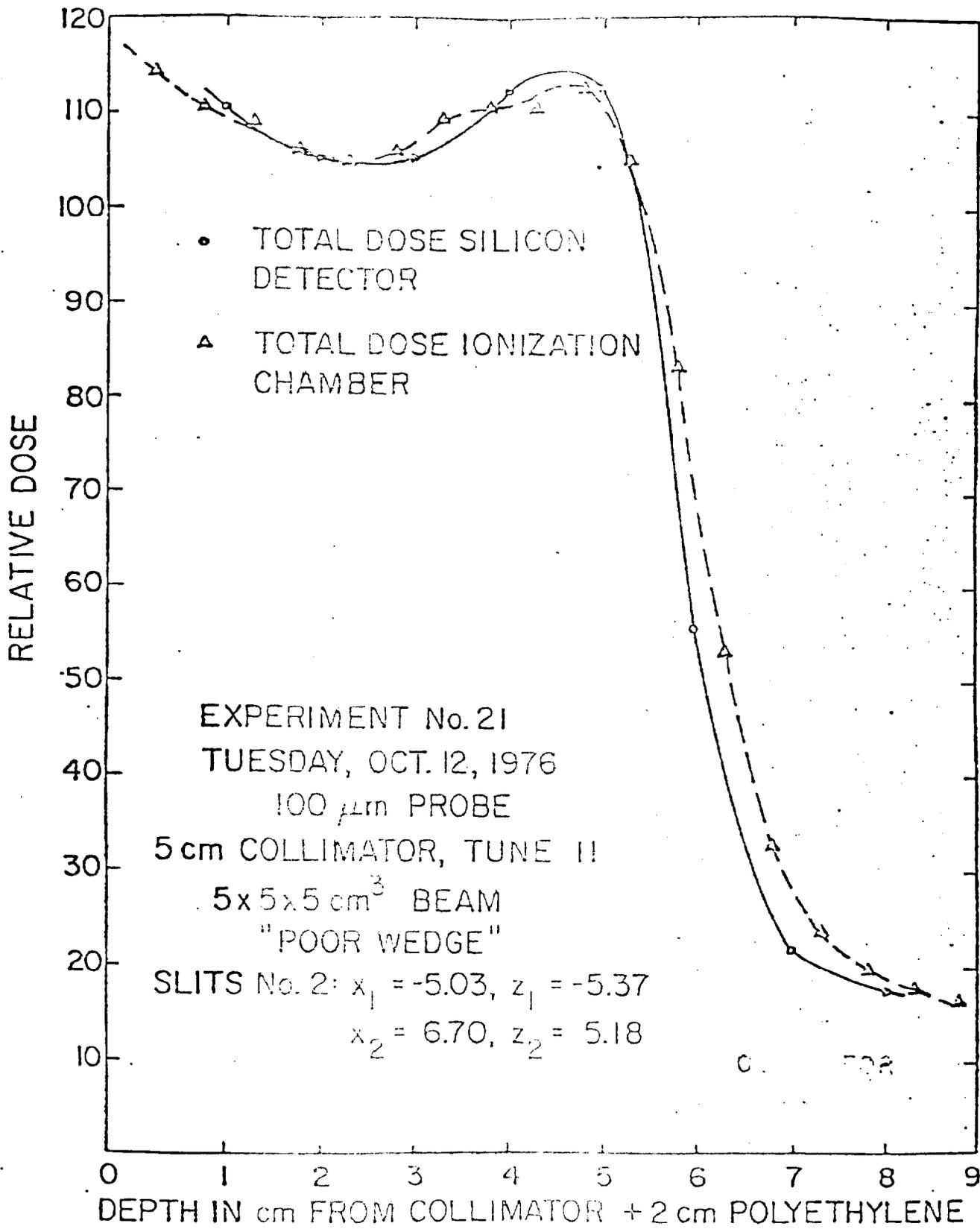


Figure 15. Total dose comparison, 5 x 5 x 5 cm beam.

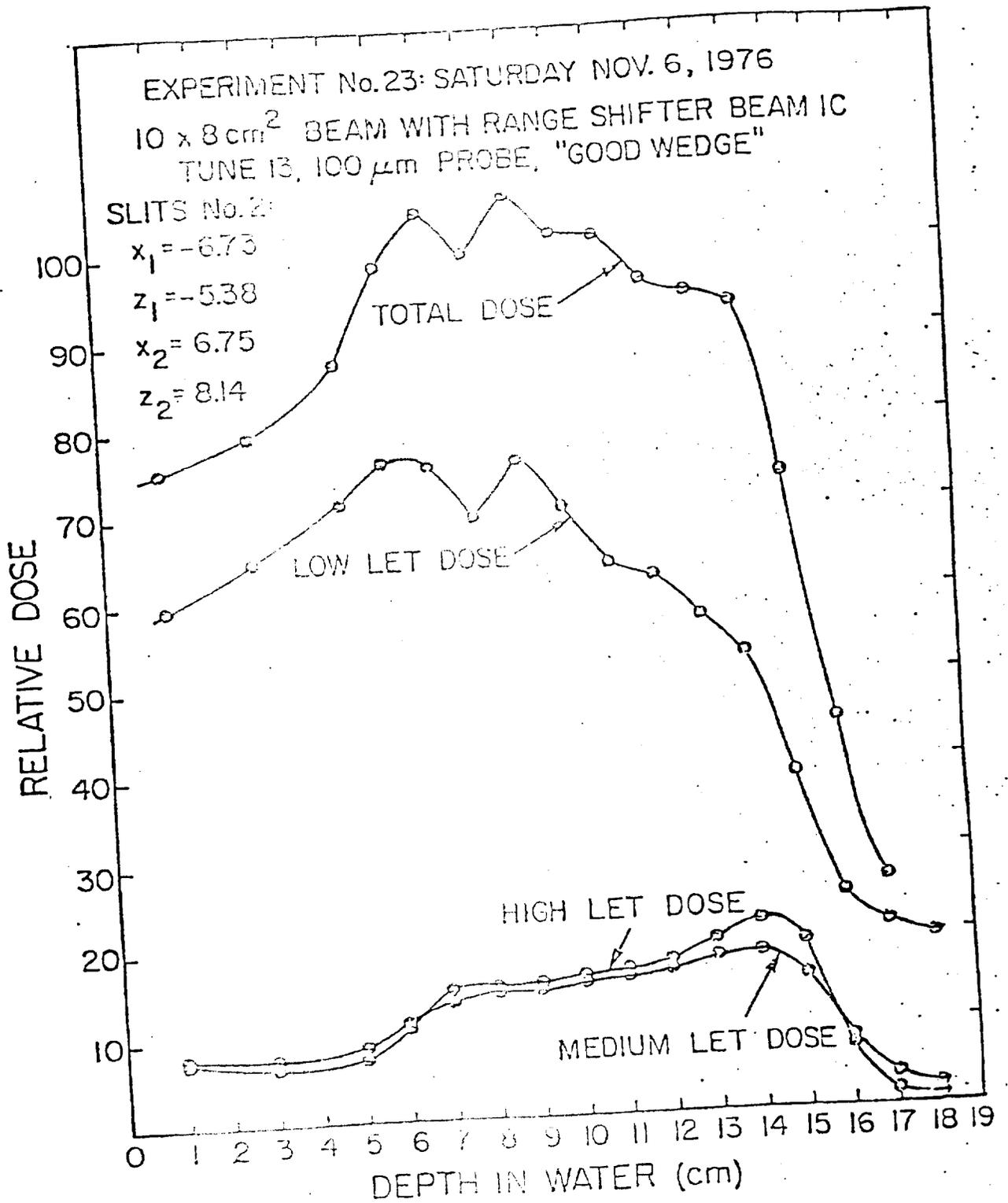


Figure 16. LET component analysis,
 8 x 10 x 8 cm beam.

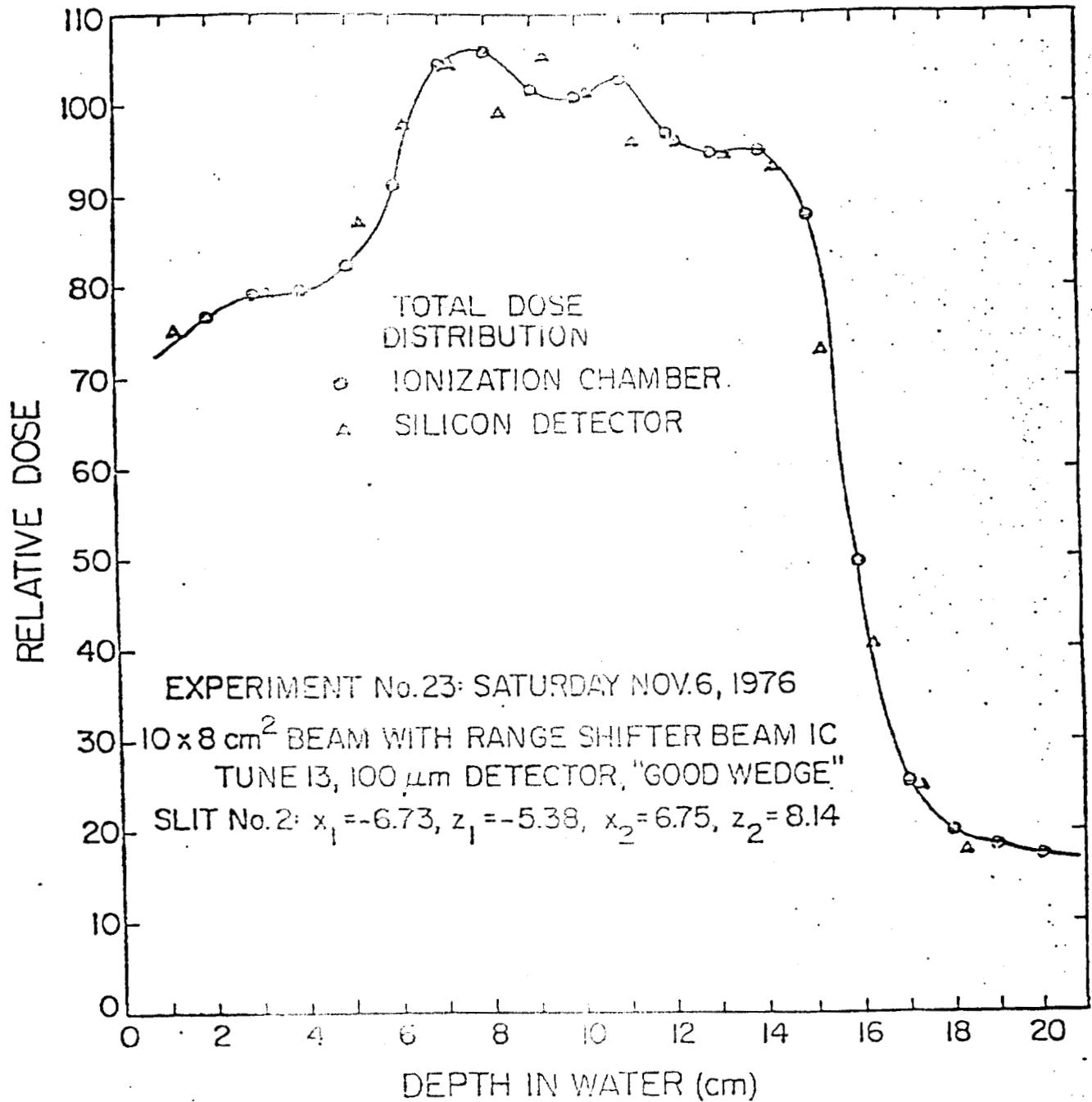


Figure 17. Total dose comparison,
8 x 10 x 8 cm beam.

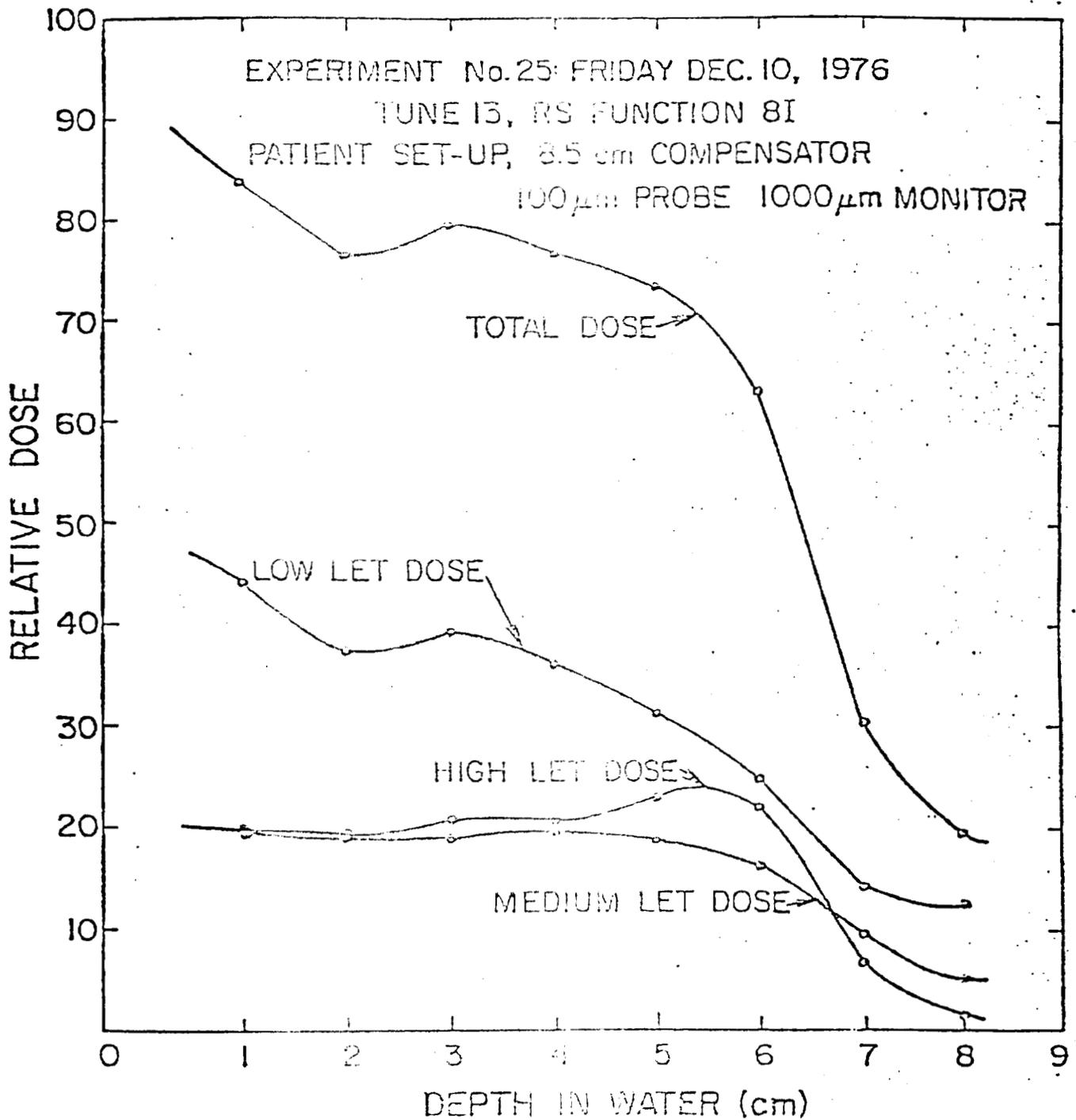


Figure 18. LET component analysis,
8 x 10 x 8 cm patient beam.

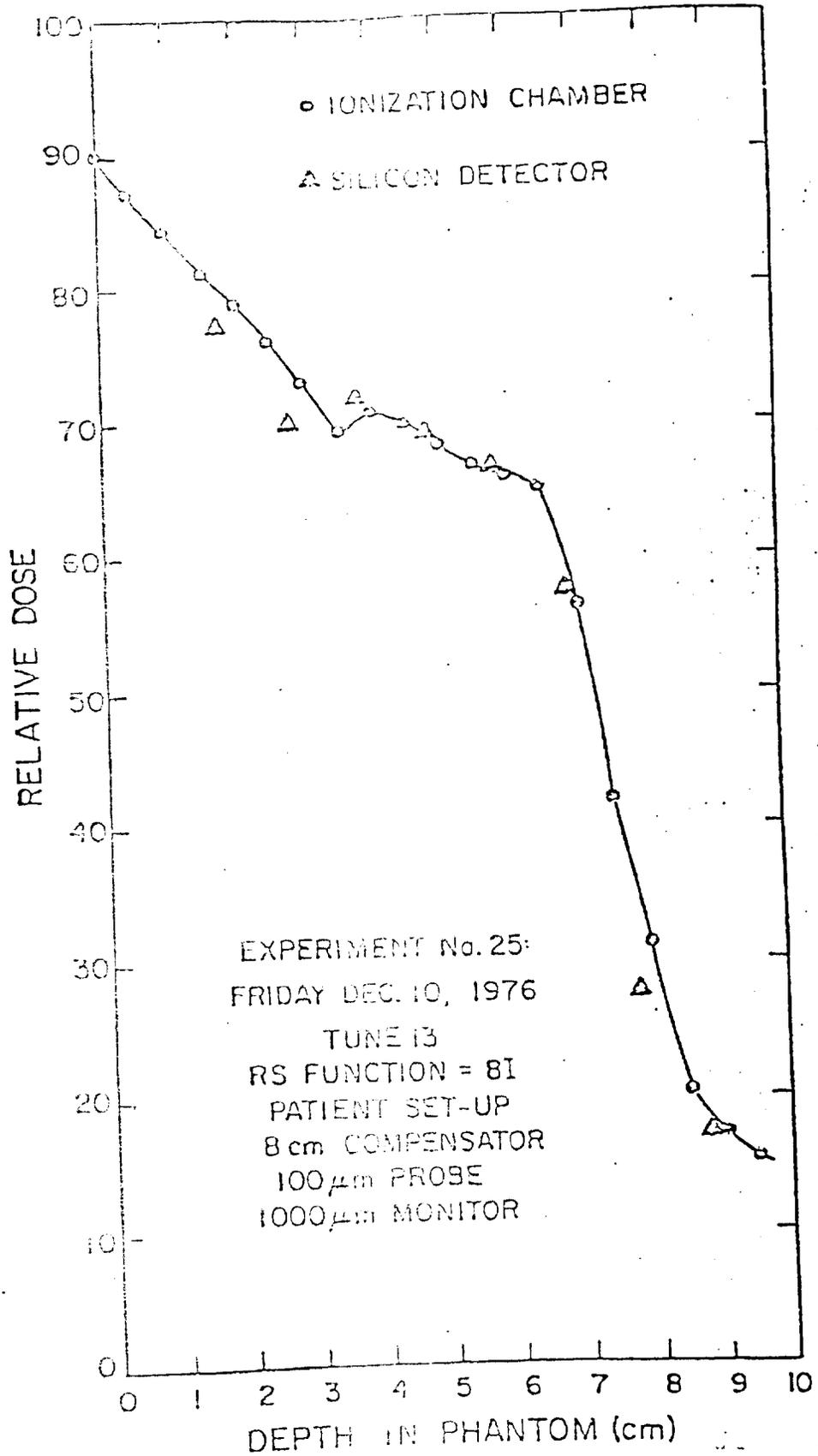


Figure 19. Total dose comparison,
8 x 10 x 8 cm patient beam.

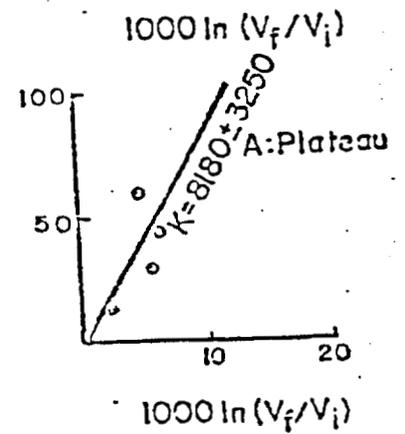
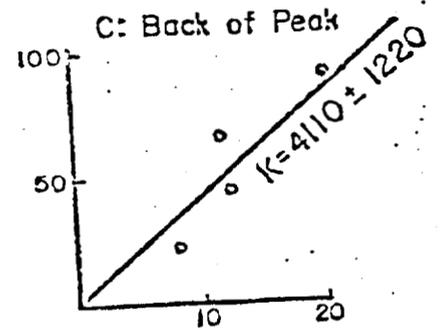
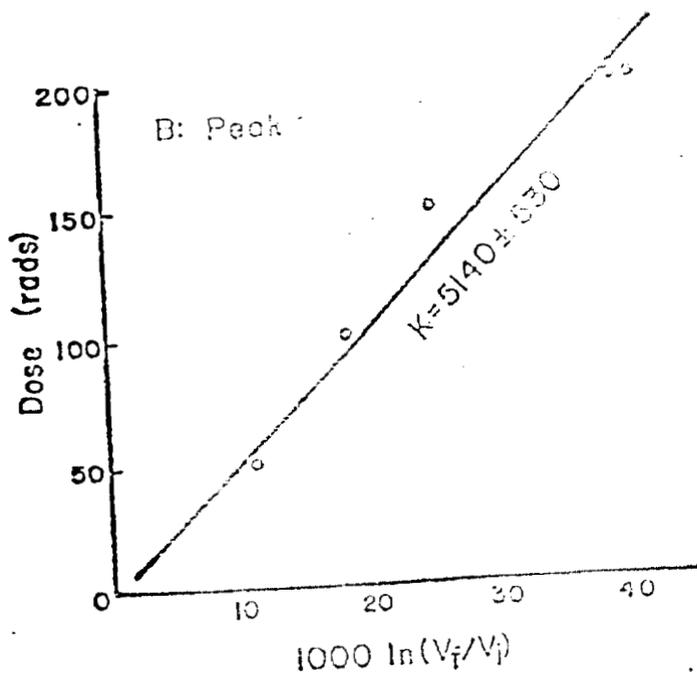
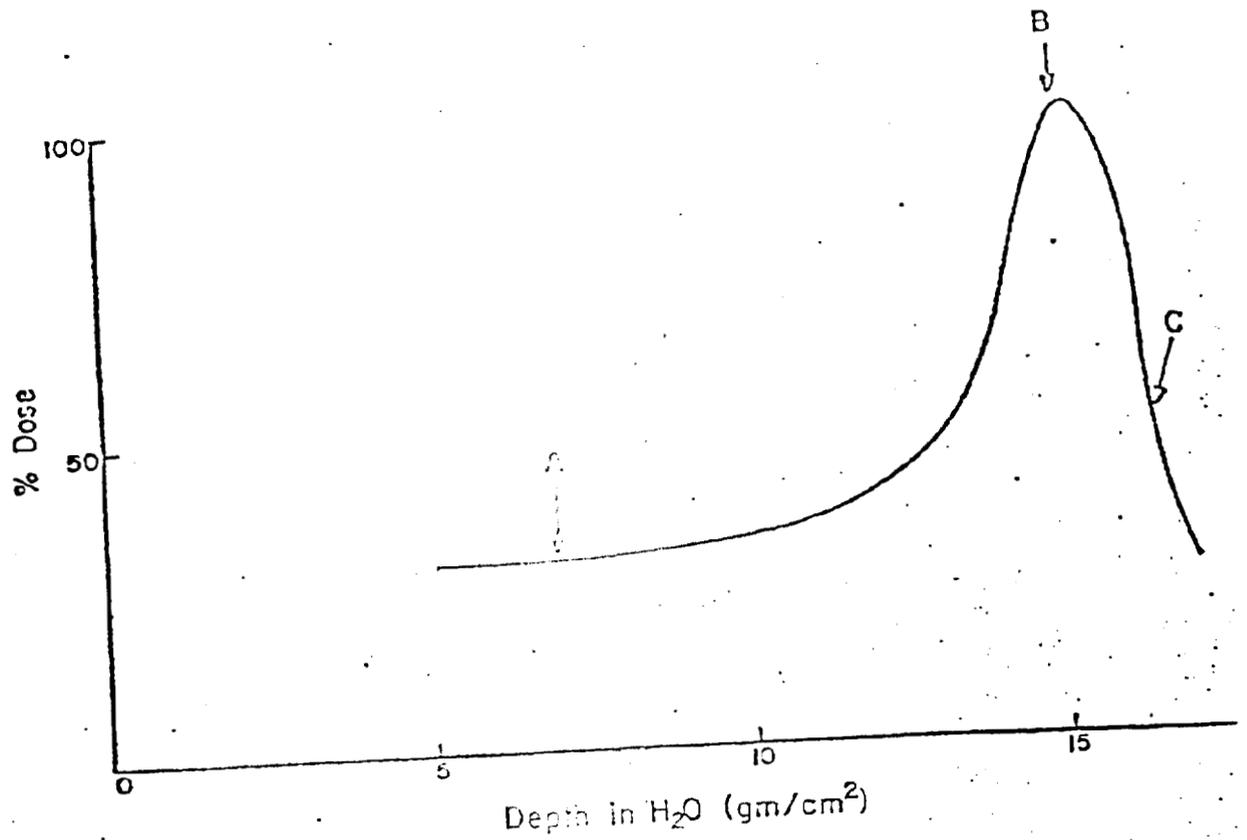


Figure 20. *In vivo* detector (silicon diode) response to pion dose.

Clinical Pion Radiotherapy Patient Setup

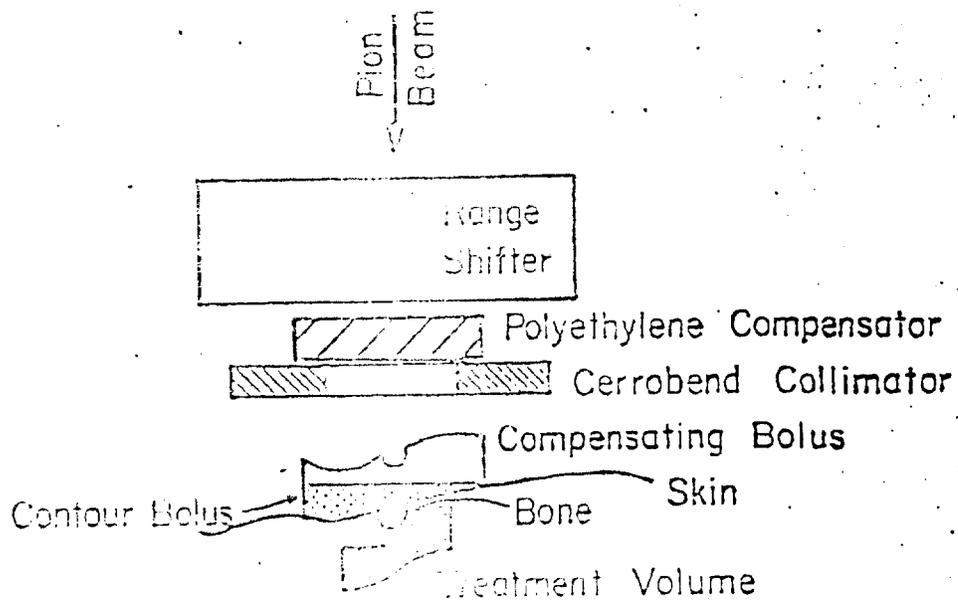


Figure 21. Patient set-up showing typical bolus and collimating configurations for pion therapy.

EFFECT OF BEAM INHOMOGENEITY on Central Axis Depth Dose

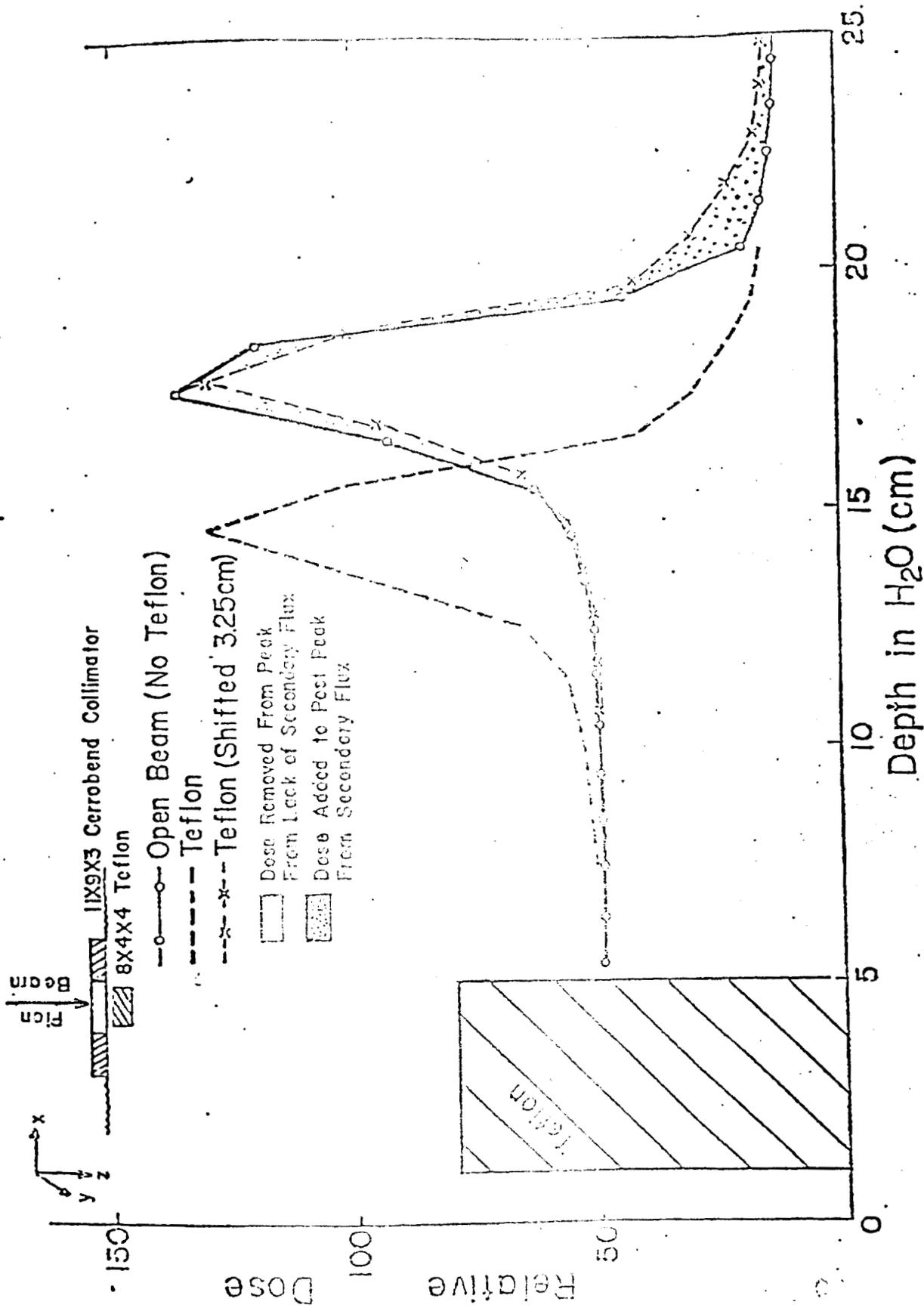


Figure 22. Change in pion peak dose with presence of inhomogeneities.

EFFECT OF PARAFFIN BOLUS IN CORRECTING FOR

Teflon Inhomogeneity

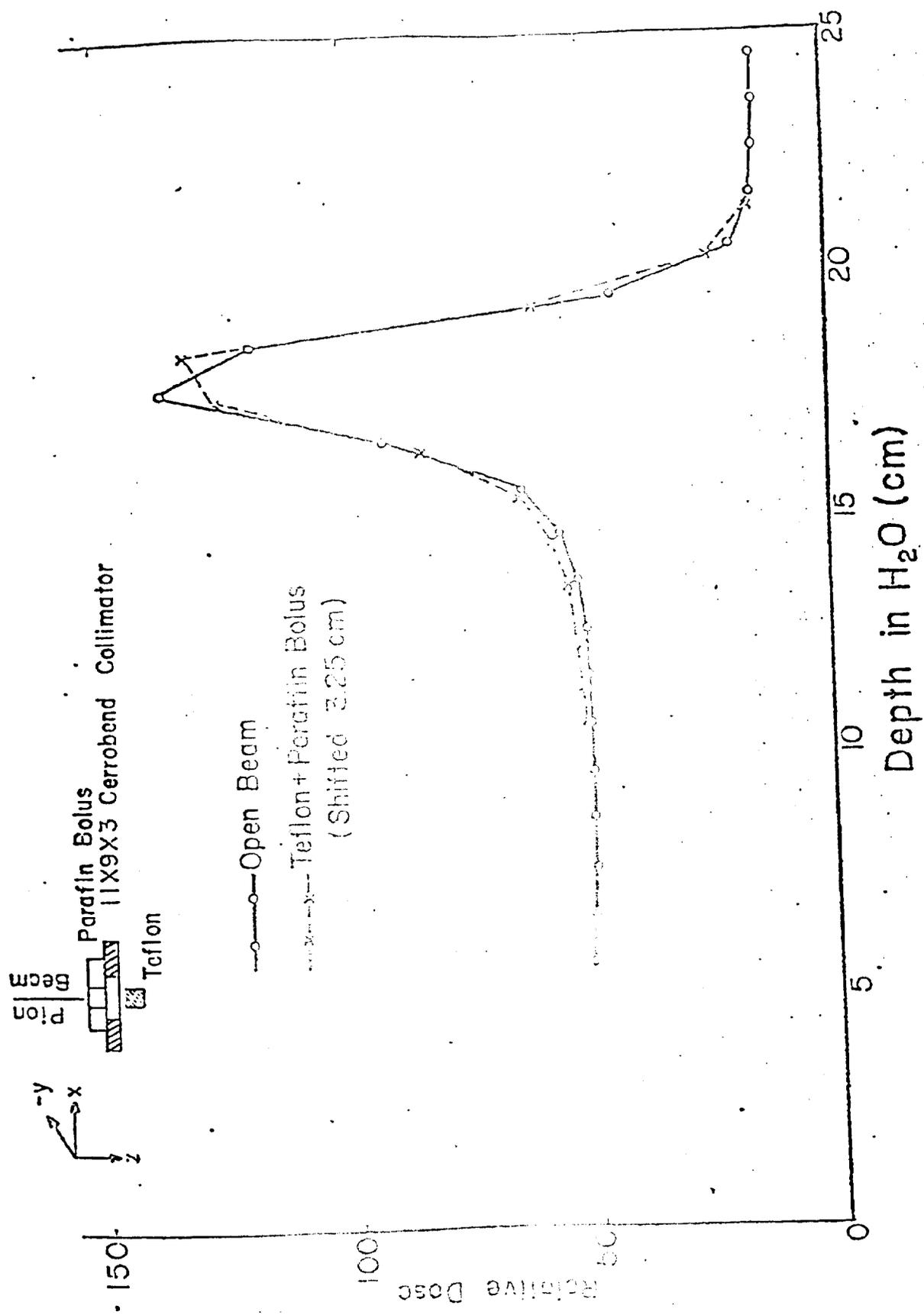


Figure 23. Compensation for inhomogeneity with parallel beam bolus correction.

Comparison of Beam Profiles at the Peak

- Open Beam
- - - Teflon + Paraffin Bolus
- x- Teflon

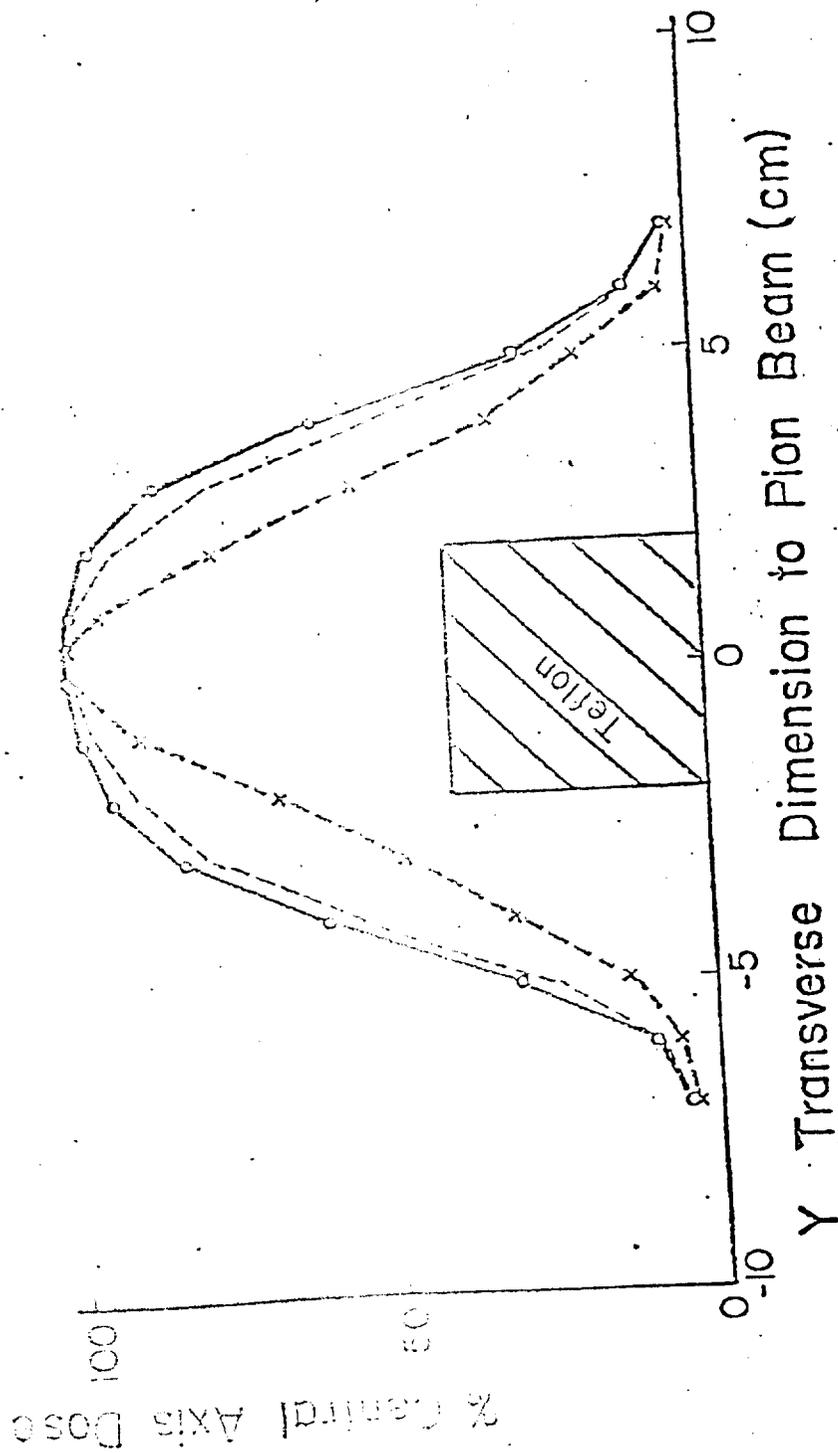


Figure 24. Transverse profiles showing profile restoration with bolus.

Effect of Air Inhomogeneity and Compensating Bolus Under,
Near, and Far From Air

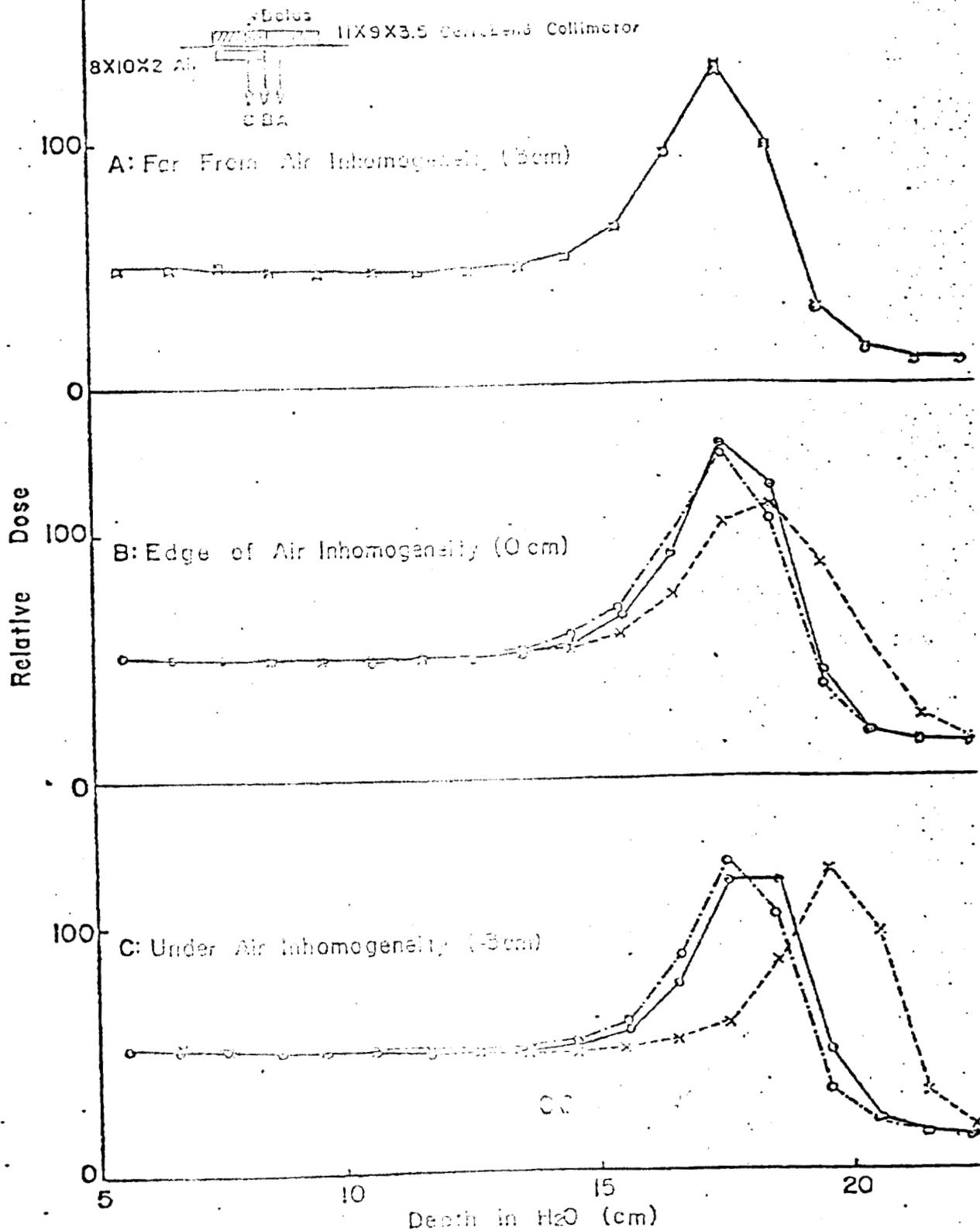
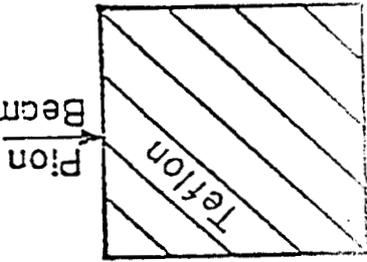


Figure 25. Bolus compensation for air inhomogeneities (- · - open beam, ---x--- air inhomogeneities, - · - · - air inhomogeneities plus.)

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Effect of Inhomogeneity on Beam Profile in Peak



- Open Beam
- x-x- Teflon Inhomogeneity
- - - Preferred Profile Under Teflon

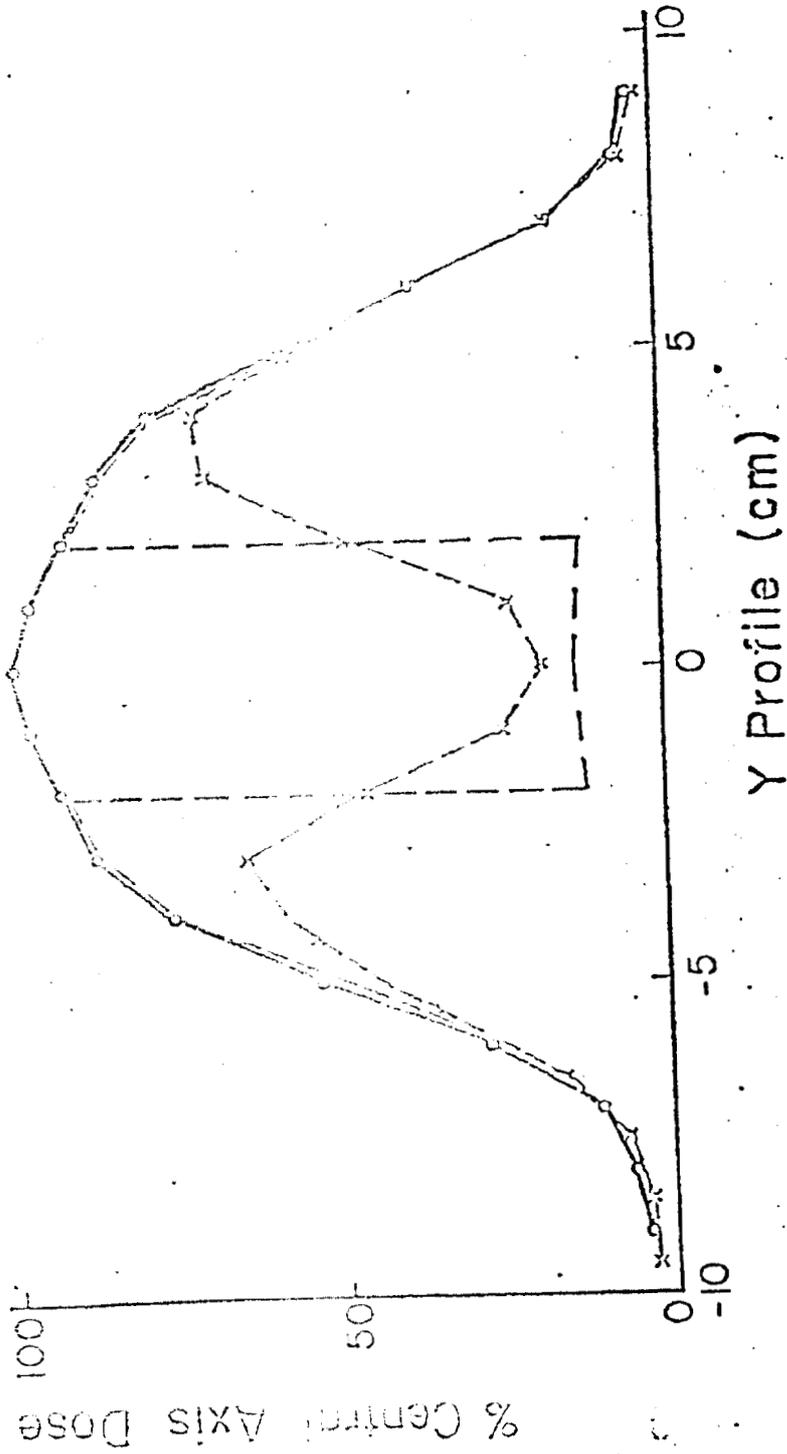


Figure 26. Dose image behind Teflon inhomogeneity.

Tune 4 Radiobiology

3cm Brass Collimator

1.9 cm Poly above, 3 cm Poly below

D_{MAX} at 1.75 cm

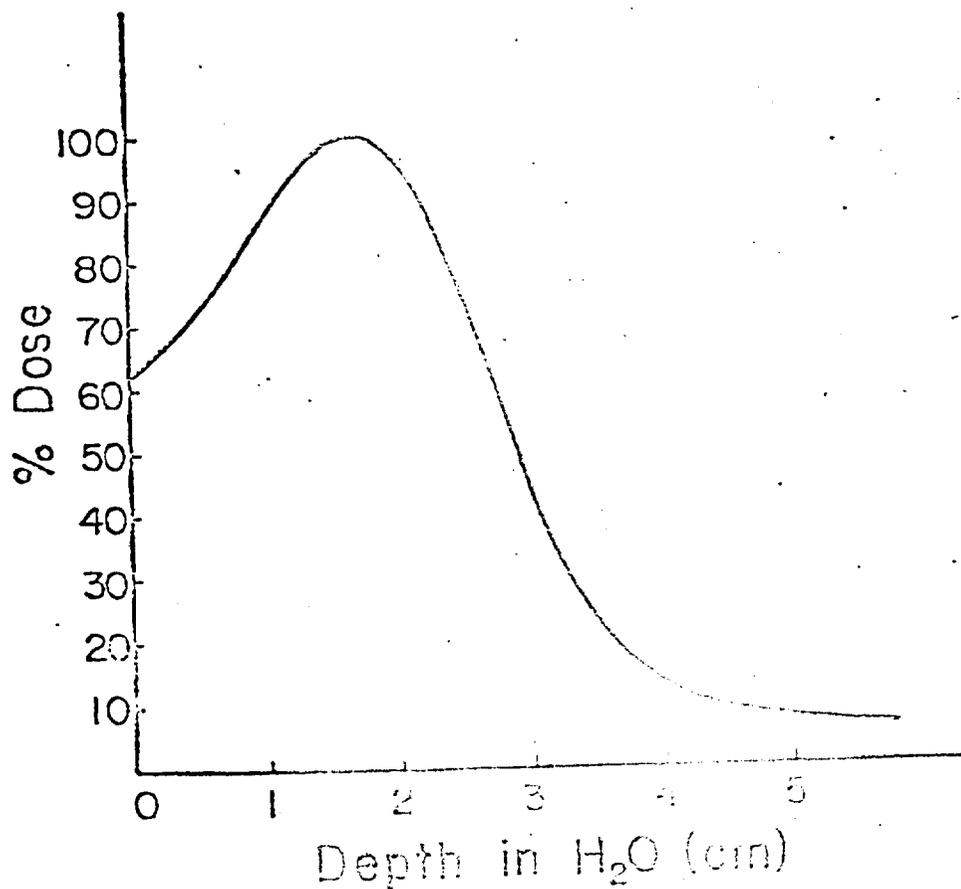
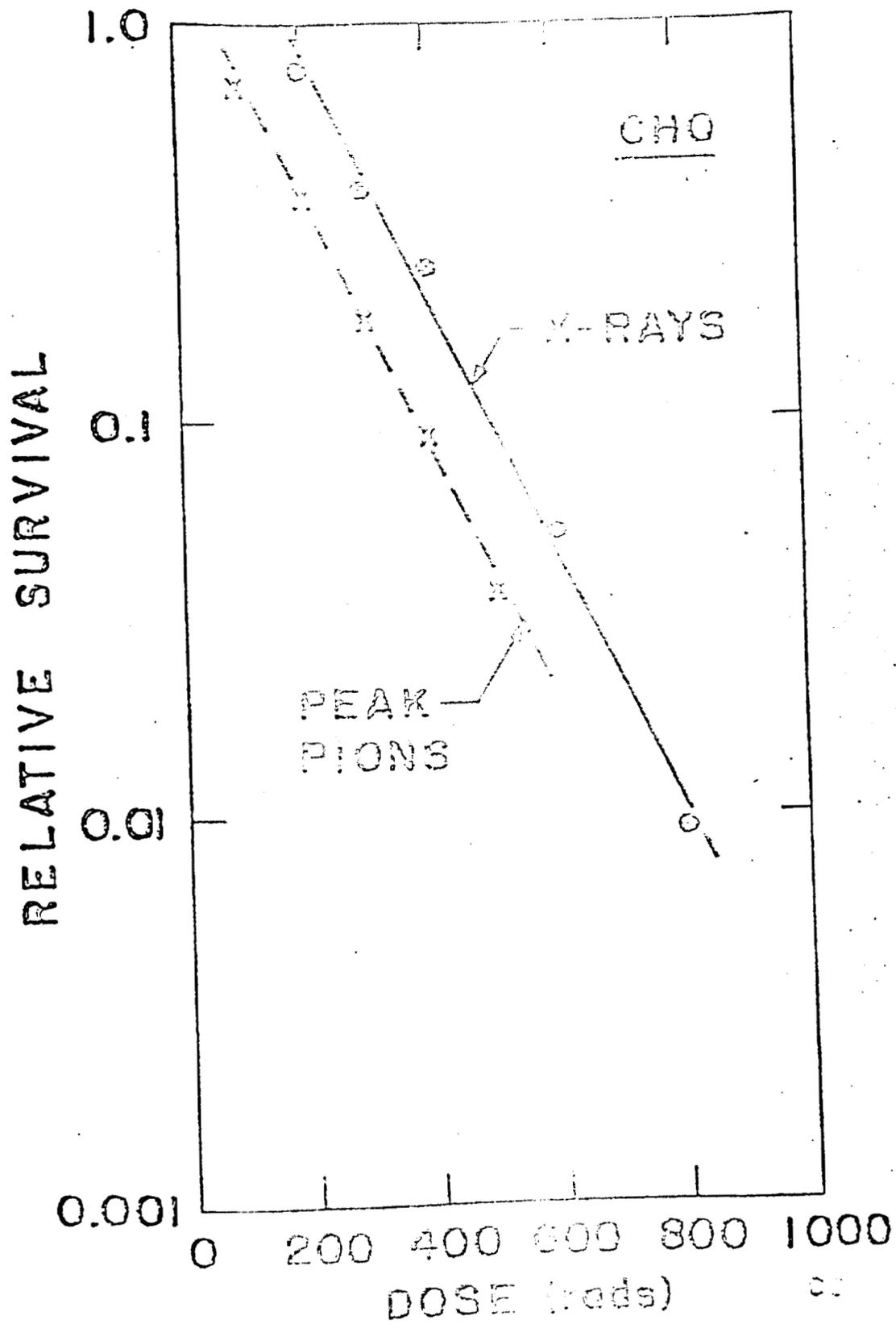


Figure 27. Radiobiology tune, 2 x 2 x 2 cm.



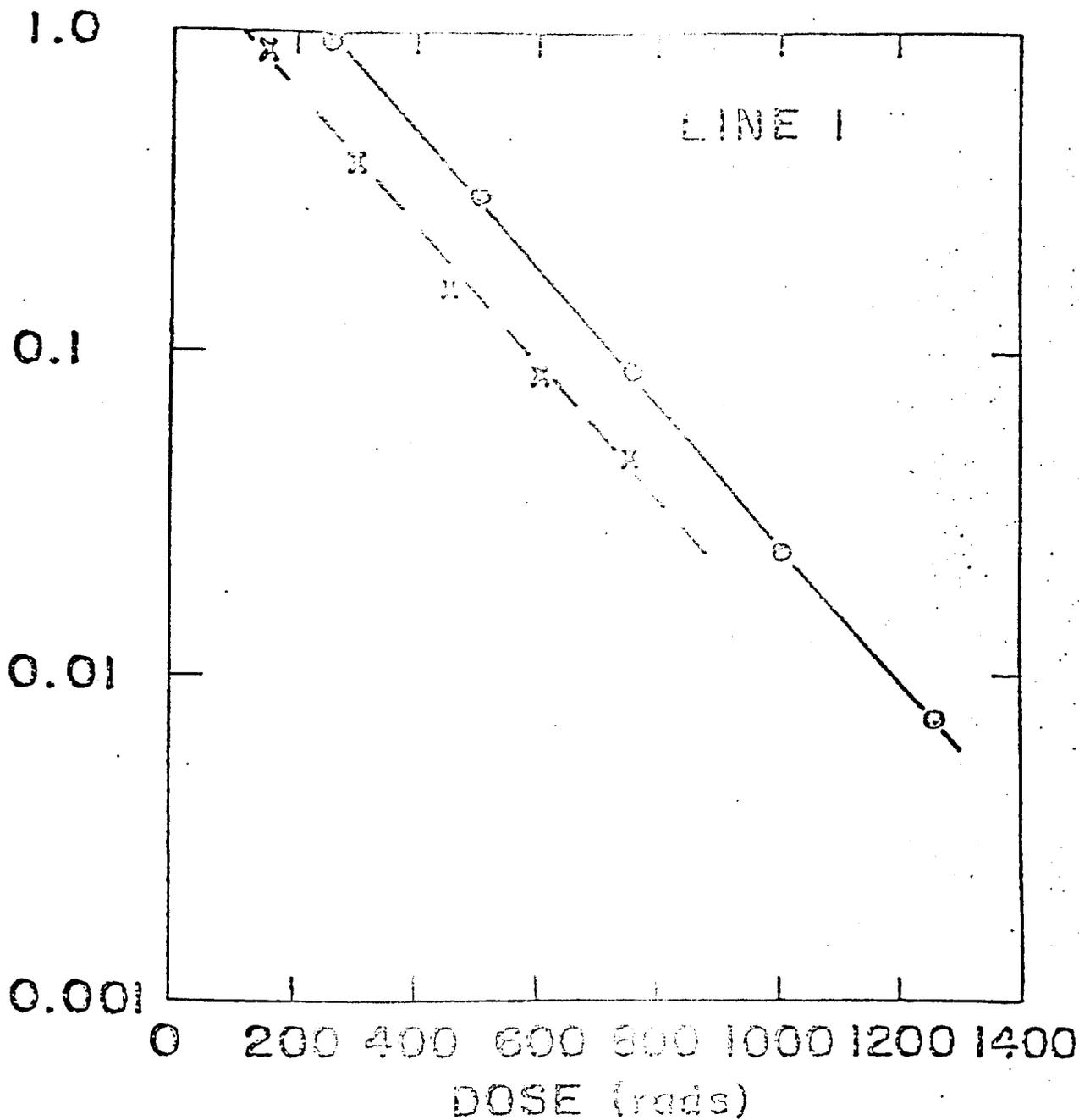


Figure 29. Relative survival, Line 1 lung carcinoma monolayers, pions versus x-rays.

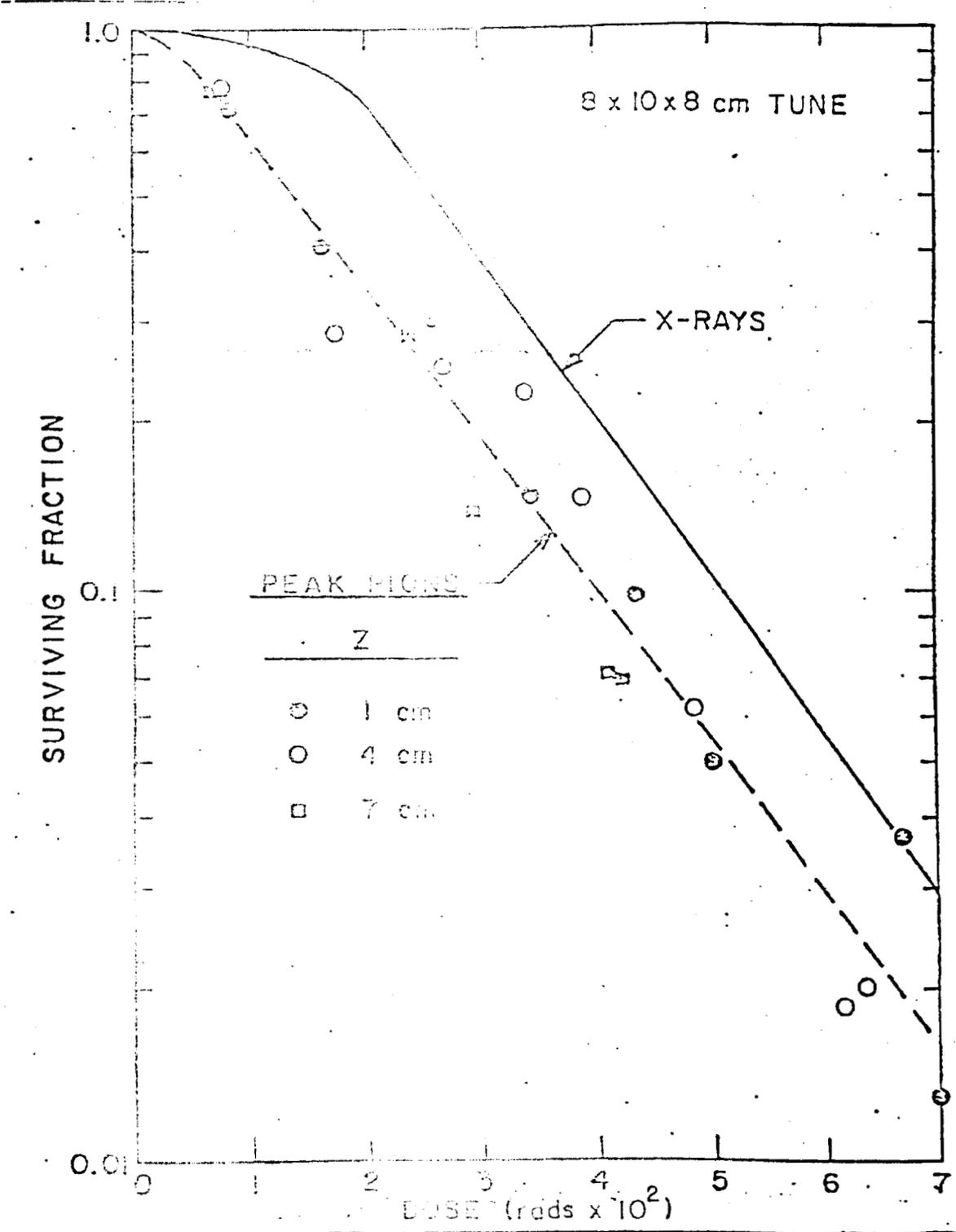


Figure 30. Relative survival, CHO monolayers, exposed to pions (8 x 10 x 8 cm tune) and x-rays.

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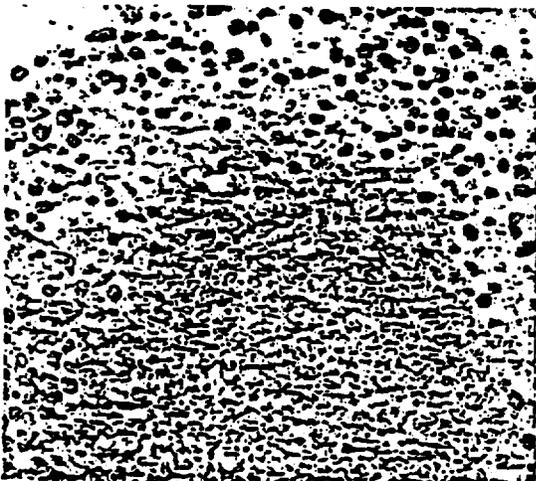
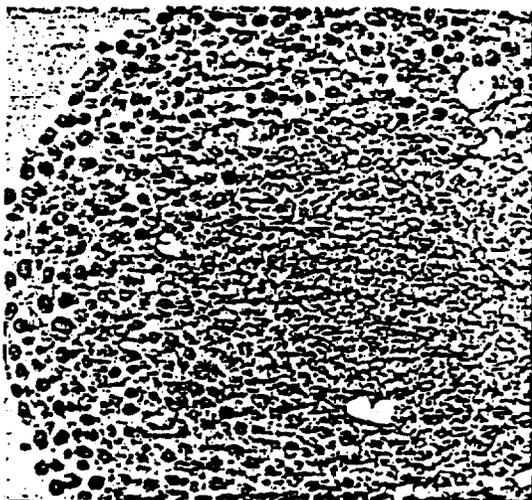
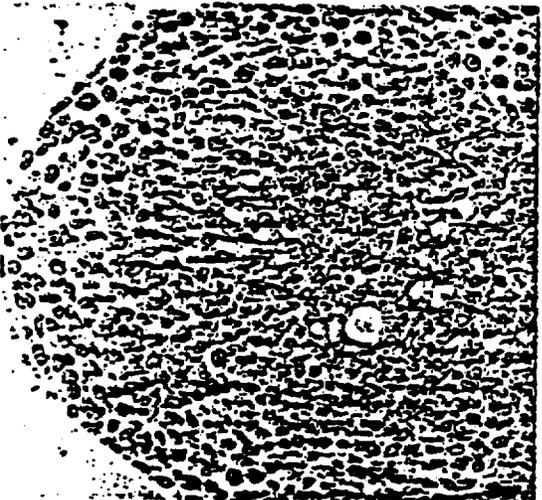
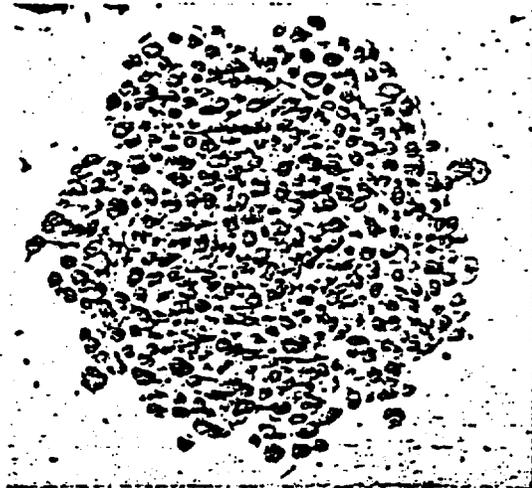
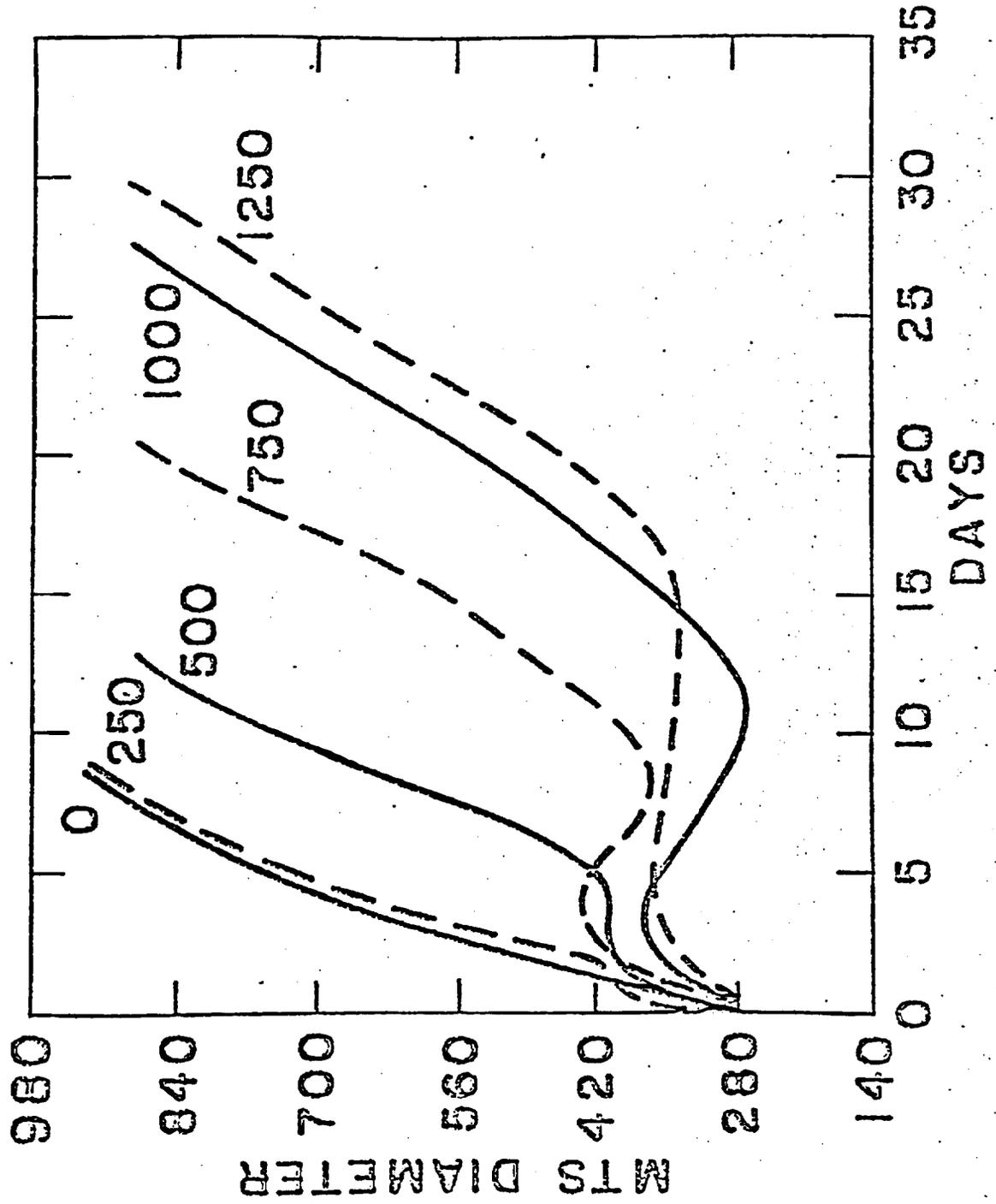


Figure 31. Multicellular
Tumor Spheroids (MIS)

LINE I CARCINOMA MTS



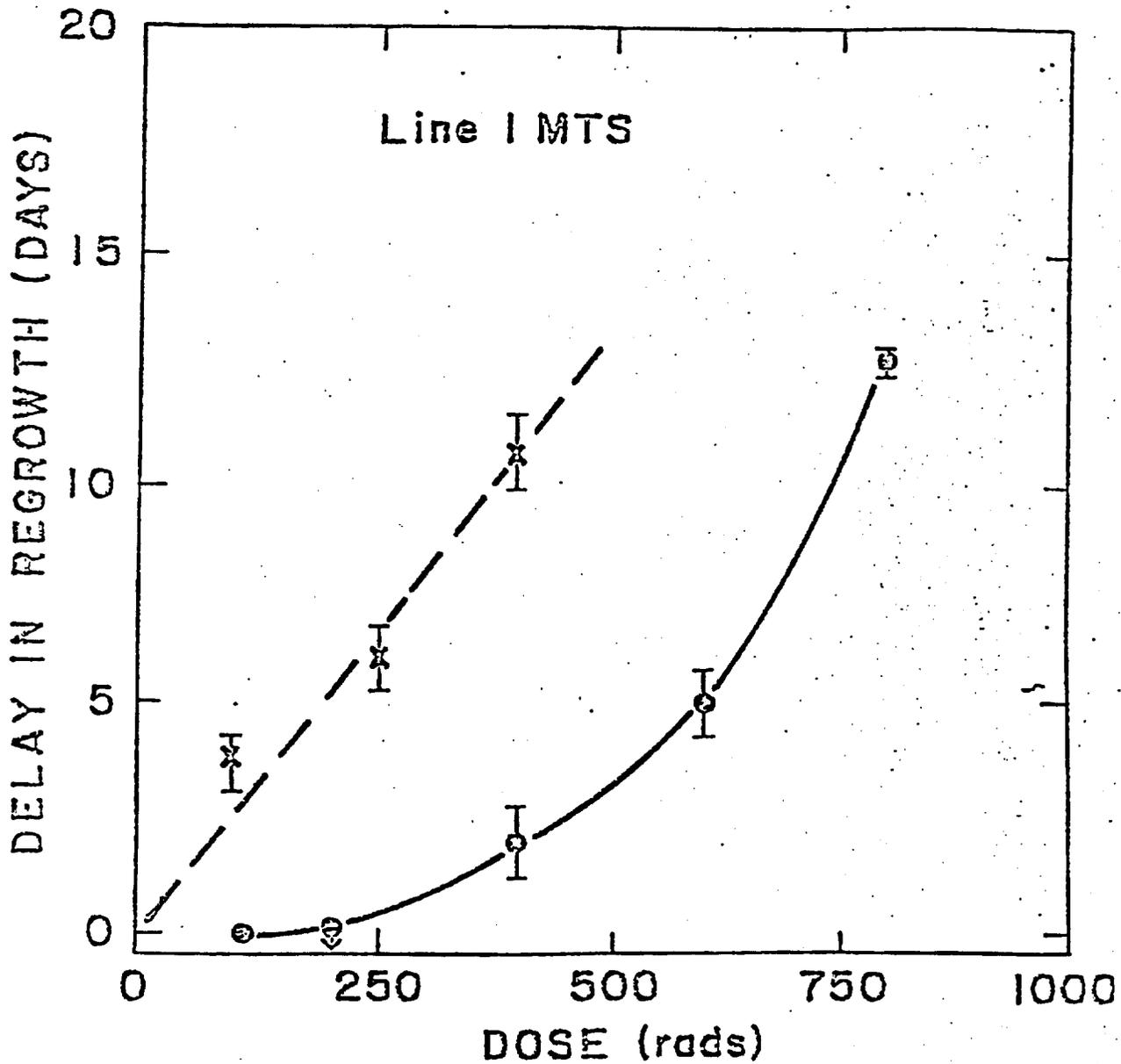


Figure 33. Radiation-induced growth delay, Line 1 lung carcinoma MTS exposed to peak pions (x) or x-rays (•).

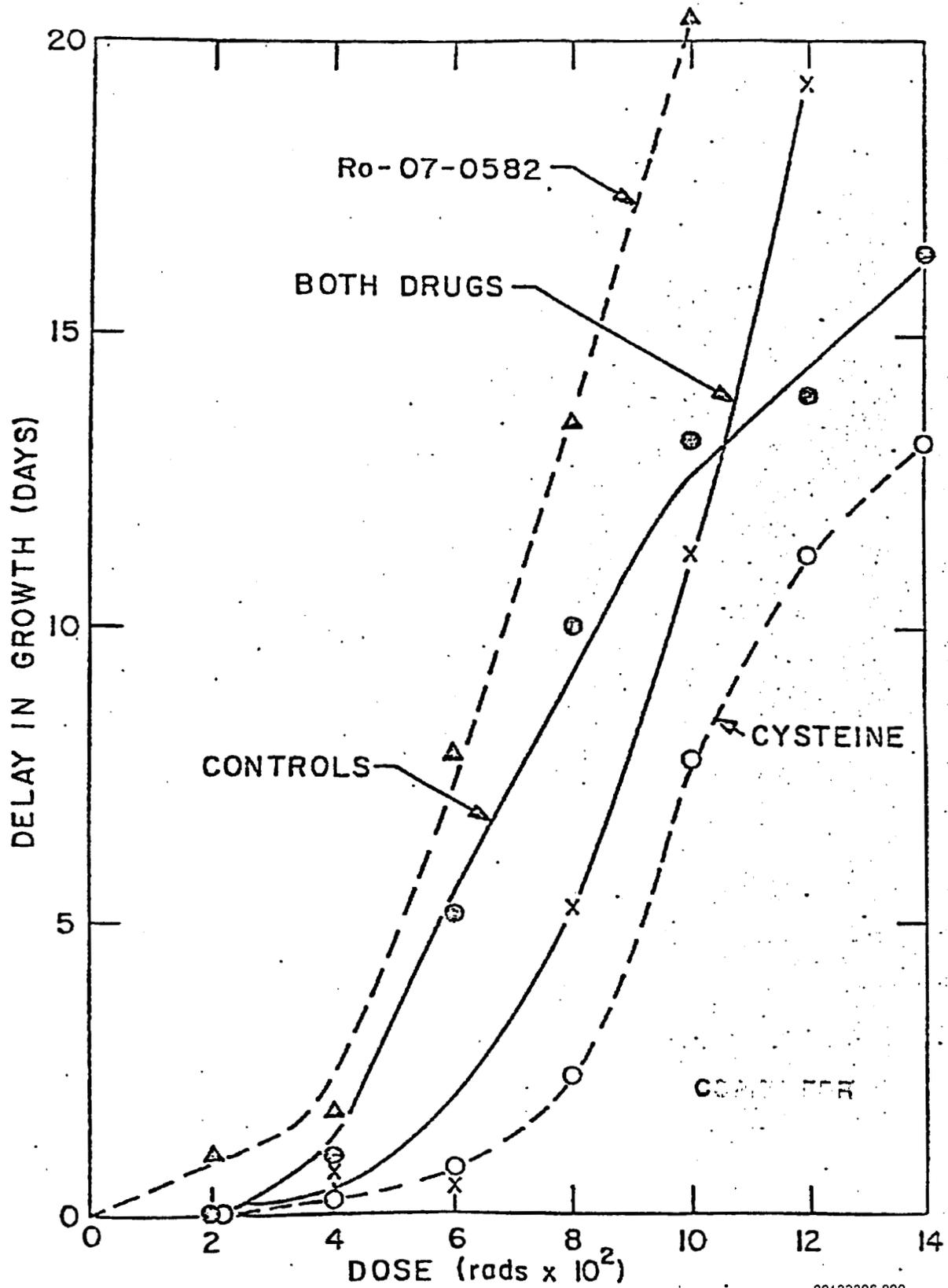


Figure 34. Radiation-induced growth delay, Line 1 lung carcinoma

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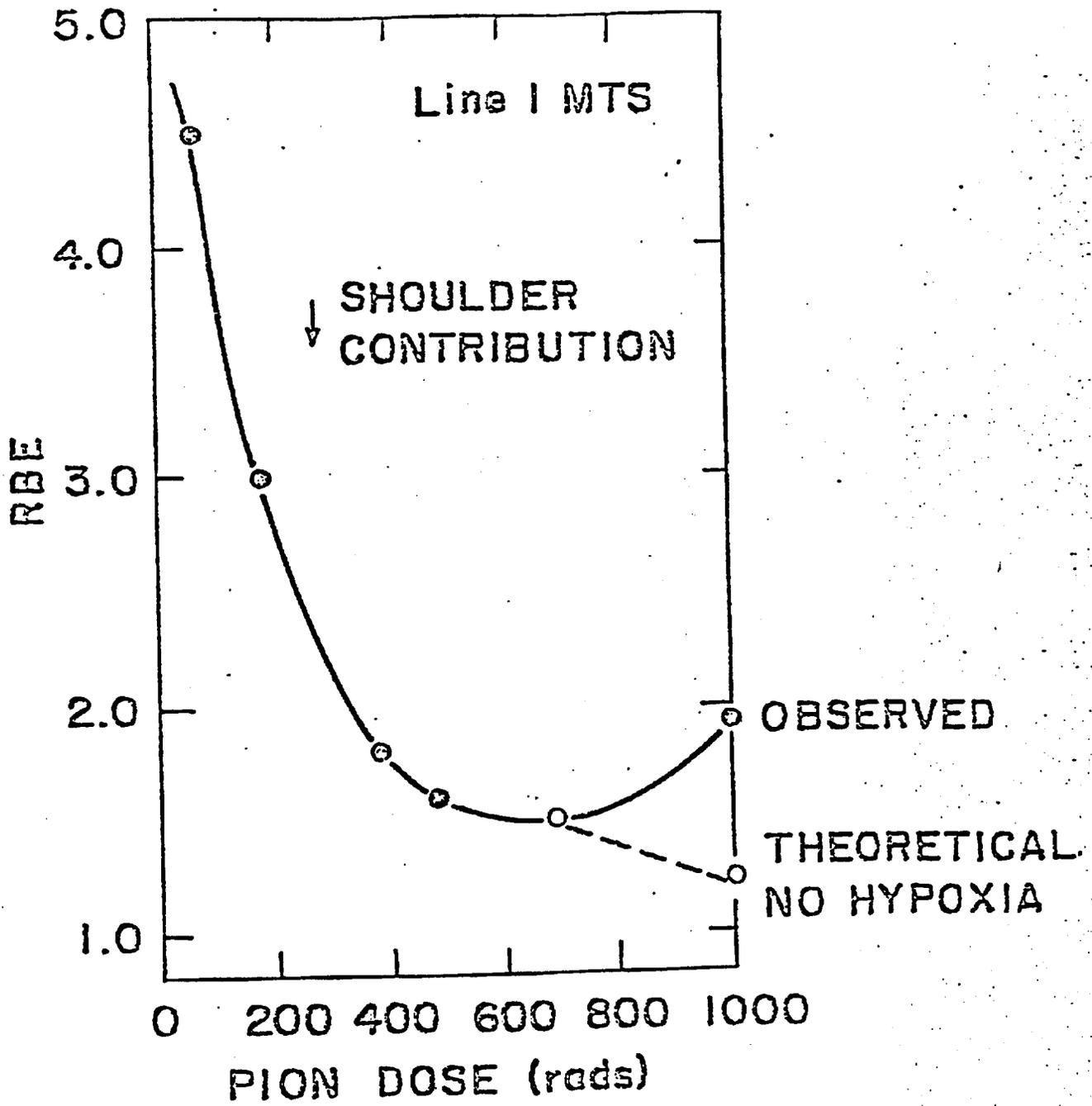


Figure 35. RBE as a function of pion dose for Line 1 lung carcinoma MTS.

LINE 1 CARCINOMA MTS

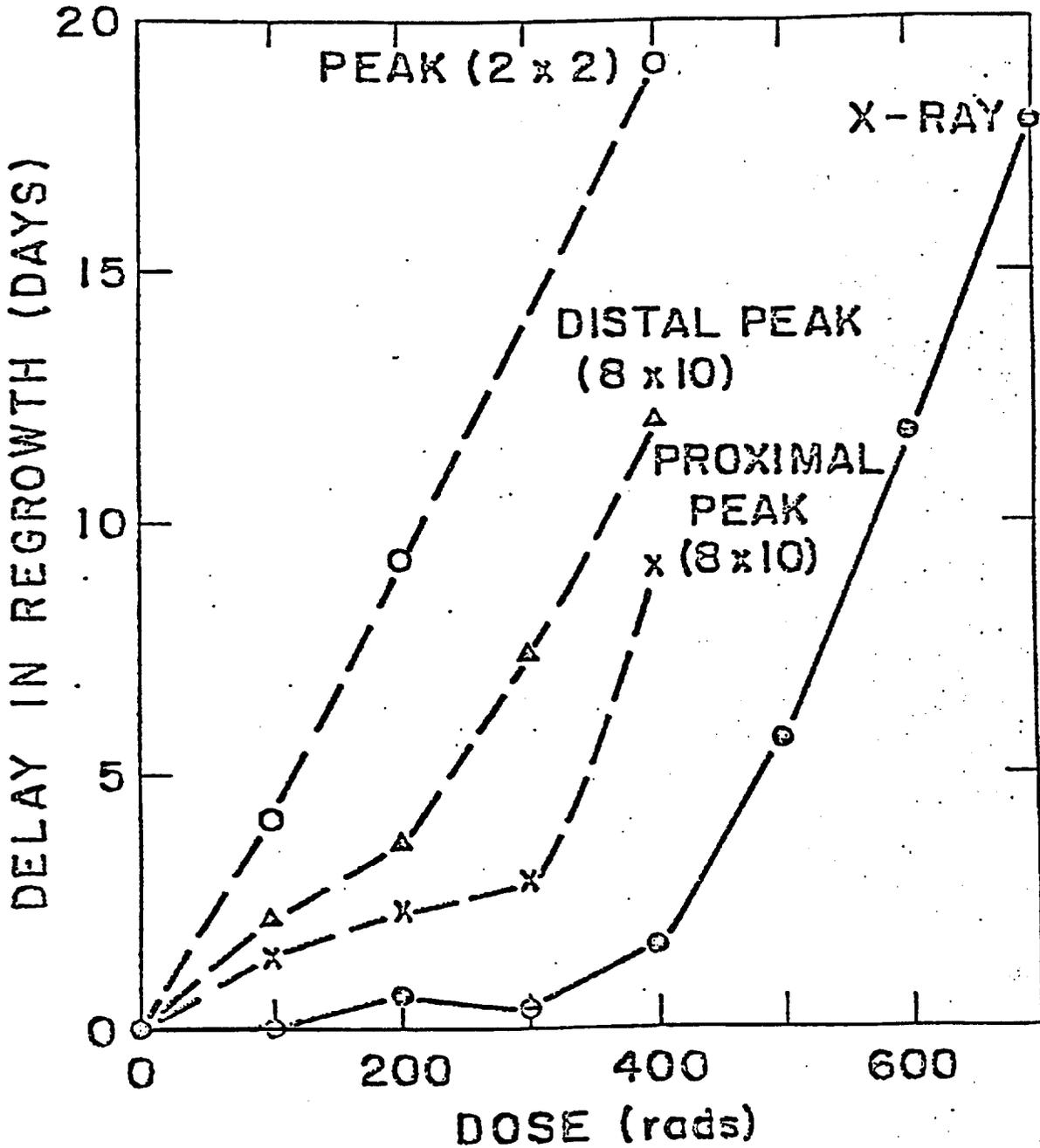


Figure 36. Growth delay, Line 1 lung carcinoma MTS, exposed to x-rays, pions (narrow peak), and pions (broad peak, distal region and proximal region).