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TITLE: UTILIZATION OF PION PRODUCTION ACCELERATORS IN BIOMEDICAL APPLICATIONS

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Biomedical Applications of Pion-Producing Accelerators

by

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ABSTRACT

A discussion will be presented of biomedical applications of pion-producing accelerators in a number of areas, but with emphasis on pion therapy for treatment of solid, non-metastasized malignancies.

The problem of cancer management will be described from the standpoint of the physicist, mangitude of the problem and its social and economic impact. Barriers to successful treatment will be identified, mainly with regard to radiation therapy.

The properties and characteristics of π mesons, first postulated on purely theoretical grounds by H. Yukawa will be described. Although these particles live but a very short time, $\sim \frac{2}{100,000,000}$ seconds. It will be shown how they can be used to treat human cancer and why they appear to have dramatic advantages over conventional forms of radiation by virtue of the fact that they permit localization of energy deposition, preferentially, in the tumor valume.

The Clinton P. Anderson Meson Physics Facility (LAMPF), and its operating characteristics, will be briefly described, with emphasis on the biomedical channel. The design of a relatively inexpensive accelerator specifically for pion therapy will be described as will also the status of clinical trials using the existing Clinton P. Anderson Meson Physics Facility. The advantages of proton over electron accelerator for the production of high quality, high intensity negative pion beams suitable for radiation therapy of malignancies will be addressed.

Other current, medically related applications of LAMPF technology will be discussed.

UTILIZATION OF PION PRODUCTION ACCELERATORS
IN BIOMEDICAL APPLICATIONS

INTRODUCTION

Not quite 50 years ago Professor Hidiki Yukawa postulated, on purely theoretical grounds, that in order to account for the stability and binding of atomic nuclei there must exist a particle of mass approximately 300 electron mass units and with strong interaction properties which would enable it to serve as the binding agent between the nucleons (neutrons and protons) in the atomic nucleus. This particle would serve as the quantum of the nuclear force field, just as the photon is required by quantum mechanics to be the quantum of the electromagnetic force field. For the next decade all efforts to find this particle were of no avail. But then in the latter half of the 1940's, when the Berkeley 184-inch cyclotron started to operate, this elusive particle was finally observed, and Professor Yukawa's brilliant prophesy and elegant mathematical formulation were completely vindicated. The reason it took so long to verify Professor Yukawa's theory is that the pi-meson does not normally appear in nature. It is a prisoner of the very nucleus which it binds together. It can, however, be made to materialize if enough energy is pumped into a nucleus, an amount of energy at least equivalent to its mass, something like 150 MeV. However, in order to pump this much energy into a nucleus requires large particle accelerators that can produce protons of several hundred MeV. In fact, in order to set free large numbers of pi-mesons requires incident protons of energy 500 MeV or more.

So we know that pi-mesons can be manufactured from energy, and that they are the messengers of the strong nuclear force -- that force which gives to atomic nuclei their great stability and to nuclear reactions their great violence. So here we have deduced one of the great scientific mysteries of all time -- we have been granted a window on the working of nature which only a few decades ago would have seemed inconceivable. We have identified a particle which is intimately involved with one of the four natural forces -- a particle which is smaller than a proton or neutron, which themselves have a radius of one ten thousandth of a billionth of a centimeter -- a truly phenomenal achievement. As you know, for all of these developments, Professor Yukawa received the Nobel Prize.

But the exciting part of the story is only now beginning to unfold. Before I talk more about pions, let me say something about a quite different problem, a very serious human problem.

II. THE PROBLEM OF CANCER

Cancer is a disease which afflicts one person in four sometime during their lifetime, and one person in five succumbs to this disease. This is true in the USA and also in Japan. In the USA, the leading cancer sites are shown in Fig. 1. In the USA about 700,000 patients per year are under treatment for cancer. More than half of these are treated with X or gamma radiation either as the primary modality or in combination with surgery and/or chemotherapy. Treatment is successful in about half the cases. The cost of cancer in human suffering is immeasurable. The monetary cost is also high -- about $20,000 per patient when the treatment is successful and about $45,000 per patient when the treatment fails.

If now you ask the question of why radiation therapy is successful only about half the time, you find that quite frequently the difficulty resides in the inability of the therapist to provide enough radiation to the tumor for its sterilization without at the same time giving an unacceptable dose to healthy tissues and organs in the vicinity of the tumor. The situation is illustrated by Fig. 2. Here we plot tissue response vs. radiation dose for healthy and cancerous tissue. The separation of the curves is arbitrary. The point I wish to illustrate is that quite often, in order to irradiate at levels where tissue response of cancer cells (solid curve) approaches 100%, one would be obliged to accept very serious tissue response in the healthy cells (dashed curve). Obviously, one would like a means of irradiating the tumor volume with a tumoricidal dose while limiting the dose to healthy tissue to a relatively low value. I will call this dose localization. But we want to accomplish something else. It is an unfortunate consequence of the cancer process that in many tumors there exist islands of cells which are anoxic -- they have a deficiency of free oxygen. Such cells are much more resistent to X or gamma radiation than are healthy cells, which is precisely what one does not want. It is known, however, that the so-called oxygen effect decreases in severity as the specific ionization, or linear energy transfer, increases. An ideal radiation modality would, therefore, be one that localizes high LET radiation to the tumor volume.

III. THE ROLE OF PI-MESONS IN THE TREATMENT OF CANCER

The pi-meson is an esoteric, shortlived particle which does not occur in nature, except as a product of high-energy nuclear interactions. Once it is produced, it interacts with matter just as any charged particle except at the end of its range. As we see in Fig. 3, a negative pi-meson behaves quantum mechanically like an electron. It executes orbits around a nucleus. However, because its mass is 300 times that of an electron, the orbits are smaller in that ratio, so much so that when the pion achieves the innermost orbit, it is captured by the nucleus and causes the nucleus to explode, as seen in Fig. 4. The nuclear shrapnel from this explosion travel very short distances, about 1 mm on the average, and are very effective in rendering cells non-productive. Figure 5 illustrates the cell-killing capability of negative pions, as a function of their range. Figure 6 shows a typical depth dose distribution from the LAMPF biomedical channel, and Fig. 7 shows how this distribution can be tailored (tuned) to provide either a flat physical dose or a flat biological dose.

Figure 8 shows a comparison of depth-dose distribution for various types of radiation, from which you can see that pions provide the best possible localization of energy deposition. The pions are collected, purified and transported by a magnetic channel, as shown in Fig. 9. The way the pions are applied is shown in Fig. 10. A critical component is a computer-controlled range-shifter, Fig. 11, which permits a predetermined distribution of stopped pions throughout the volume being treated. Figure 12 shows a patient undergoing treatment. Figure 13 shows a two-port treatment plan for a tumor of the pancreas and how pions permit avoiding critical structures. Thus far over 100 patients have been treated with encouraging results. Randomized clinical trials will start late this year.

Figure 14 summarizes the advantages of negative pions for radiation therapy. The in-treatment monitoring of the treatment volume will be accomplished as shown in Fig. 15.

IV. PIGMI

A substantial effort, sponsored by the National Cancer Institute (NCI) is currently underway to develop a small facility for pion therapy. In this effort we have the collaboration of some very good Japanese scientists, just as we have collaboration of Japanese physicians in carrying out our clinical trials.

Figure 16 is a schematic representation of the pion generator under development, identifying its major characteristics. Figure 17 is an artist's conception of how such a facility would fit under a hospital parking lot. Development work is proceeding well, and we expect that within the next 12-16 months we shall have tested the critical components of such an accelerator.

We recently had a pleasant visit from Dr. Sasumi Haniuda, the Japanese Parliamentary Vice-Minister for Science and Technology. Figure 18 shows him and Dr. Kondo, a very gifted radiotherapist, in front of the LAMPF Biomedical Building where the clinical trials with pions are being conducted. Figure 19 shows our Japanese visitors as they are about to depart. Figure 20 shows Dr. Kondo and Dr. Kligerman with a patient who is under treatment.

V. LAMPF

I wish to conclude by showing you the overall LAMPF program, Figure 21. You can see that LAMPF does a great many things besides pion therapy. Figure 22 shows an aerial view of LAMPF. Figure 23 summarizes the practical applications at LAMPF. Figure 24 shows our remote maintenance robot which we expect will be very useful in the reactor industry. Figure 25 is a device we have developed for treating superficial tumors in animals. It looks as in Fig. 26 and has been most effective in the treatment of cancer eye in cattle, as can be seen from Fig. 27. I am hopeful that this device or a derivative thereof will prove useful for making available localized rf heating therapy for superficial tumors to large areas of the world where more advanced methods are not feasible.

In the LAMPF beam stop area, we have an isotope production facility. It looks schematically as in Fig. 28. Figures 29 and 30 identify some of the isotopes presently under production, and their uses. I have described how high energy accelerators, which only a few years ago were thought to have no practical application, are being applied to the betterment of human life. Although not all of us will agree completely on the purpose of human existence, certainly most of us would subscribe to the thesis that developing ways to ameliorate human suffering must be an absolute good. Radioisotopes are facilitating the diagnosis and treatment of many diseases on a monumental scale. I am hopeful that, someday, pion therapy will make a comparable contribution to the management of cancer.

FIGURE CAPTIONS

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AUTHOR: LOUIS ROSEN

Fig. 1. Cancer Statistics.

Fig. 2. General relationship between probability of local tumor control or production of moderate to severe complications as a function of Co-60 dose in rads.

Fig. 3. Schematic representation of the capture of a negative pion by ^{16}O.

Fig. 4. Capture of a π^- by an oxygen nucleus in a photographic emulsion.

Fig. 5. Survival of T_1 kidney cells for a negative pion beam compared with the relative dose as a function of depth. Corresponding data for 250 kVp x rays are also shown.

Fig. 6. Relative dose as a function of depth for a π^- beam with a relatively narrow spread in momentum.

Fig. 7. Depth dose curves for the original narrow beam and two beams broadened as a function of depth in order to produce large treatment volumes.

Fig. 8. Depth dose distributions for various types of radiations.

Fig. 9. The magnetic channel for the Biomedical Facility at LAMPF.

Fig. 10. A schematic illustration of a typical patient treatment.

Fig. 11. LASL Biomedical range shifter and jib boom drive.

Fig. 12. Patient undergoing treatment with a pion beam at the LAMPF Biomedical Facility.

Fig. 13. Isodose contours for two overlapping fields of negative pions.

Fig. 14. Potential advantages of π^- mesons for radiation therapy.

Fig. 15. A technique for the visualization of the irradiated volume during treatment.

Fig. 16. Pion Generator for Medical Irradiation (PIGMI) under development at LASL.

Fig. 17. A conceptual layout of a PIGMI Facility in a medical center.

Fig. 18. Shown from left to right are Dr. Louis Rosen with distinguished visitors from Japan -- Dr. Sasumi Haniuda and Dr. Makoto Kondo -- in front of the Biomedical Facility at LAMPF.

Fig. 19. Drs. Rosen and Kondo with Japanese visitors prior to departure from Los Alamos.

Fig. 20. Dr. Morton Kligerman and Dr. Kondo treating patient at LAMPF Biomedical Facility.

Fig. 21. Fields of research at LAMPF.

Fig. 22. Aerial view of LAMPF.

Fig. 23. Practical applications at LAMPF.

Fig. 24. Remote maintenance robot used in conjunction with the LAMPF accelerator.

Fig. 25. A schematic representation of a hyperthermia technique developed at LAMPF for the treatment of superficial tumors.

Fig. 26. A compact instrument developed at LAMPF for the effective treatment of cancer eye in cattle.

Fig. 27. Typical results of the treatment of bovine cancer eye with hyperthermia.

Fig. 28. A schematic drawing of the Isotope Production Facility at LAMPF.

Fig. 29a. Radionuclides being produced at LAMPF along with their application
Fig. 29b. in research, medicine and industry.

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CANCER STATISTICS

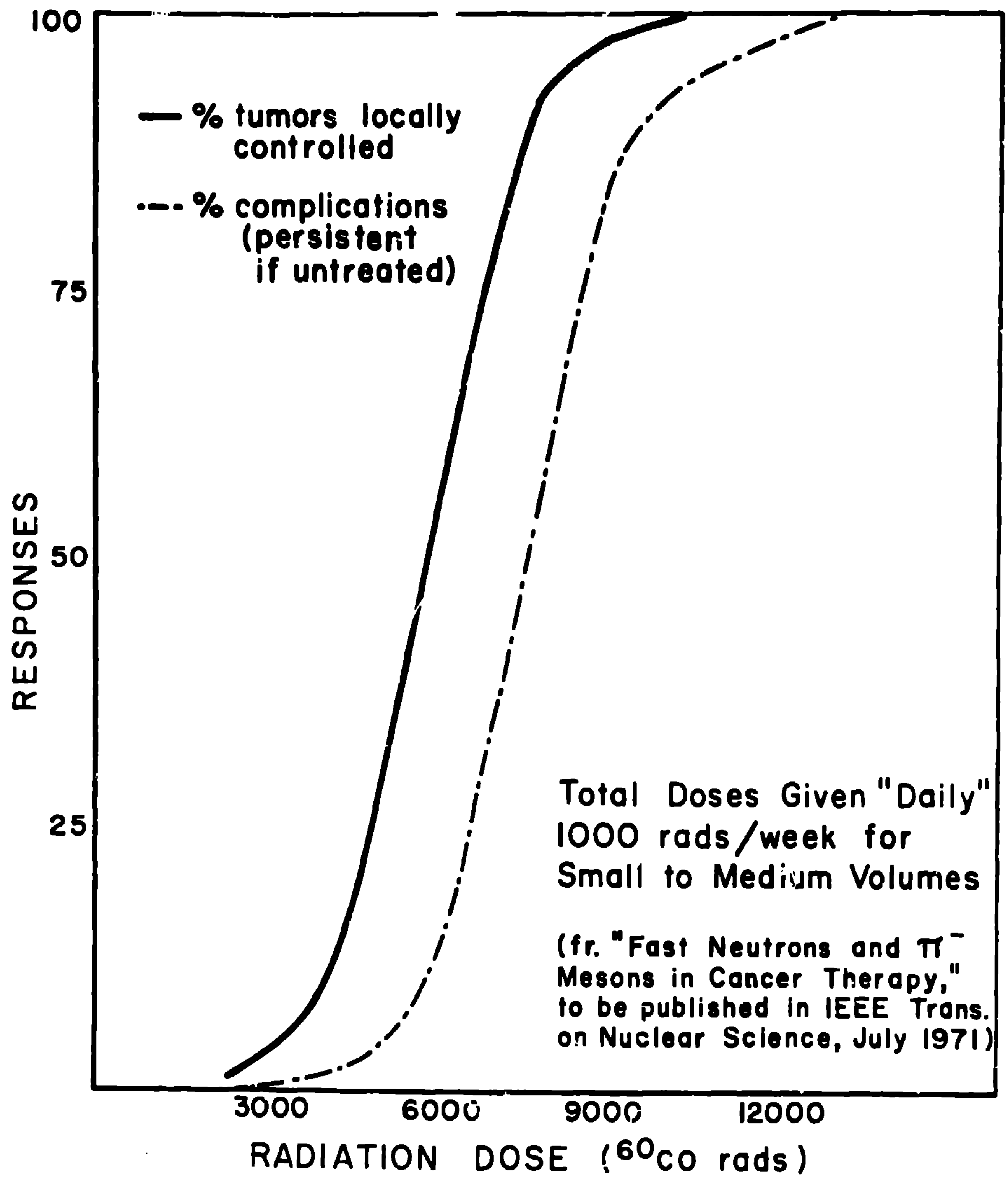
CANCER RISK FOR U.S. POPULATION	EXPECTED NEW CASES IN '70	NO. OF CANCER PATIENTS UNDER CARE IN 1970	EXPECTED NO. DEATHS IN '70	SURVIVAL RATE WITH CURRENT THERAPY
1 in 4 persons	625,000	960,000	330,000 (1/2 less than 65 yrs of age)	1 in 3 persons

<u>LEADING CANCER SITES IN 1970</u>

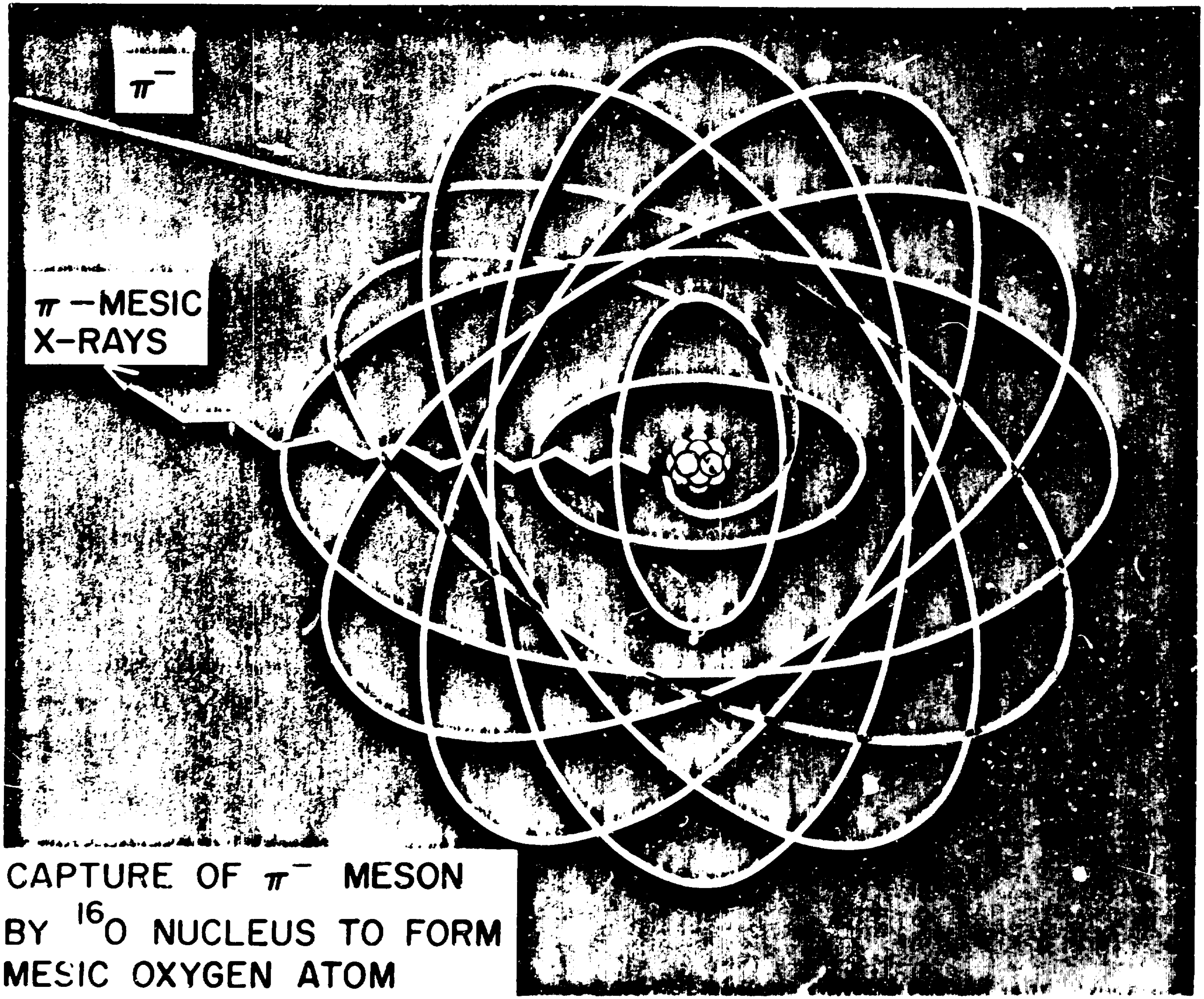
Skin	-- 112,000	Kidney & Bladder	-- 32,000
Colon-Rectum	-- 75,000	Lymphomas	-- 23,000
Breast	-- 69,000	Leukemia	-- 19,000
Lung	-- 68,000	Stomach	-- 17,000
Uterus	-- 42,000	Head & Neck	-- 14,000
Prostate	-- 35,000	Larynx	-- 7,000

Of above 12 cancer sites, 9 are treated primarily by X-ray therapy.

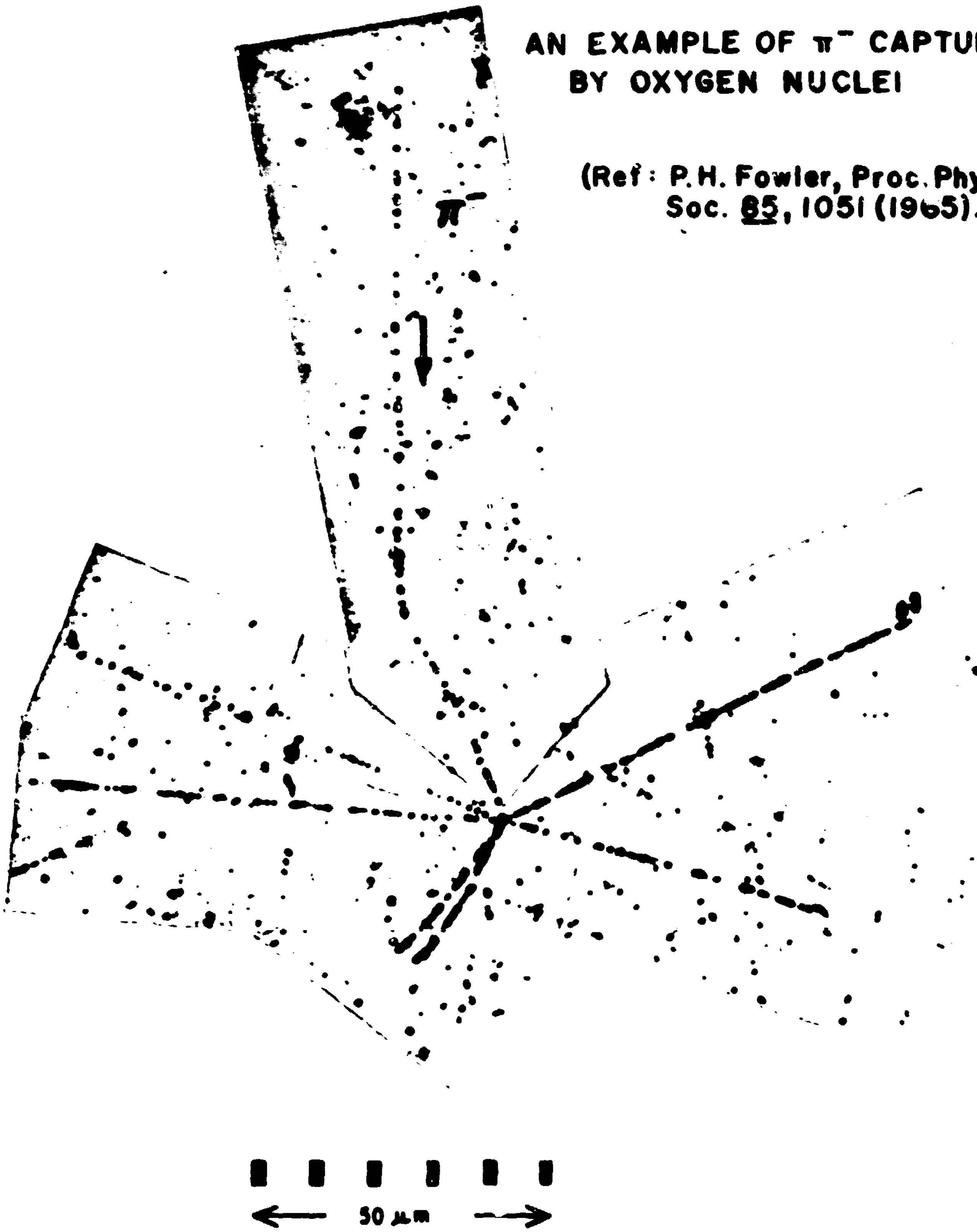
(Source: 1970 Cancer Facts and Figures, published by the American Cancer Society.)



100
75
50
25
RESPONSES
— % tumors locally controlled
·—· % complications (persistent if untreated)
Total Doses Given "Daily" 1000 rads/week for Small to Medium Volumes
(fr. "Fast Neutrons and π⁻ Mesons in Cancer Therapy," to be published in IEEE Trans. on Nuclear Science, July 1971)
3000
6000
9000
12000
RADIATION DOSE (60CO rads)

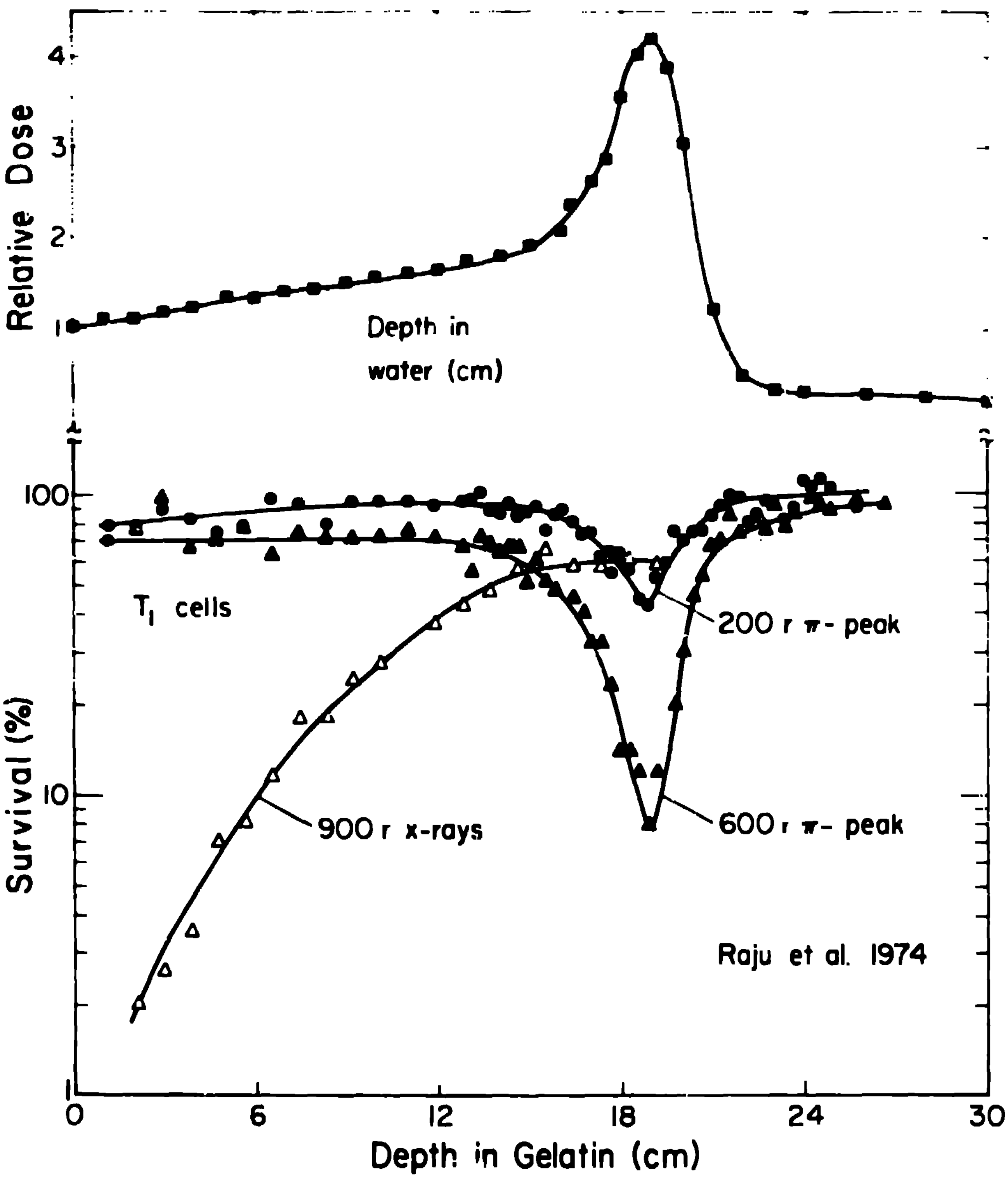


CAPTURE OF π^- MESON BY ^{16}O NUCLEUS TO FORM MESIC OXYGEN ATOM

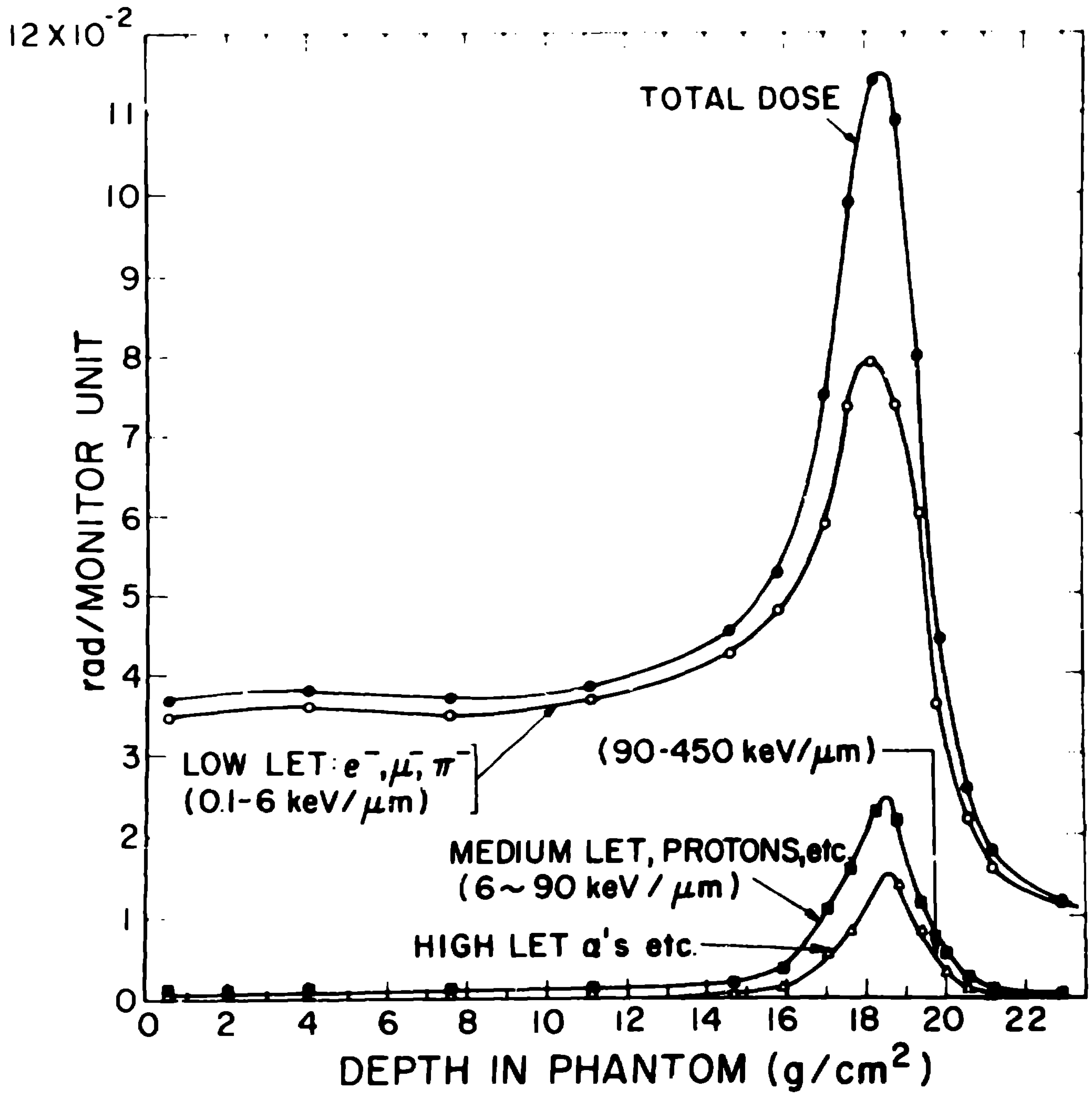


AN EXAMPLE OF π^- CAPTURE BY OXYGEN NUCLEI

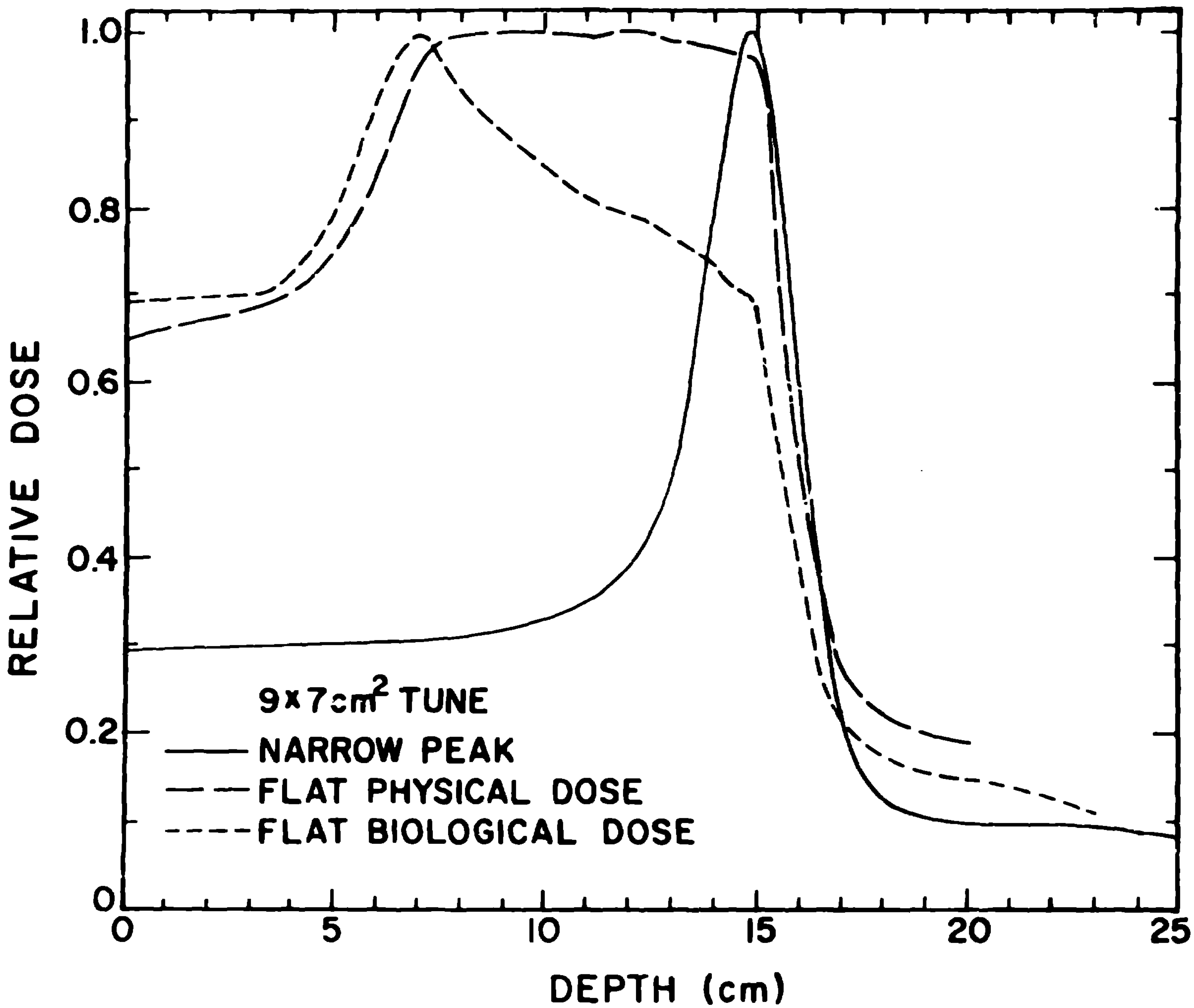
(Ref: P.H. Fowler, Proc. Phys. Soc. 85, 1051 (1965).)



Relative Dose
4
3
2
1
Depth in
water (cm)
100
10
1
T1 cells
200 r π- peak
600 r π- peak
900 r x-rays
Raju et al. 1974
Survival (%)
0
6
12
18
24
30
Depth in Gelatin (cm)

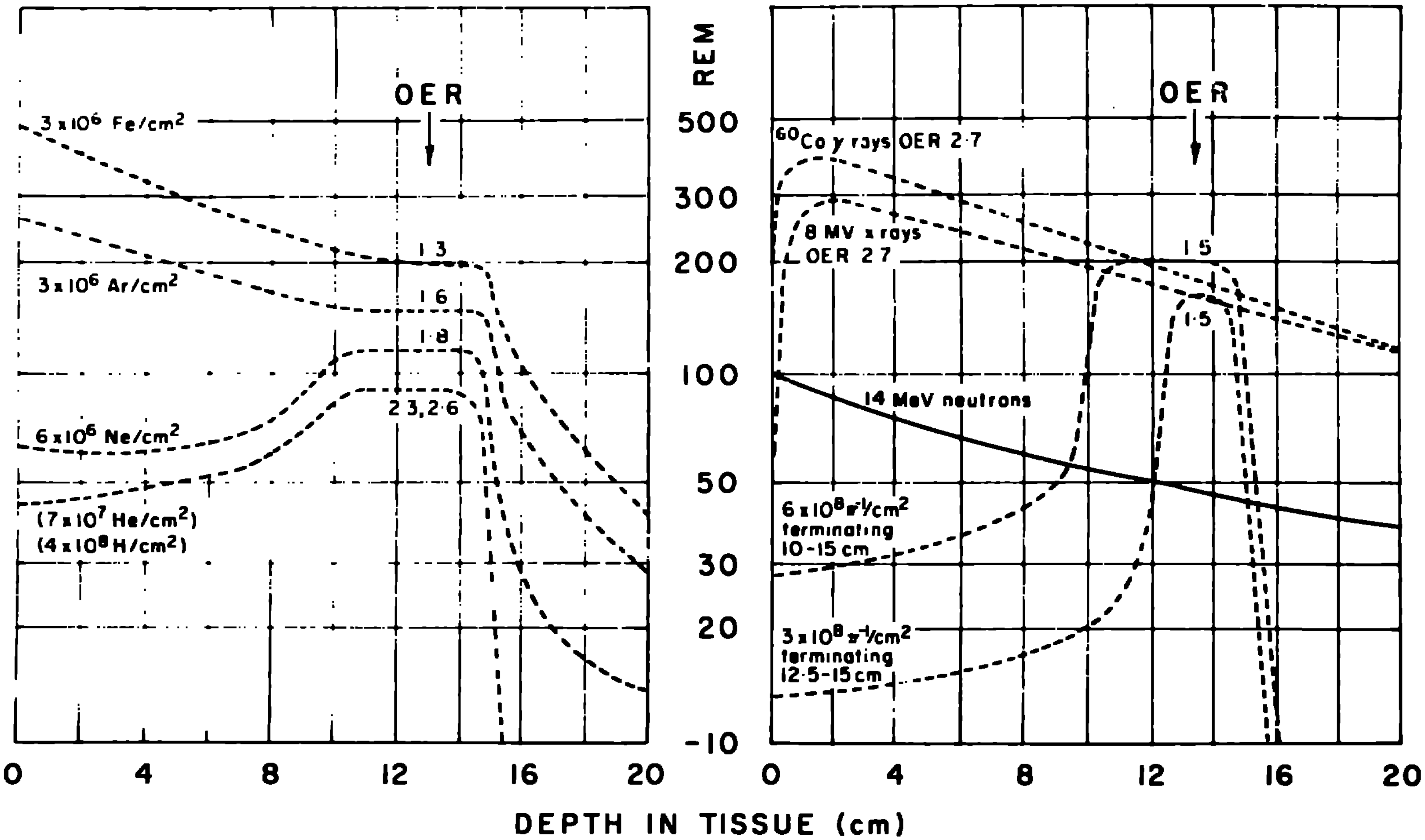


12 X 10⁻²
11
10
9
8
7
6
5
4
3
2
1
0
rad/MONITOR UNIT
TOTAL DOSE
LOW LET: e⁻, μ⁻, π⁻
(0.1-6 keV/μm)
(90-450 keV/μm)
MEDIUM LET, PROTONS, etc.
(6 ~ 90 keV / μm)
HIGH LET α's etc.
0
2
4
6
8
10
12
14
16
18
20
22
DEPTH IN PHANTOM (g/cm²)



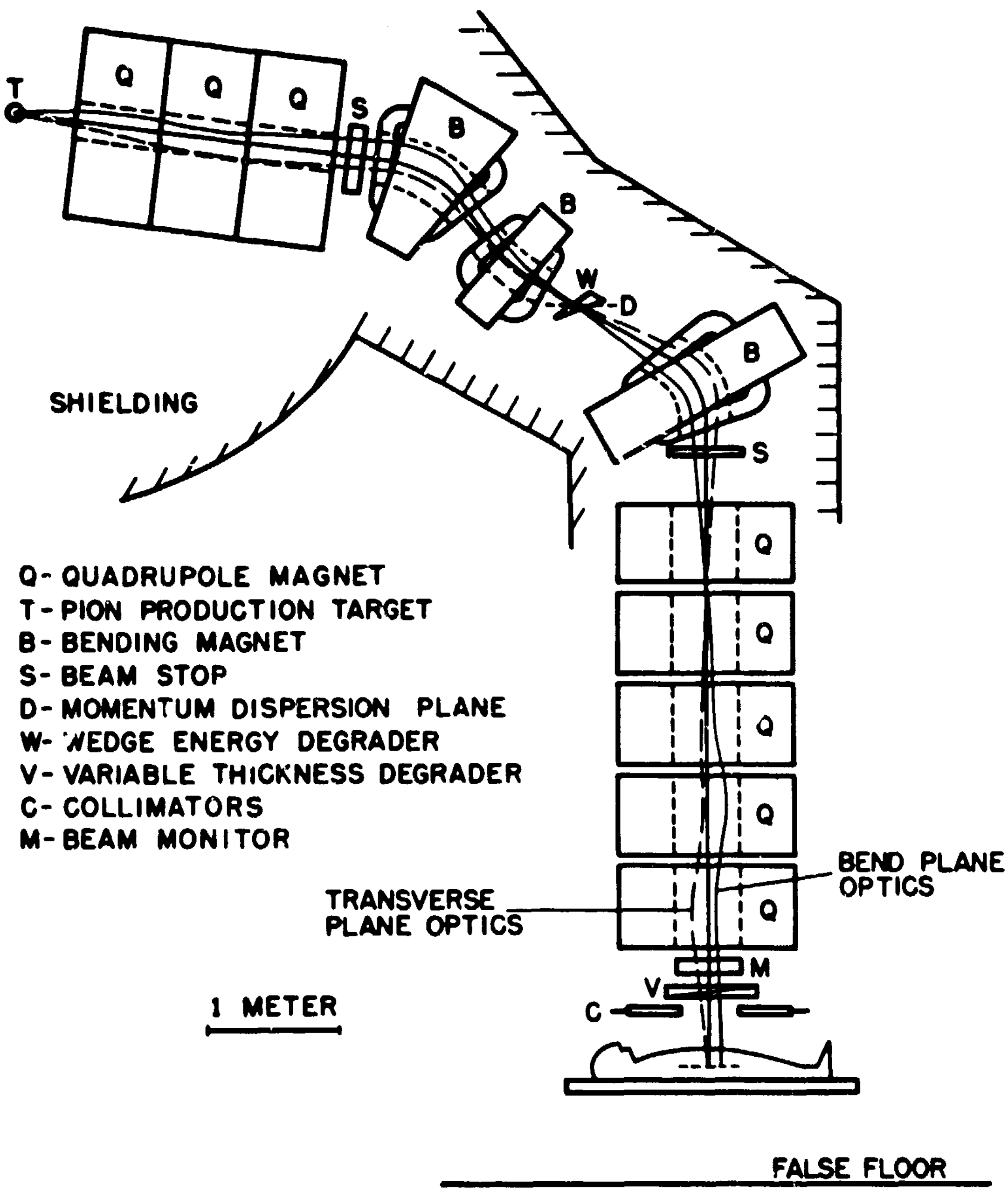
1.0
0.8
0.6
0.4
0.2
0
RELATIVE DOSE
0
5
10
15
20
25
DEPTH (cm)
9×7cm² TUNE
NARROW PEAK
FLAT PHYSICAL DOSE
FLAT BIOLOGICAL DOSE

DEPTH DOSE DISTRIBUTIONS



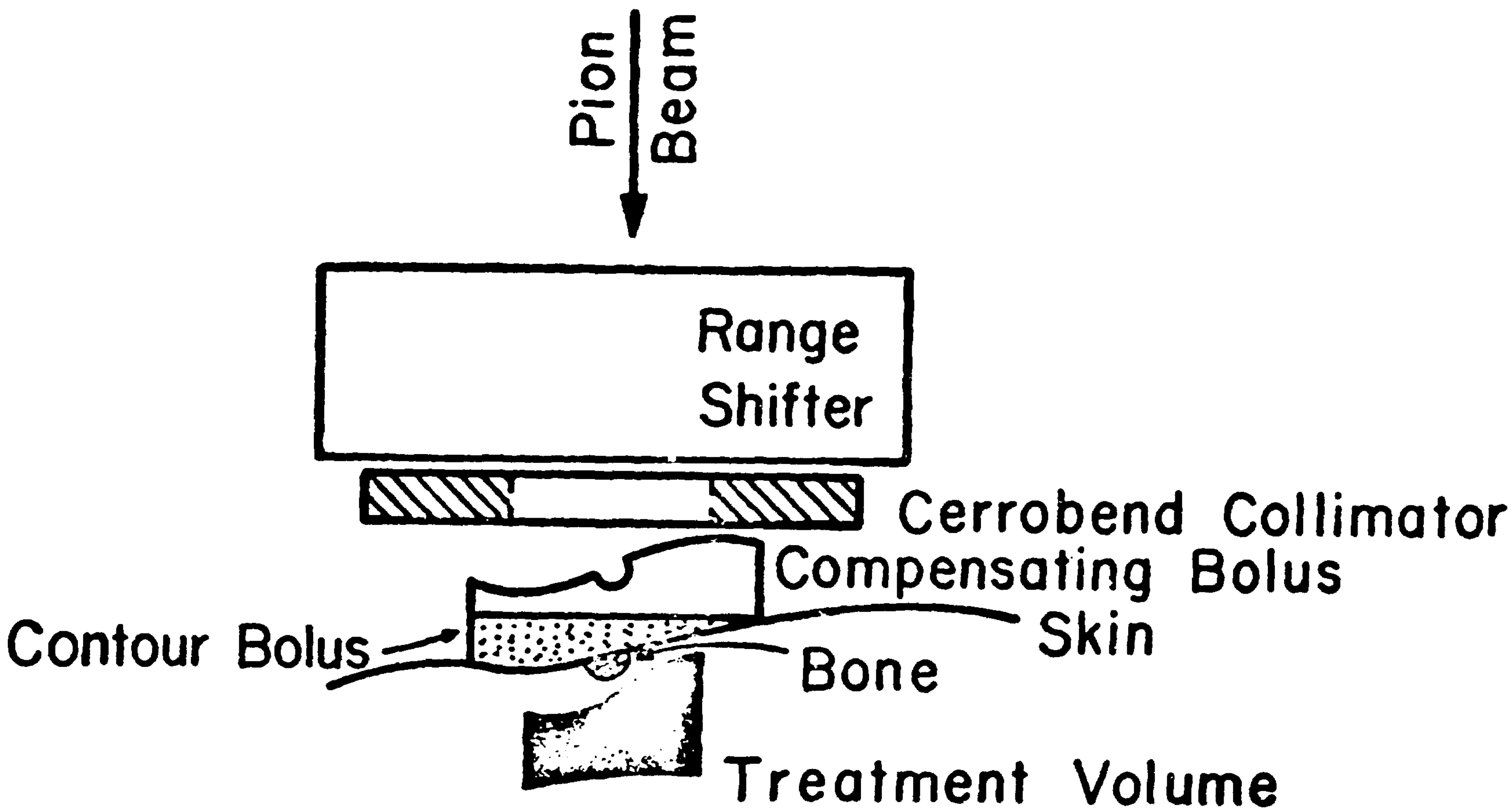
---- (Fowler, Proc. Phys. Soc. 85, 1051 (1965))

——— (Horst and Conrad, Fortschritte auf dem Gebiete der Röntgenstrahlen u der Nuklearmedizin, Diagnostik, Physik, Biologie, Therapie 105, 299 (1966))



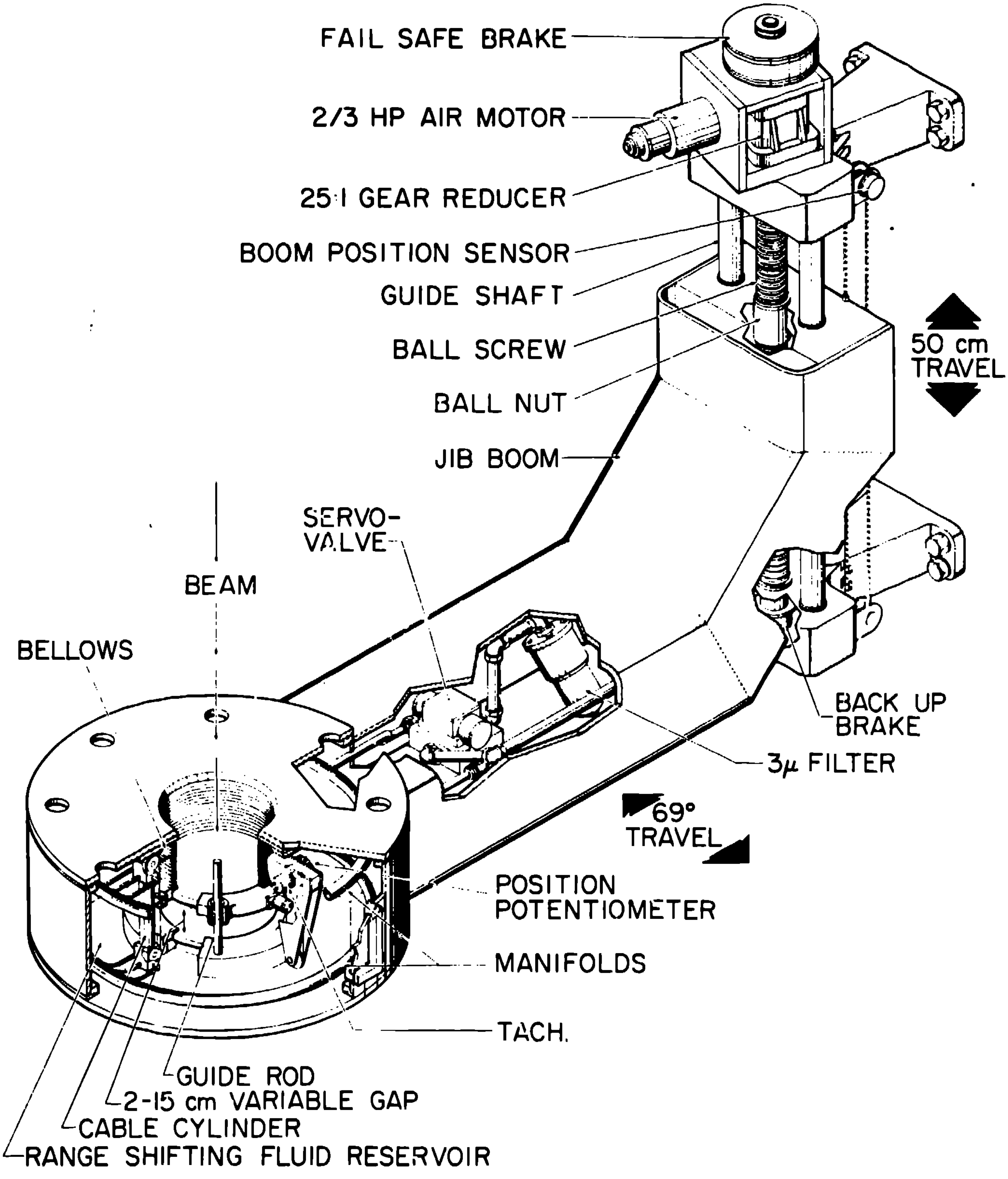
THE LOS ALAMOS MESON PHYSICS FACILITY
BIOMEDICAL PION CHANNEL

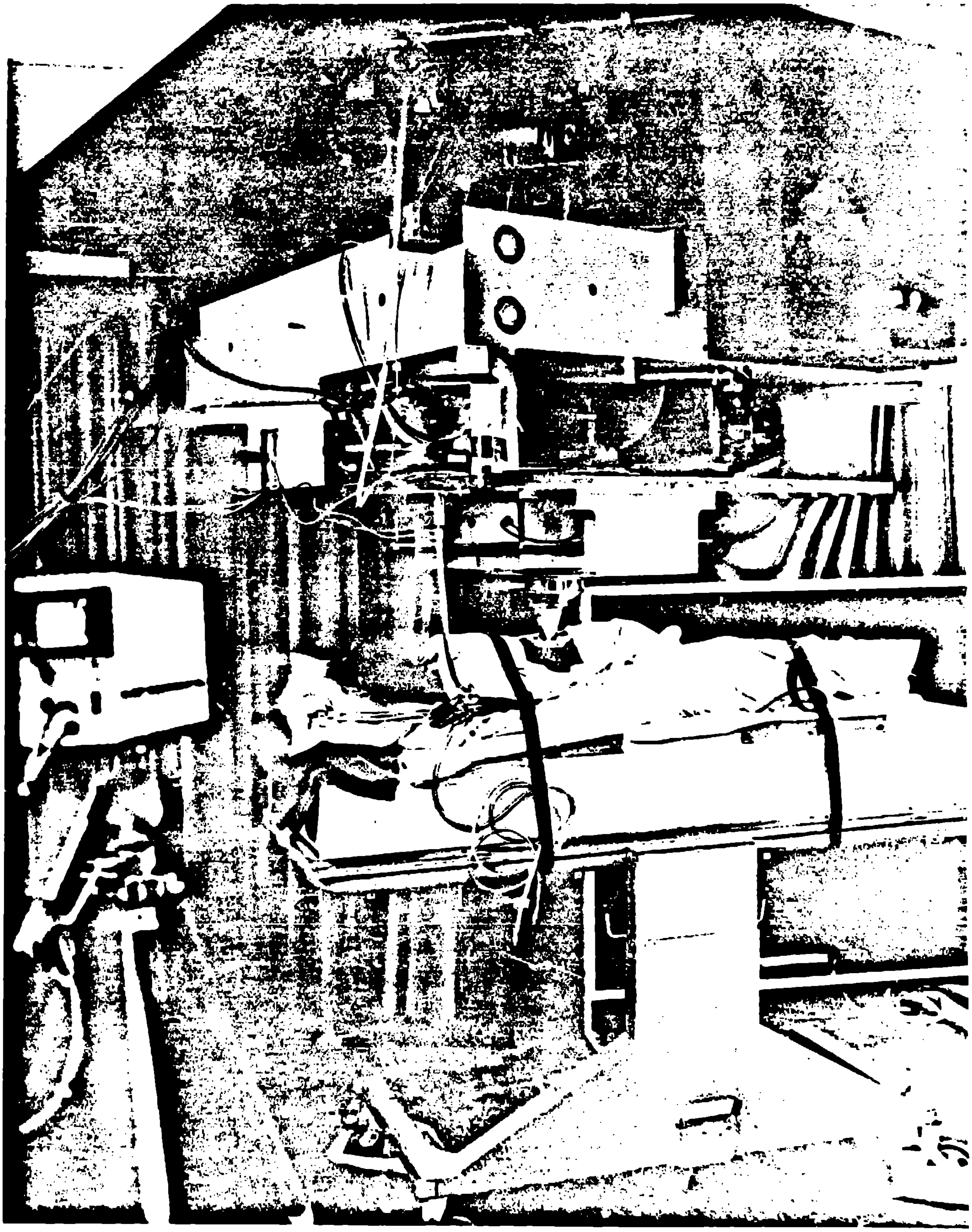
STUBOUT FLOOR

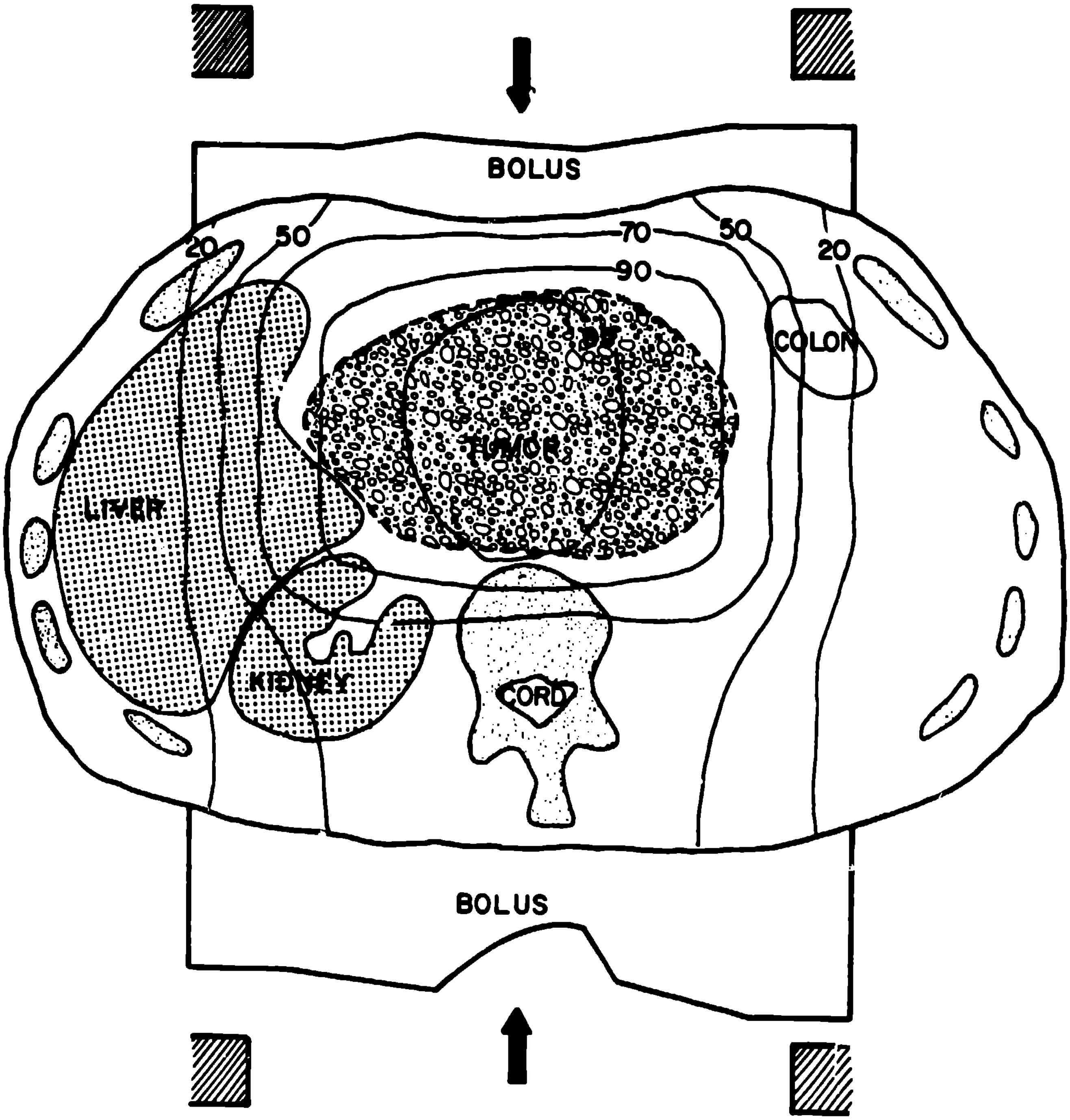


Pion
Beam
Range
Shifter
Cerrobend Collimator
Compensating Bolus
Contour Bolus
Skin
Bone
Treatment Volume

LASL BIOMEDICAL RANGE SHIFTER AND JIB BOOM DRIVE



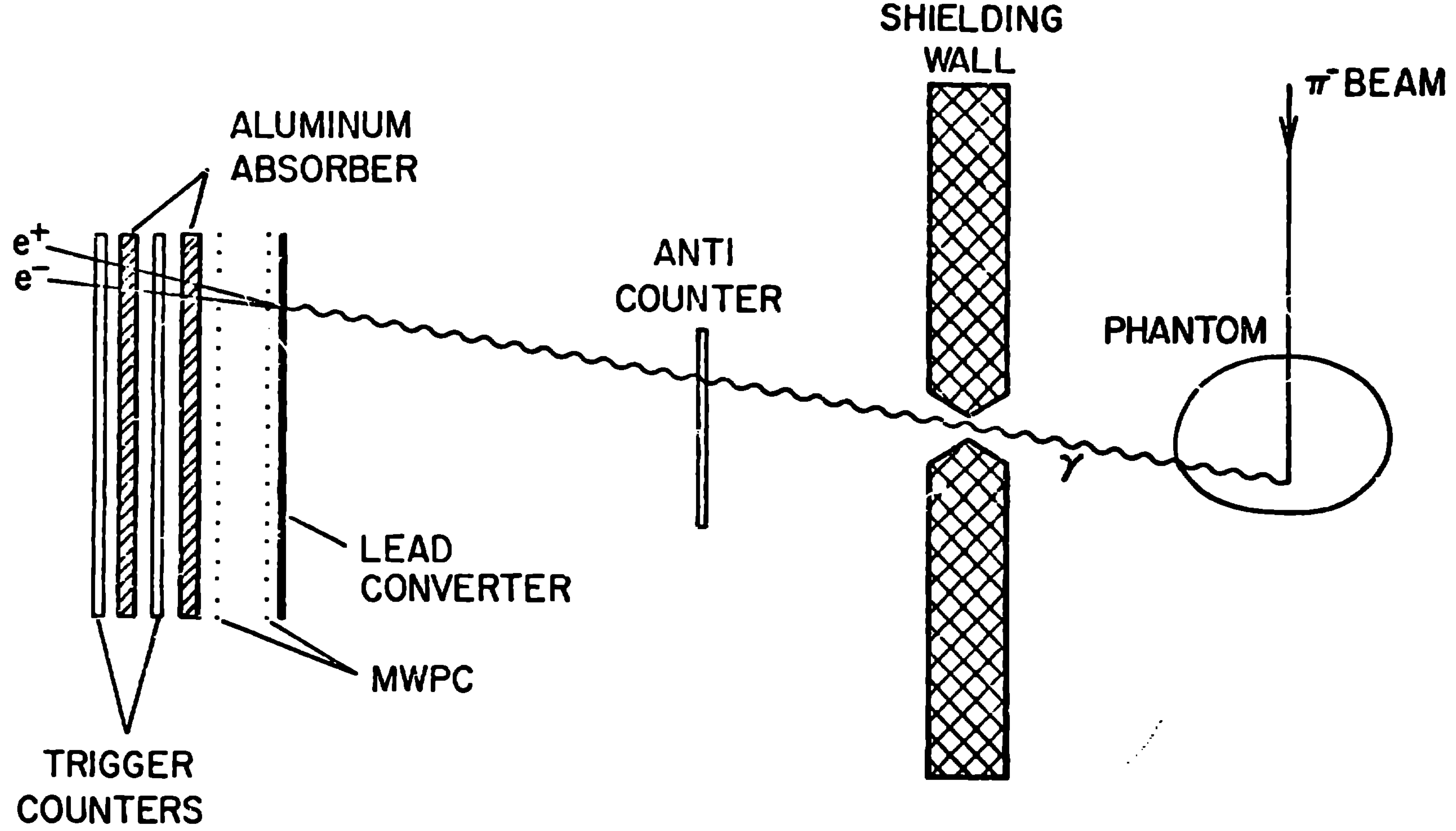



BOLUS
20
50
70
50
90
20
COLON
TUMOR
LIVER
KIDNEY
CORD
BOLUS

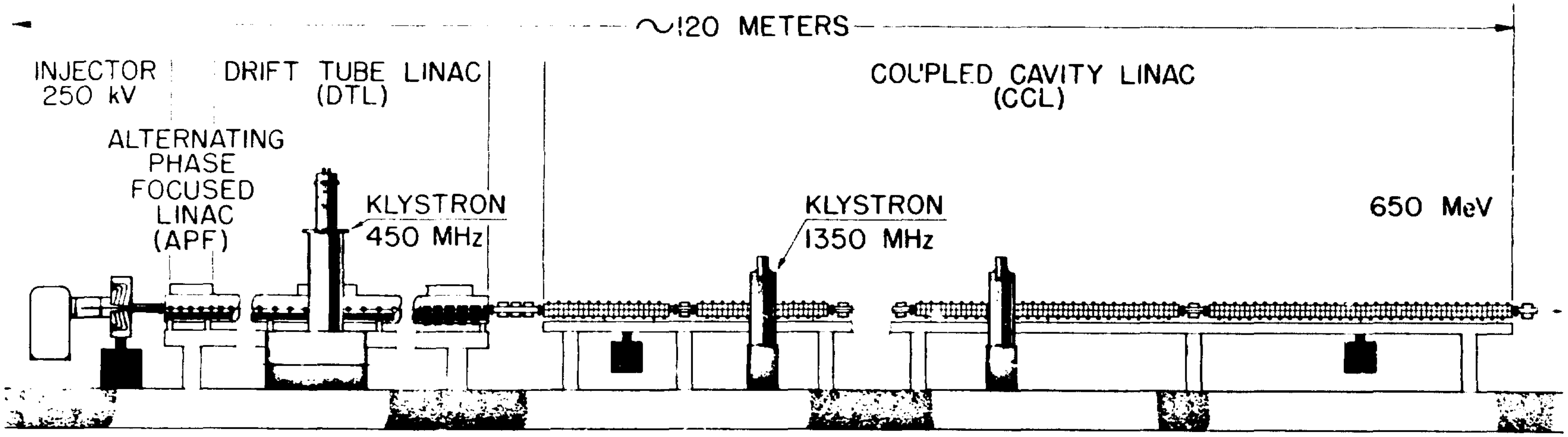
POTENTIAL OF π^- MESONS FOR THERAPY

1.	Depth-to-entrance dose ratio	favorable (2-3/1)
2.	Exit dose	highly favorable
3.	RBE (terminal portion)	favorable (2-3)
4.	RBE (plateau region)	highly favorable (1 or less)
5.	OER (terminal portion)	favorable (about 1.6)
6.	OER (plateau region)	favorable (about 2.7)
7.	Beam control (computerized)	highly favorable
8.	Beam shaping (dose, dose equivalent or effective dose)	possible
9.	*In situ* monitoring of treatment volume	possible

STOPPED PION VISUALIZATION



PION GENERATOR FOR MEDICAL IRRADIATION (PIGMI)



MAJOR TECHNICAL INNOVATIONS

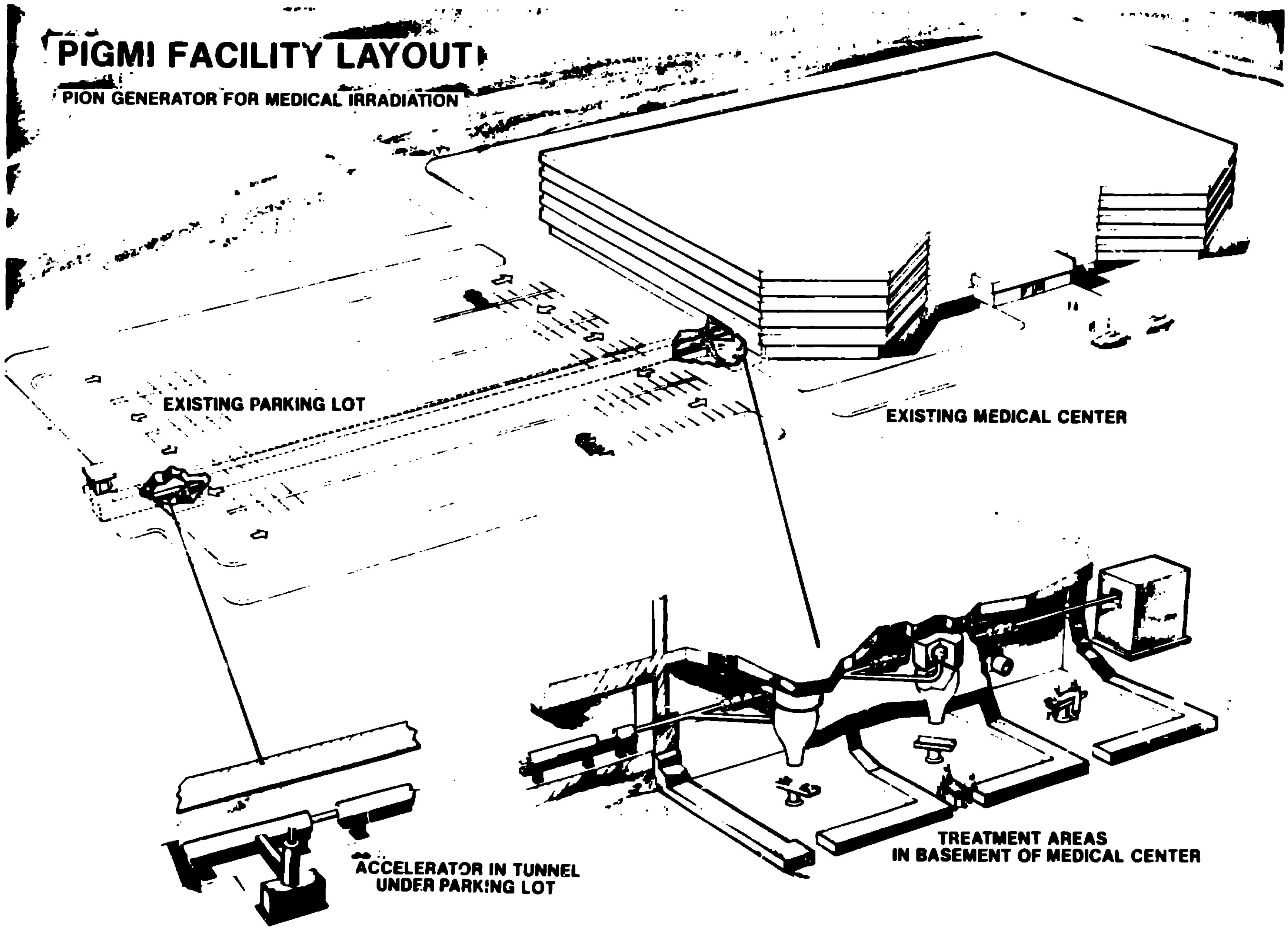
HIGHER FREQUENCY
HIGHER GRADIENT
ALTERNATING PHASE FOCUSING
LOWER INJECTION ENERGY
DOUBLE HARMONIC BUNCHER
PERMANENT-MAGNETIC QUADRUPOLES
DISK & WASHER LINAC STRUCTURE
RF MANIFOLD POWER DISTRIBUTION
DISTRIBUTED MICROPROCESSOR CONTROL

PROTON BEAM PARAMETERS

INJECTION ENERGY	250 keV
FINAL ENERGY	650 MeV
PEAK BEAM CURRENT	30 mA
PULSE LENGTH	10 μs
REPETITION RATE	360 Hz
AVERAGE BEAM CURRENT	100 μA

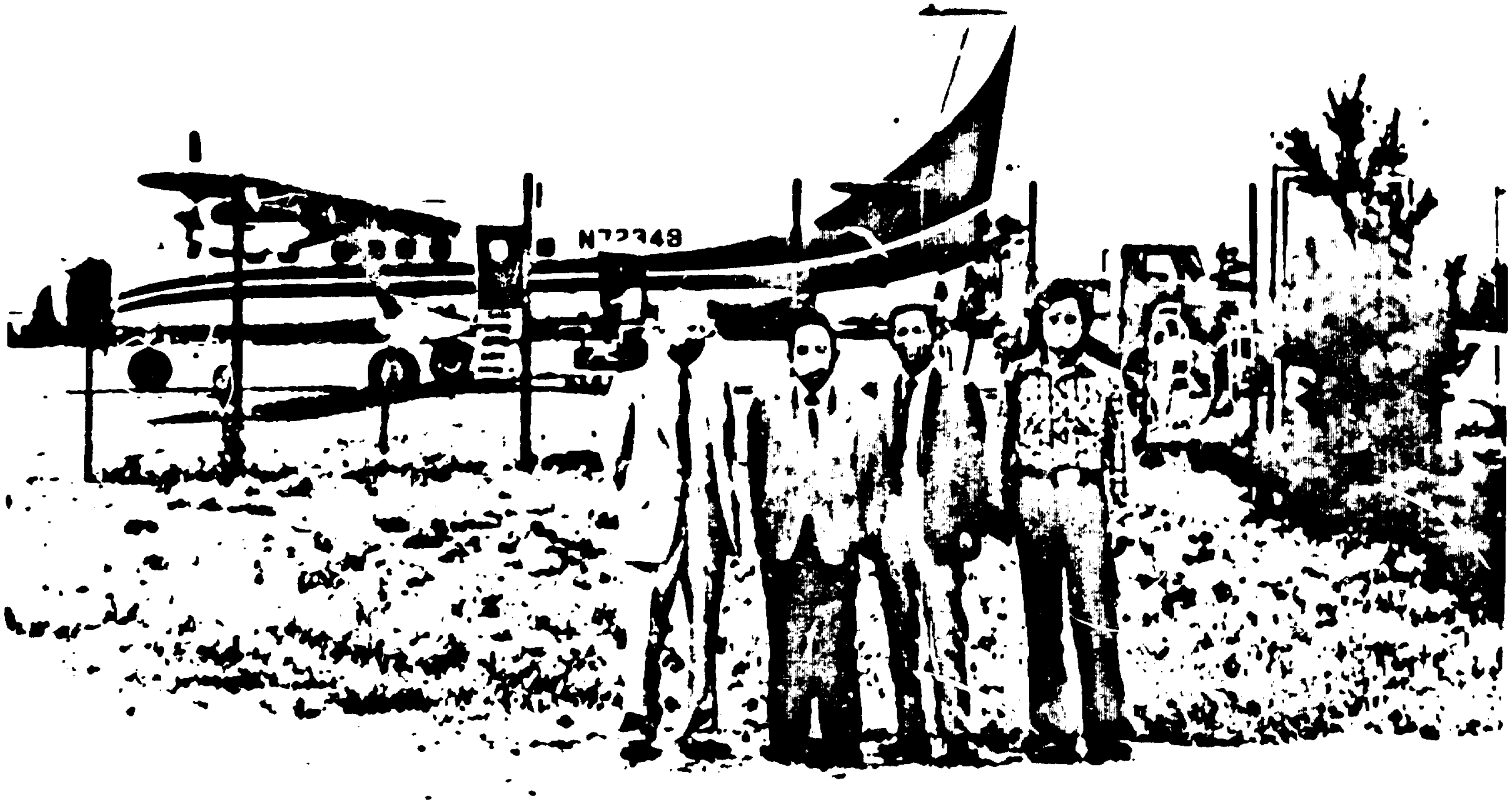
PROTON LINAC PARAMETERS

FREQUENCY	APF & DTL SECTION	450 MHz
	COUPLED CAVITY SECTION	1350 MHz
GRADIENT	APF & DTL SECTION	6 MV/m
	COUPLED CAVITY SECTION	8 MV/m
TRANSITION ENERGIES	APF/DTL	7 MeV
	DTL/CCL	150 MeV



PIGMI FACILITY LAYOUT
PION GENERATOR FOR MEDICAL IRRADIATION
EXISTING PARKING LOT
EXISTING MEDICAL CENTER
TREATMENT AREAS
IN BASEMENT OF MEDICAL CENTER
ACCELERATOR IN TUNNEL
UNDER PARKING LOT


NO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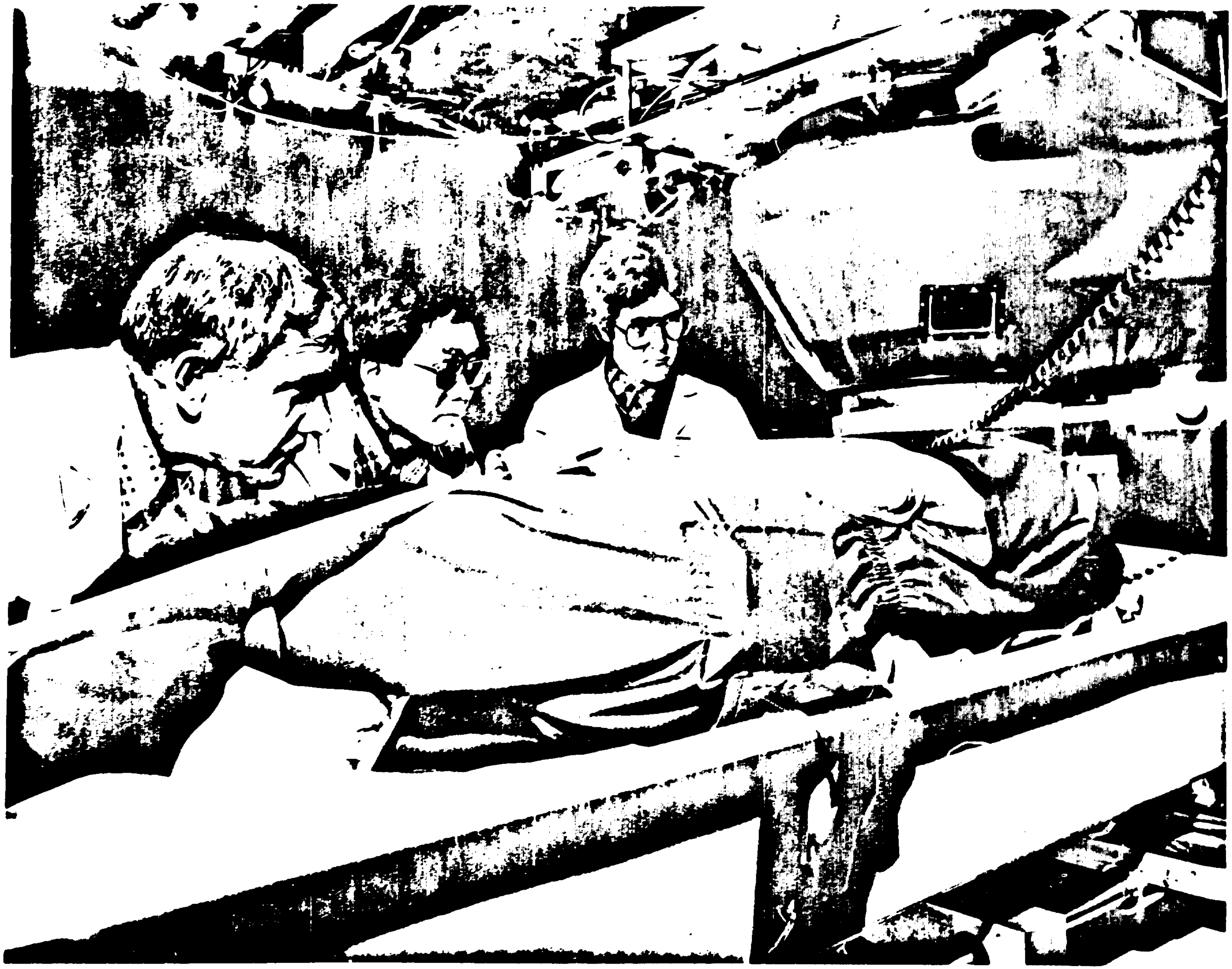
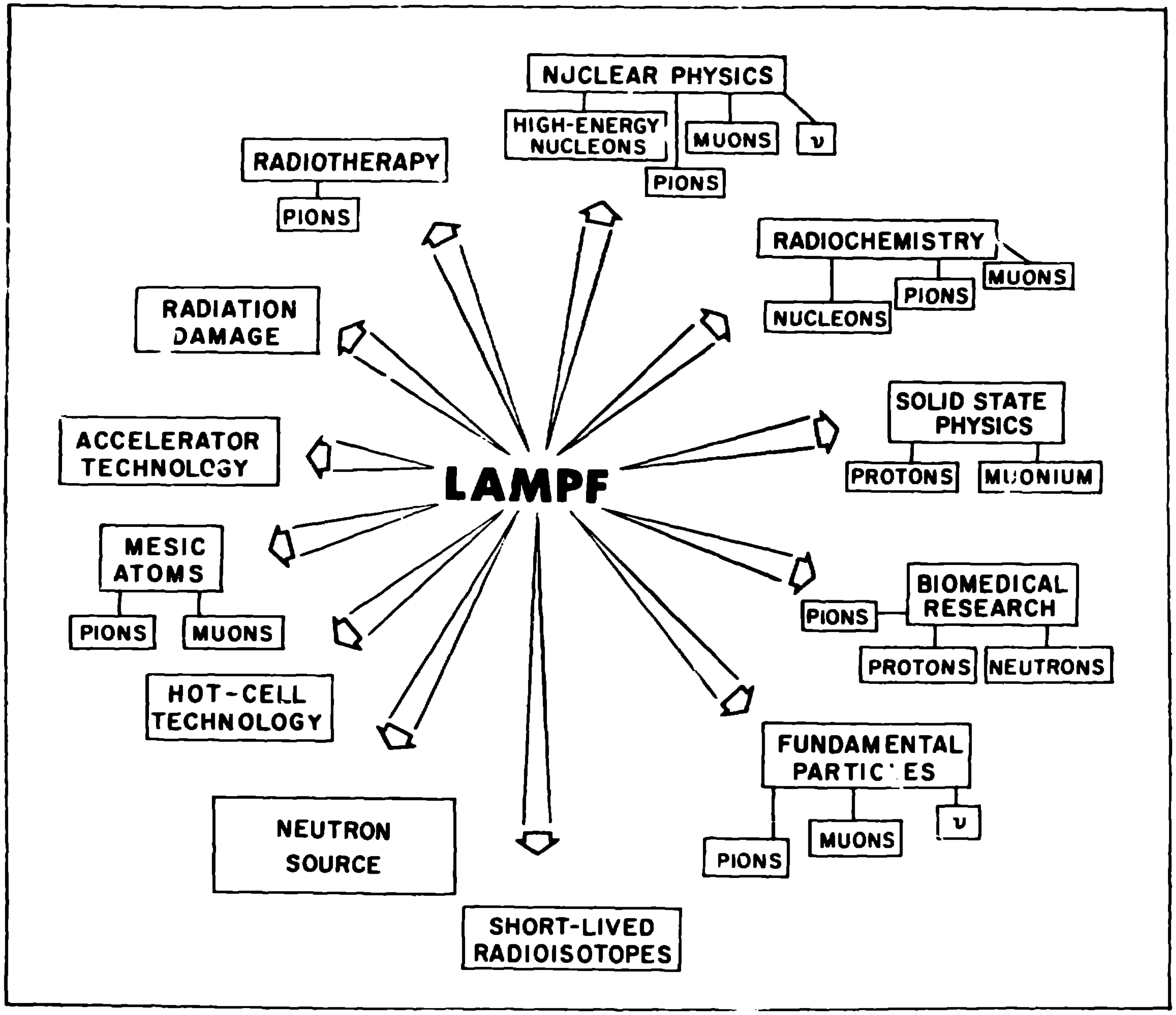
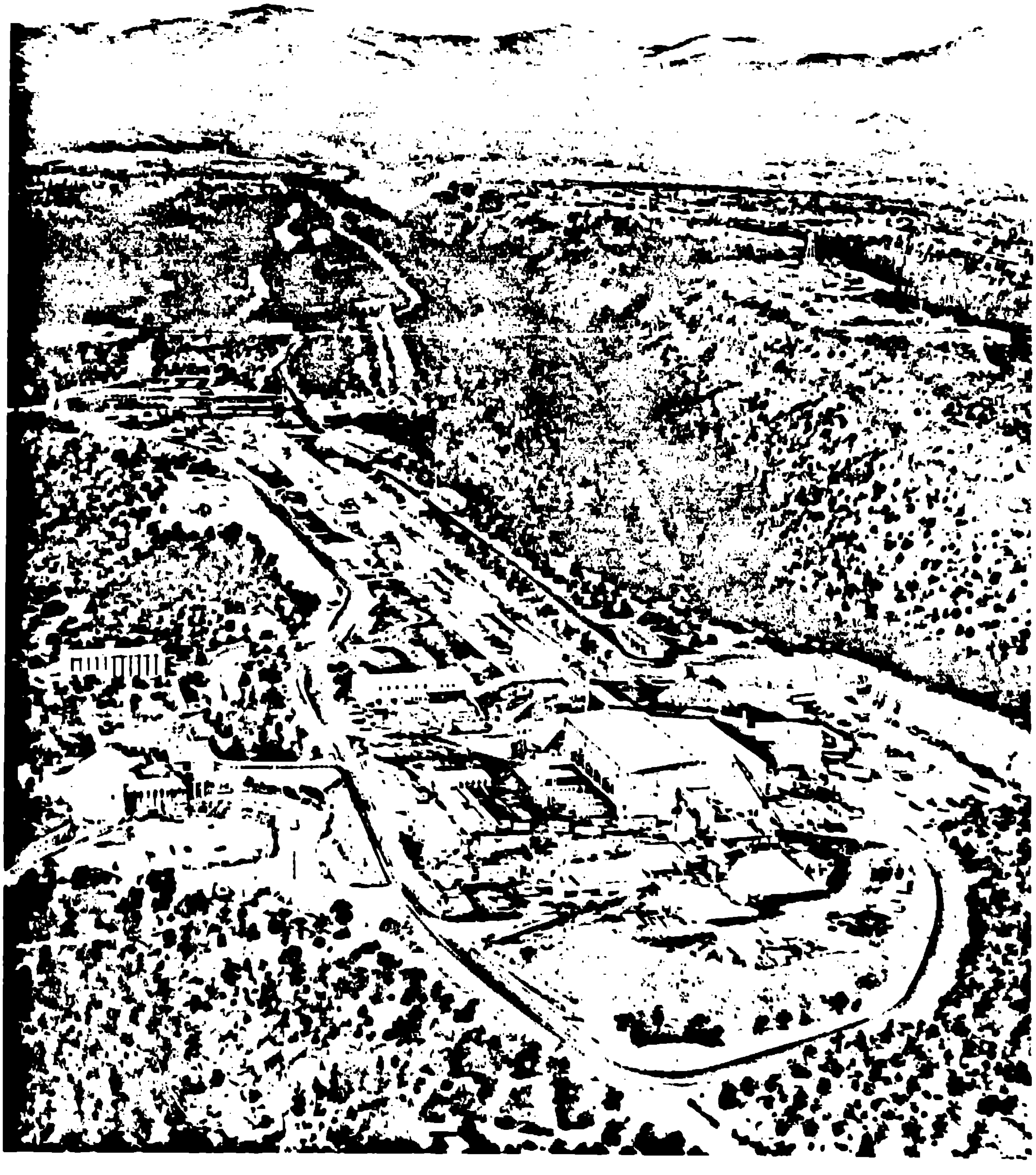



NUCLEAR PHYSICS
HIGH-ENERGY NUCLEONS
MUONS
ν
PIONS
RADIOTHERAPY
PIONS
RADIOCHEMISTRY
MUONS
PIONS
NUCLEONS
RADIATION DAMAGE
SOLID STATE PHYSICS
PROTONS
MUONIUM
ACCELERATOR TECHNOLOGY
LAMPF
MESIC ATOMS
PIONS
MUONS
BIOMEDICAL RESEARCH
PIONS
PROTONS
NEUTRONS
HOT-CELL TECHNOLOGY
FUNDAMENTAL PARTICLES
PIONS
MUONS
ν
NEUTRON SOURCE
SHORT-LIVED RADIOISOTOPES



PRACTICAL APPLICATIONS AT LAMPF

SOLID STATE PHYSICS AND MATERIALS ANALYSIS

- μSR RESEARCH
- MUONIC X-RAY ANALYSIS
- RADIATION DAMAGE STUDIES
- PROTON COMPUTED TOMOGRAPHY
- PULSED NEUTRONS

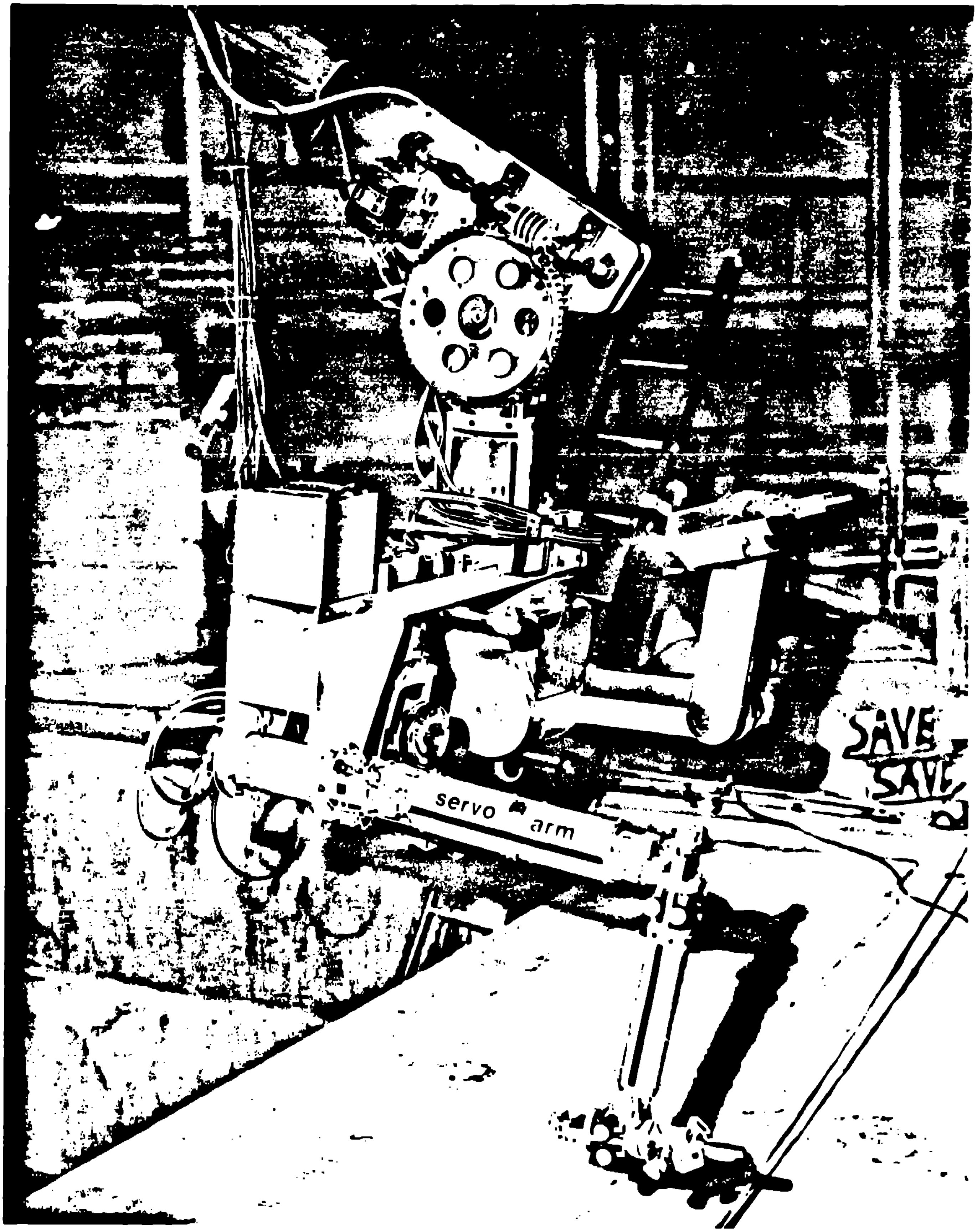
RADIATION DAMAGE STUDIES

- PROTONS; NEUTRONS

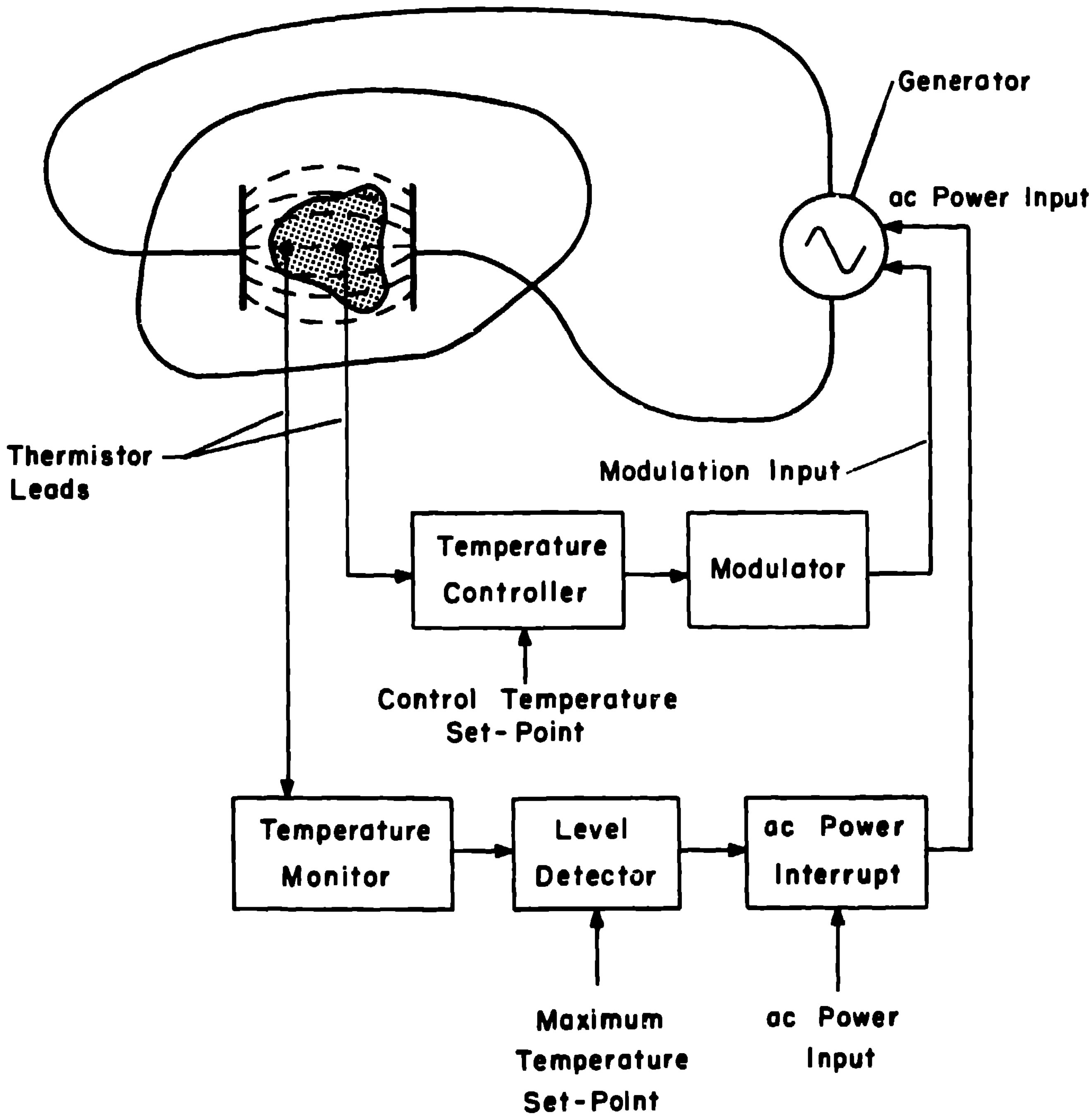
RADIOISOTOPE PRODUCTION

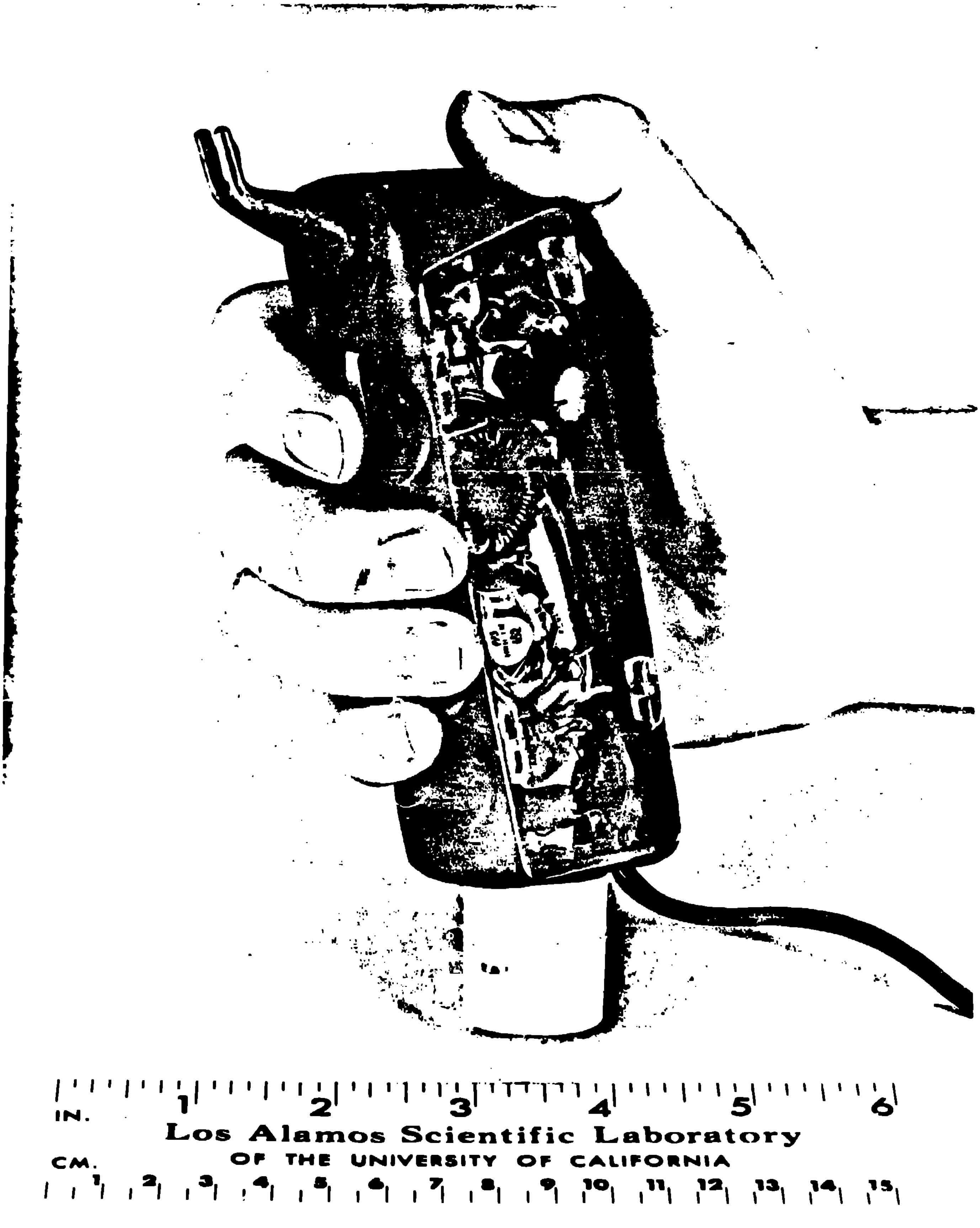
RADIATION BIOLOGY AND CANCER THERAPY

ELECTRONUCLEAR FUEL BREEDING



SAVE
SAVE
servo arm


Generator
ac Power Input
Thermistor Leads
Modulation Input
Temperature Controller
Modulator
Control Temperature Set-Point
Temperature Monitor
Level Detector
ac Power Interrupt
Maximum Temperature Set-Point
ac Power Input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Los Alamos Scientific Laboratory
OF THE UNIVERSITY OF CALIFORNIA
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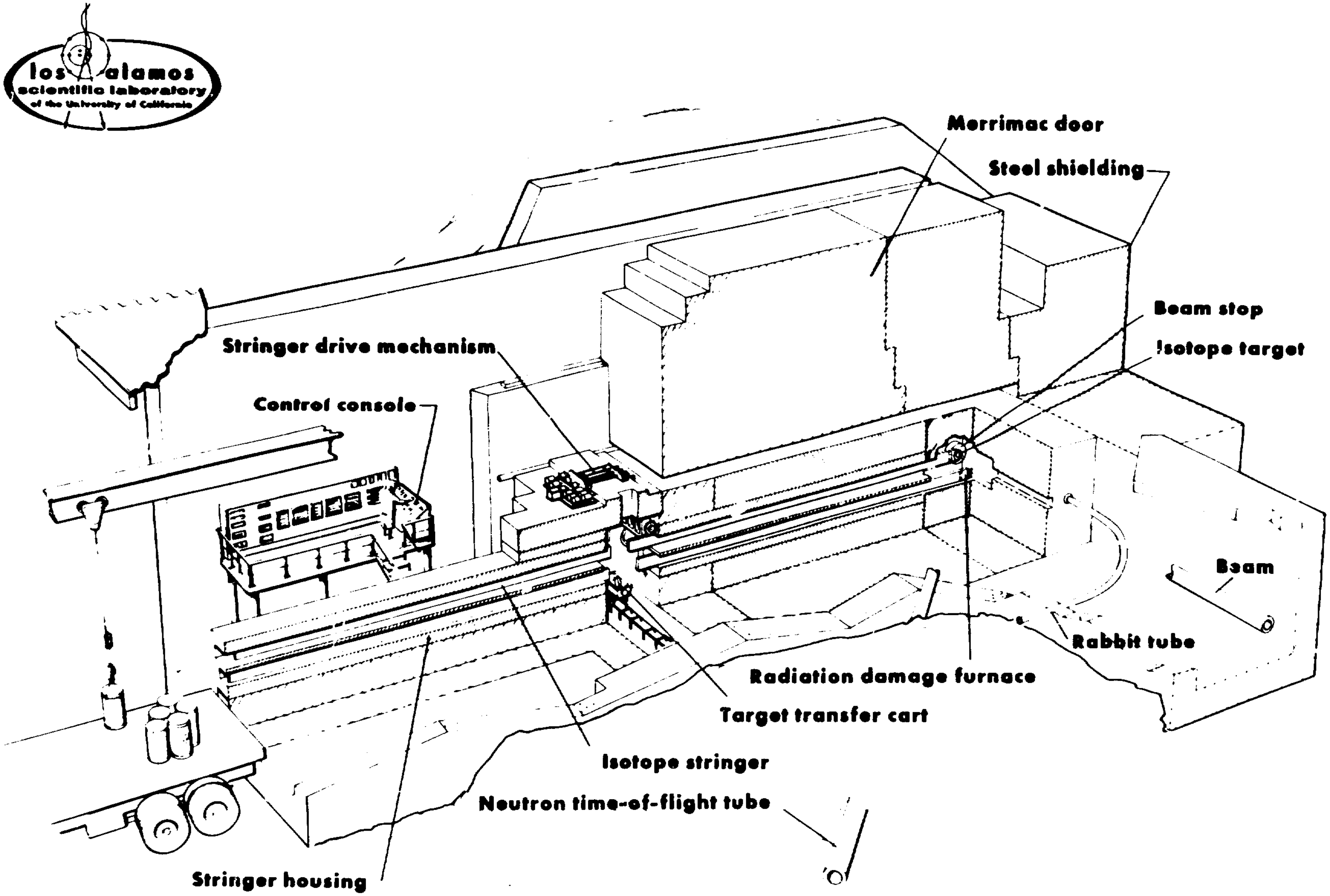
#3 (HEREFORD)
July 1, 1976

10 WEEKS LATER
September 8, 1976



ISOTOPES PRODUCTION FACILITY

Production Targets For LAMPF Isotope Production Facility

Target	Nuclide Sought	Application
Al	^{22}Na	Positronium Source & Gamma Standard
Si	^{26}Al	Geochemistry & Metallurgy Research
V	^{32}Si	Geochemistry & Metallurgy Research
	^{43}K	Cardiovascular Study
	^{44}Ti	Bone Imaging & Biological Research
Ni	^{48}V	Biological Research
	^{52}Fe	Brain, Bone Marrow & Heart Studies
Cu	^{60}Fe	Nuclear Chemistry & Cosmochemistry Studies
Rb Br	^{67}Cu	Wilson's Disease & Biological Research
	^{67}Ga	Lymphatic & Soft Tissue Tumor Study
	^{68}Ge	Ge/Ga Biomedical Generator
	^{73}As	Low-Energy Photon Source
	^{72}Se	Biomedical Research - Se/As Generator
Mo	^{77}Br	Biochemical Labeling Reserach
	^{82}Sr	Cardiovascular Study
	^{88}Y	Photoneutron Source & Weapons Diag.
	^{88}Zr	Photoneutron Source & Weapons Diag.
In	^{109}Cd	Cd/Ag Biomedical Generator
La	^{123}I	Diagonostic Nuclear Medicine - Thyroid
	^{127}Xe	Lung Ventilation & Perfusion Study
Ta	146 & ^{148}Gd	Nuclear Chemistry Study
	^{173}Lu	Nuclear Chemistry Study
	^{172}Hf	Hf/Lu Biomedical Generator

Biomedical Generators

25.6-D ^{82}Sr - 76.4 -s ^{82}Rb

287-D ^{68}Ge - 68-min ^{68}Ga

57-H ^{77}Br - 17.4-s ^{77m}Se

453-D ^{109}Cd - 39.6-s ^{109m}Ag

1.87-Y ^{172}Hf - 6.7-D ^{172}Lu