Use of Protons for Radiotherapy

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Abstract

An important trend in the development of radiation therapy has been the utilization of radiation sources permitting greater uniformity of dose within the target volume and a reduction of dose to tissues outside the target volume. A beam of high energy protons can be used to irradiate large volumes with excellent uniformity and with doses to extraneous tissues much lower than with photons or electrons. Detailed treatment planning and verification in phantom experiments is expected to confirm this general result. At the same time, enough experience has already been gained through the irradiation of some patients with such beams to minimize the risk involved in applying a new treatment modality to larger numbers of cases. The time seems appropriate to make clinical trials with existing proton accelerators, with the object of placing this promising tool at the disposal of most radiotherapists in the near future.

Use of Protons for Radiotherapy

Useful Properties of Protons

Robert R. Wilson's paper[1] published in Radiology in 1946 was evidently the first to call attention to the physical parameters of a beam of fast protons tending to make this form of ionizing radiation especially attractive as a tool for radiation therapy. Qualitatively stated, his arguments may be summarized as follows:

1. Protons can be produced with sufficient energy to penetrate to any part of the human body.

2. A mono-energetic beam of protons has a well defined range in tissue making possible a sharp reduction of dose, essentially to zero, delivered to structures immediately beyond the target.

3. A small proton beam suffers only a modest amount of broadening, due to multiple Coulomb scattering, as it penetrates tissue. Similarly the edge of a larger beam will remain well defined.

4. The dose delivered by the beam increases with depth in the absorbing tissue and reaches a sharp maximum near the end of range.

5. The density of ionization or linear energy transfer (LET) increases markedly near the end of range, with possible biological consequences.

6. Proton beams of large diameter can be produced as well as very small ones.

7. The useful extent in depth of the high-dose region can be extended by manipulation of the incident proton energy, for instance by use of a rotating variable absorber.

8. Monitoring of the administered beam-intensity with a thin ionization chamber is particularly convenient.

9. Dosimetry in terms of tissue dose is simple because the wall effect in an ionization chamber is virtually absent.

In addition to this list of advantageous factors, Wilson also correctly anticipated the modifying effects of nuclear absorption and nuclear elastic scattering which make the experimentally observed properties somewhat less advantageous than first anticipated. Not only were these various considerations discussed qualitatively, but numerical estimates were given for most of them which have proved to be substantially correct. The extension of these considerations to beams of charged particles heavier than protons was also indicated.

Experiments along lines implicit in Wilson's paper were started at Berkeley under the direction of J. H. Lawrence and C. A. Tobias in 1948, as soon as a suitable beam was in fact available. Most of the more recent work at Berkeley has been with alpha particles. At Uppsala, Sweden experiments with protons were started about 1955 by

B. Larsson, B. Leksell and others. At about that time a pre-therapeutic project was carried out by S. D. Warshaw at the University of Chicago synchrocyclotron, and in 1959 a group of people from the Massachusetts General Hospital and the Department of Physics at Harvard started using the Harvard synchrocyclotron for such purposes. The possibility of delivering very high doses to targets as small as 1 cm^3 while sparing neighboring structures is the one that was initially pursued by each of the three groups which have gone on to clinical trials. Today, a summary of patients treated at Berkeley, Uppsala and Harvard would probably show a total of 1000 cases involving a small target, such as the pituitary gland, and only about 60 cases involving extensive targets more typical of most malignant disease. (Experience in this latter group has been accumulated mainly at Uppsala and will be reported by Dr. Stenson in the following paper). This statistical imbalance is sometimes taken as an indication that it is very difficult to apply the proton beam to large targets or that no advantage remains over conventional forms of radiation when the proton beam is so applied. In fact, the necessary techniques of beam handling have been worked out, with varying degrees of sophistication, at each of the laboratories mentioned. The improvement in dose distribution obtainable, as compared to conventional modalities, is striking.

Range Modulation

The terminal portion of the depth dose curve of a broad proton beam in water, measured at Harvard, is shown in Figure 1(a). Note the "Bragg Peak" which occurs near the end of the range, beyond which the curve drops rapidly to zero. Curve S of Figure 1, designed for a target having 2.5 cm extent in depth, can be built up by the addition of the curves a, b, c, d and e, representing five beams of different integrated intensity and different range. The adjustments in range can be accomplished by means of absorbers placed in the beam before it reaches the patient or the phantom in which measurements are made. The adjustments of integrated intensity can be made by varying the length of time that each absorber thickness is allowed to remain in the beam. It is possible to achieve the same overall result by using a single absorber having closely spaced grooves of varying width and depth carefully machined into it[2,3].

A range modulator using a rotating wheel with sectors of different thickness is shown schematically in Figure 2, and a photograph of the device in Figure 3. The wheel is made up of sheets of plastic which may be cut out on the band saw so that changes in program can be tried out at modest cost. Figure 4 shows the result of an early attempt which illustrates that dose uniformity of ±5 percent is rather easy to achieve over nearly 5 cm extent in depth. Agreement between the measured points and the calculated

curve is good, indicating that scattering at the edges of the sectors is not a problem. More elegant range-modulation programs have been worked out to improve dose uniformity and to cover greater extent in depth. The objective of this line of development is to compare dose distributions measured in rather detailed phantoms exposed to protons, photons and electrons according to treatment plans appropriate for several real tumors.[4] Such information is not yet available.

Dose Distributions Compared to Photons

We have also calculated dose distributions which may be obtained in more idealized geometries. Figure 5 compares the axial dose of Co-60 gammas, 20 MV x-rays[5] and protons when two symmetric opposed fields 10 x 10 cm in area are directed at a 10 cm spherical target centered in a 22 cm slab of uniform tissue-equivalent absorber. Figure 6 shows isodose contours in a central plane for the same three cases. The reduction of dose to the tissues outside the target volume when protons are used is striking and is in no way confined to this choice of geometry.

For the comparison shown in Figure 7 we have taken dose distributions for Co-60 gamma rays and 22 MV x-rays from W.E.C. Allt's paper describing the clinical results when these two types of radiation were applied in a randomized test to the treatment of advanced carcinoma of the uterine

cervix (Stages IIb and III)[6]. In this treatment plan four fields are employed in two opposed pairs with their axes inclined at 110 degrees. Treatment plan and dosimetry are described in detail in Ref. 6. A similar plan was assumed in calculating the proton dose distribution, using range-modulation to cover a 6 cm extent in depth. Because of the four field geometry, the dose to tissues outside the target volume is only 60 to 75 percent of the tumor dose when Co-60 gammas are used, but is reduced still more, to 30 to 45 percent of tumor dose, when the more penetrating betatron radiation is used. Protons would provide still more reduction of this dose to about 22 percent of tumor dose. While the number of patients in Allt's cobalt and betatron comparison is not large (approximately 60 each) his reported improvement in 5 year survivals from 34 percent to 60 percent, and the reduction of serious complications from 15 percent to 5 percent suggest that the better dose distribution obtainable with the betatron is clinically advantageous. It is reasonable to suppose that the proton dose distribution would be even better. In effect, the skin sparing advantage of the 22 MV x-ray beam is extended to <u>all</u> of the overlying tissues when protons are used.

The distribution of dose with depth resulting from a single field of 22 MV x-rays is shown in Figure 8. A region of high dose with ±5 percent uniformity extends from 2 cm to 8 cm depth below the surface, while the surface

dose is about 22 percent of tumor dose. The exit dose, however, is 55 percent of the tumor dose assuming 22 cm body thickness. As shown in the figure, an opposed pair of proton fields of unequal magnitudes can provide the same tumor dose with better uniformity over the same extent in depth with essentially the same "entrance" and "exit" doses. The proton irradiation, however, reduces considerably the dose to tissue between the surface and the target volume. Whether or not this asymmetric mode of irradiation is preferrable to that shown in Figures 5 and 6 depends on the sensitivity of the tissues involved.

Dose Distributions Compared to Electrons

Electron beams are used to good effect in irradiating lesions extending to a limited distance below the surface. As shown in Figure 9, the electron beam can provide a fairly uniform dose to a depth determined by electron energy and a fairly rapid decrease of dose at greater depths.[7] When higher energies are used to reach greater depths this decrease becomes more gradual resulting in greater dose to underlying tissue. Under these circumstances, x-rays can often provide a more favorable dose distribution.[8] Figure 9 illustrates that the proton beam can maintain a very sharp cut-off even at great depth.

Electron beams tend to have rather poor transverse distributions because of scatter. This effect, as well

as the poor depth cut-off, is illustrated by the isodose contours shown in the upper portion of Figure 10, measured in a water phantom exposed to an 8 x 10 cm, 35 MeV electron beam.[9] We have assumed a 10 cm diameter target, and show in the lower half of the figure the isodose contours calculated for proton irradiation, again using range-modulation for uniform coverage over the 10 cm extent in depth. The proton technique provides much better uniformity of dose throughout the target and much lower dose to most of the neighboring tissues. It would require only a little more effort to eliminate the projecting corner of the proton dose distribution by means of a concave bolus over the target.

Clinical Experience with Heavy Charged Particles

Although some 1000 patients have been treated at Berkeley (mostly with the alpha beam) and at Harvard (protons), the vast majority of these were treated with a very small beam, usually directed at the pituitary gland. Dose-response information derived from such cases is of rather limited usefulness in treatment planning for more extensive malignant lesions in other parts of the body. A few of these patients, however, were treated with larger beams, and some useful data, especially with respect to normal tissue tolerance, are potentially available. The impression seems to be that, for equal physical doses, the biological response to exposure in the low LET portion of

these beams is about the same as to x-ray exposure. Histopathological examination of the brains of ten patients irradiated with stopped protons[10] shows a similar result.

At Uppsala, radiation therapy of malignant disease using the proton beam has received greater emphasis. A monograph by Stenson[11] summarizes the experience of the past ten years including 34 human cases: 17 genital carcinomas, 7 brain tumors, and 10 naso-pharyngeal malignancies. It could be concluded at least that the proton beam is a practical tool to treat a variety of malignant tumors, and again that protons and high energy x-rays produce approximately the same dose-response relationship.

Conclusion

Clinical response is inevitably a rather crude measure of the radiobiological effectiveness of radiation, and indeed there are radiobiological experiments showing that the Bragg peak region of a heavy charged particle beam differs significantly from lower LET radiations. However, the absence of any anomalous clinical response in the patients already treated with proton beams reduces drastically the risk involved in more extensive trials. At the same time it suggests that much of the knowledge which radiotherapists have acquired by decades of experience with x-rays and electrons can be applied directly to proton treatment planning, without exhaustive evaluation of correction

factors by means of various radiobiologic test systems.

The advantages offered by proton beams in radiotherapy are primarily those of precision and flexibility in treatment planning, accompanied by significant reduction of unwanted dose. The value of these advantages may be assessed promptly, at minimal risk and relatively modest cost by clinical trials using existing accelerators. If their value is proven, there should be no great technical difficulty in designing proton accelerators for therapy which will be compatible in size, cost and ease of operation with the requirements of the radiotherapy departments of large hospitals.

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Figure Captions

Figure 1. Illustration of the method of building up a proton depth dose curve suitable for irradiating a thick deep-lying target by the superposition of beams of different intensity and range. Curve S is the sum of Curves a through e.

Figure 2. Schematic illustration of a rotating absorber wheel with sectors of different thicknesses. Such an abosrber will produce in rapid sequence depth dose curves similar to Curves a through e in Figure 1.

Figure 3. Range modulator consisting of a rotating absorber and its drive system. The absorber is 15 cm in diameter.

Figure 4. Measured and calculated depth dose curve using the range-modulator of Figure 3. This modulation program provides approximately 5 percent uniformity over 4.7 cm extent in depth. Several programs with other specifications have been designed.

Figure 5. Comparison of the axial dose from two opposed 10 x 10 cm fields irradiating a 10 cm thick target centered in a 22 cm slab. Substantial reduction in the dose delivered outside the target is evident when protons are used. (Photon data from Ref. 5, proton data based on

our measurements.)

Figure 6. Comparison of isodose contours corresponding to Figure 5. A for Co-60 gammas, B for 20 MV x-rays, and C for protons.

Figure 7. Dose distributions designed for irradiation of the uterine cervix: four fields in two opposed pairs with axes at 110 degrees. The dose along one axis is shown. A for Co-60 gammas, B for 22 MV x-rays (both from Ref. 6) and C for protons based on our measurements.

Figure 8. Dose distributions for a target extending from 2 to 8 cm depth. Taking account of the exit dose, the skin-sparing effect of the 22 MV x-rays can be matched by two opposed proton beams up to a total body thickness of 22 cm.

Figure 9. Comparison of proton and electron depth dose curves. (Electron data from Ref. 7).

Figure 10. Comparison of isodose contours in the central plane for an 8 x 10 cm beam of 35 MeV electrons and for protons. Protons provide superior uniformity of dose within the target and minimal extraneous dose (Electron data from Ref. 9).

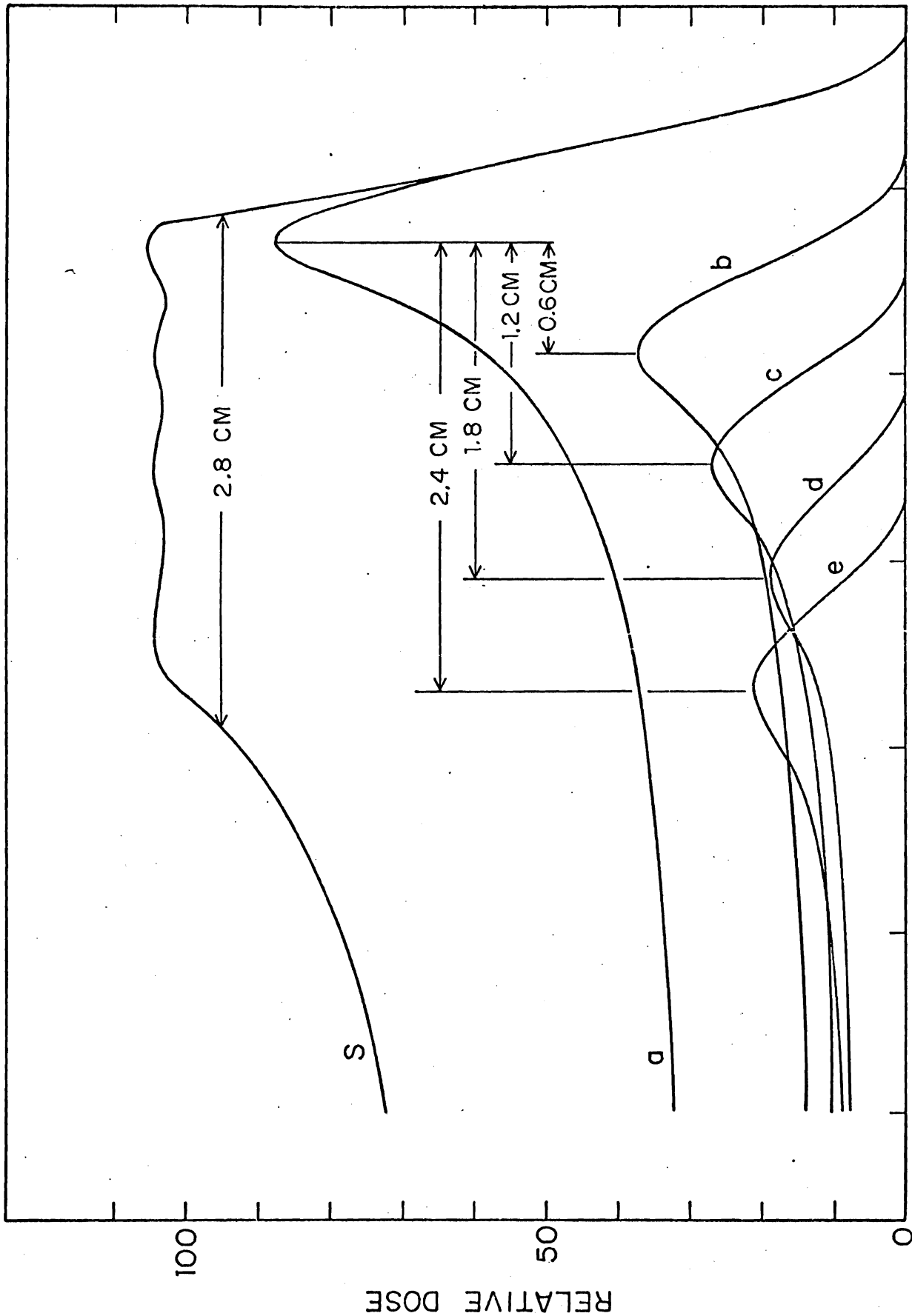
RELATIVE DOSE
100
50
0
DEPTH IN WATER (CM)
8
9
10
11
12
13
S
a
b
c
d
e
2.8 CM
2.4 CM
1.8 CM
1.2 CM
0.6CM

Fig. 1

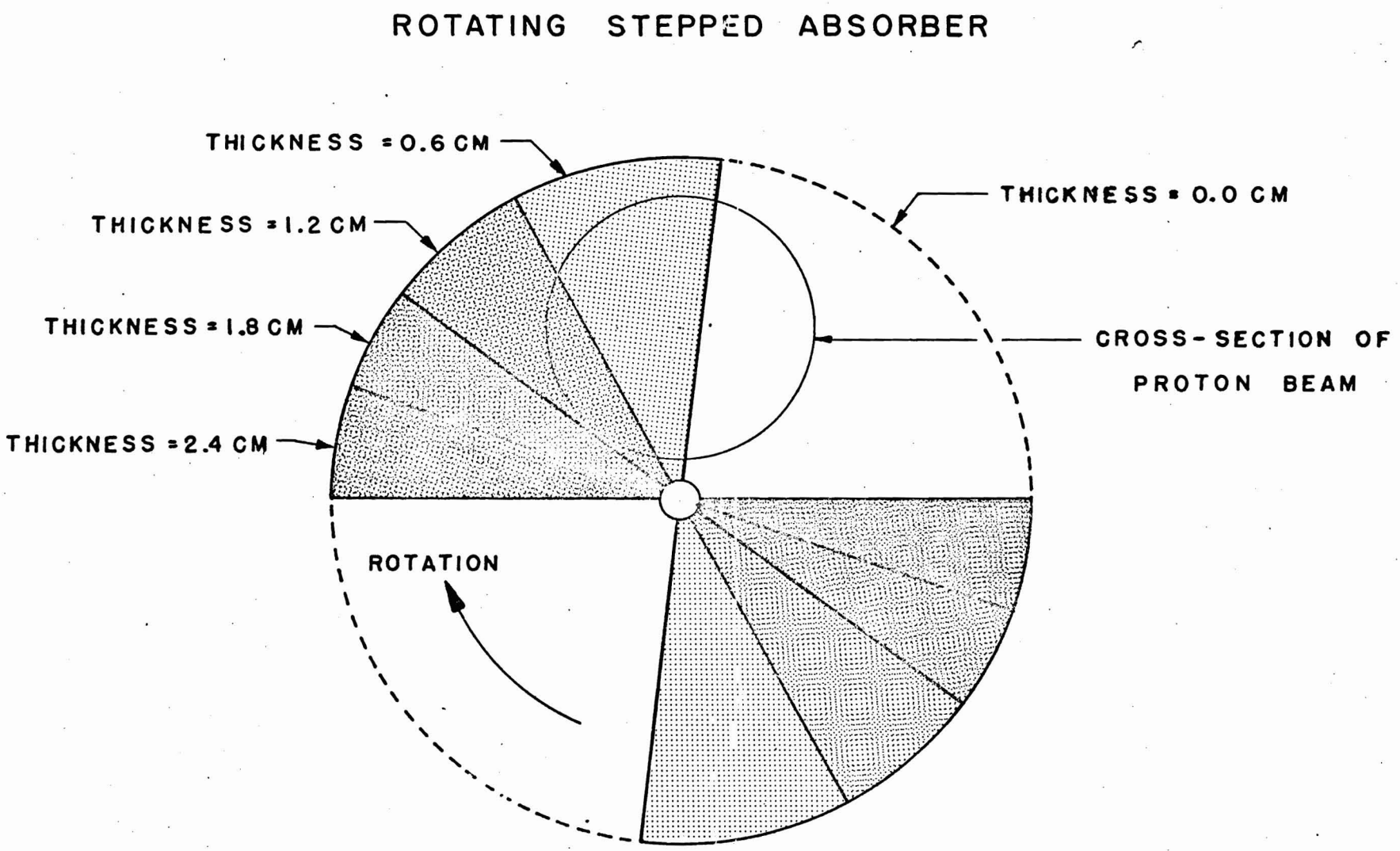
ROTATING STEPPED ABSORBER
THICKNESS = 0.6 CM
THICKNESS = 1.2 CM
THICKNESS = 1.8 CM
THICKNESS = 2.4 CM
THICKNESS = 0.0 CM
CROSS-SECTION OF PROTON BEAM
ROTATION

Fig. 2

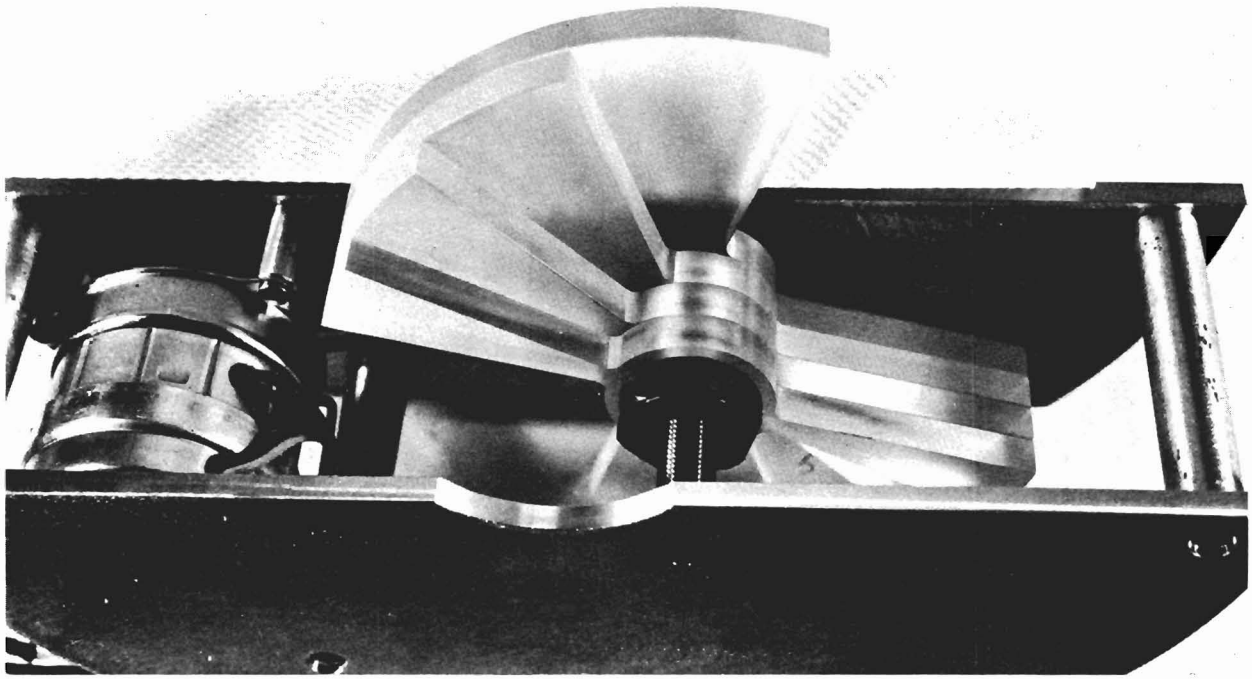

Fig. 3

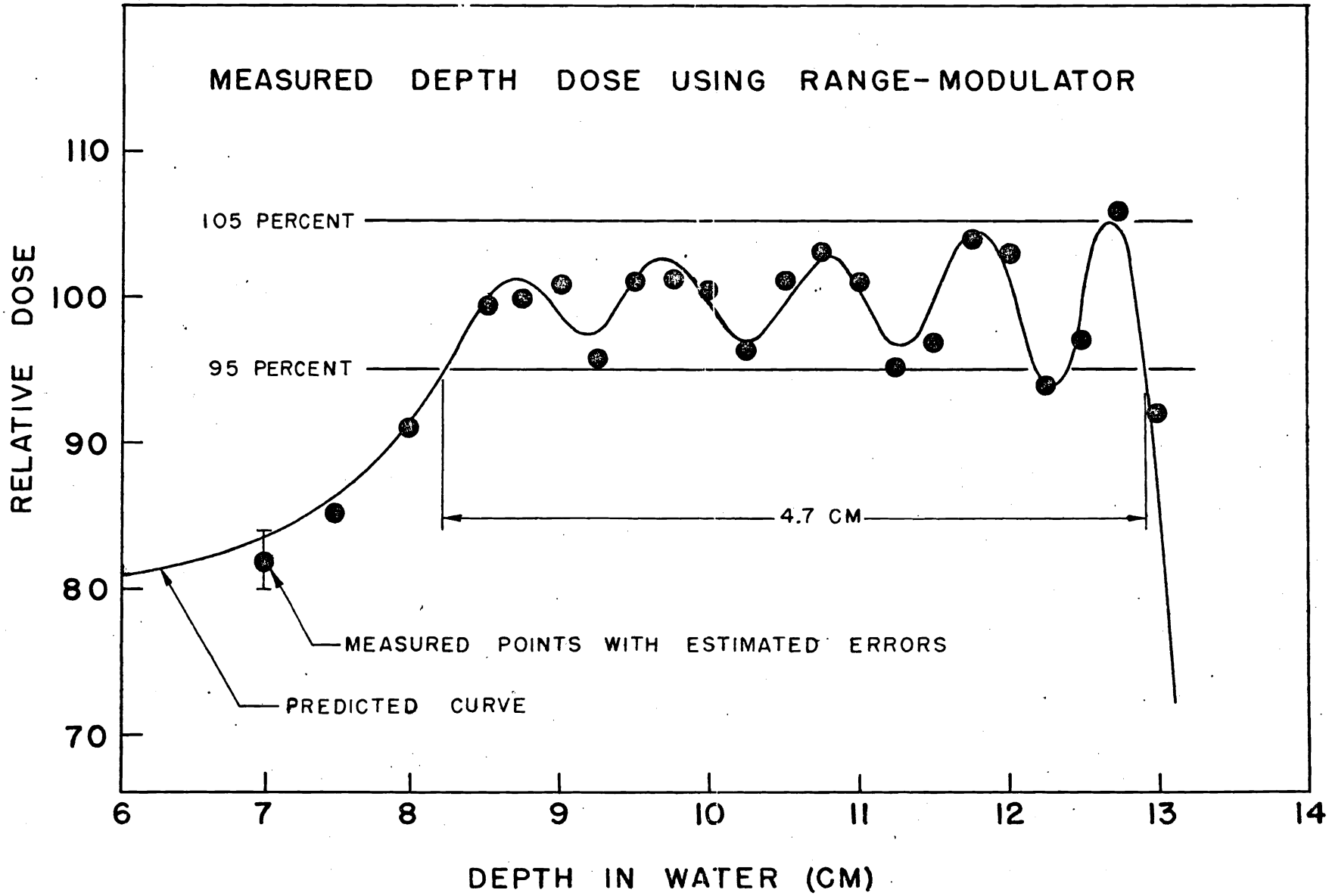
MEASURED DEPTH DOSE USING RANGE-MODULATOR
RELATIVE DOSE
110
100
90
80
70
105 PERCENT
95 PERCENT
4.7 CM
MEASURED POINTS WITH ESTIMATED ERRORS
PREDICTED CURVE
6
7
8
9
10
11
12
13
14
DEPTH IN WATER (CM)

Fig. 4

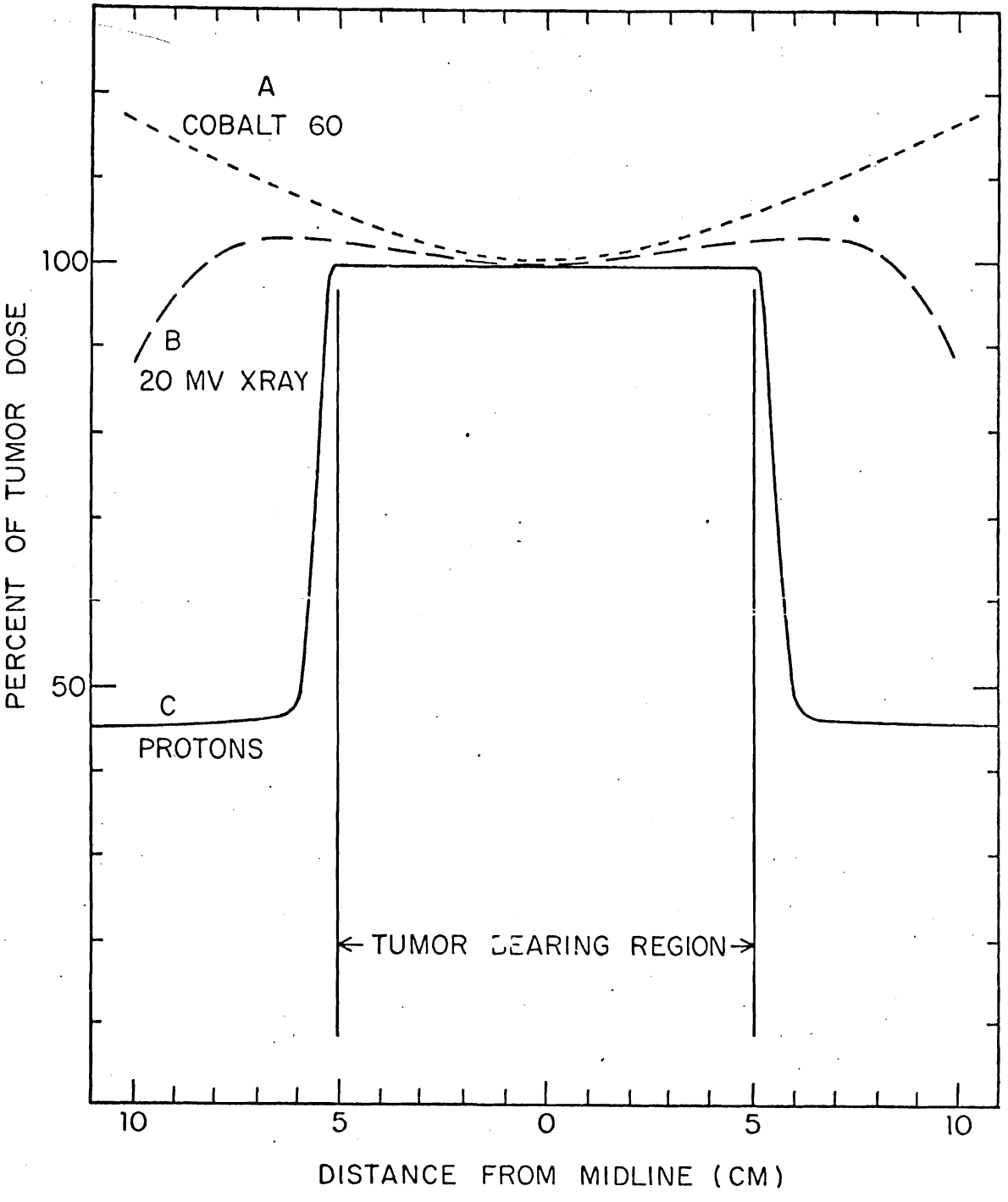
A
COBALT 60
B
20 MV XRAY
C
PROTONS
100
50
PERCENT OF TUMOR DOSE
← TUMOR BEARING REGION →
10
5
0
5
10
DISTANCE FROM MIDLINE (CM)

Fig. 5

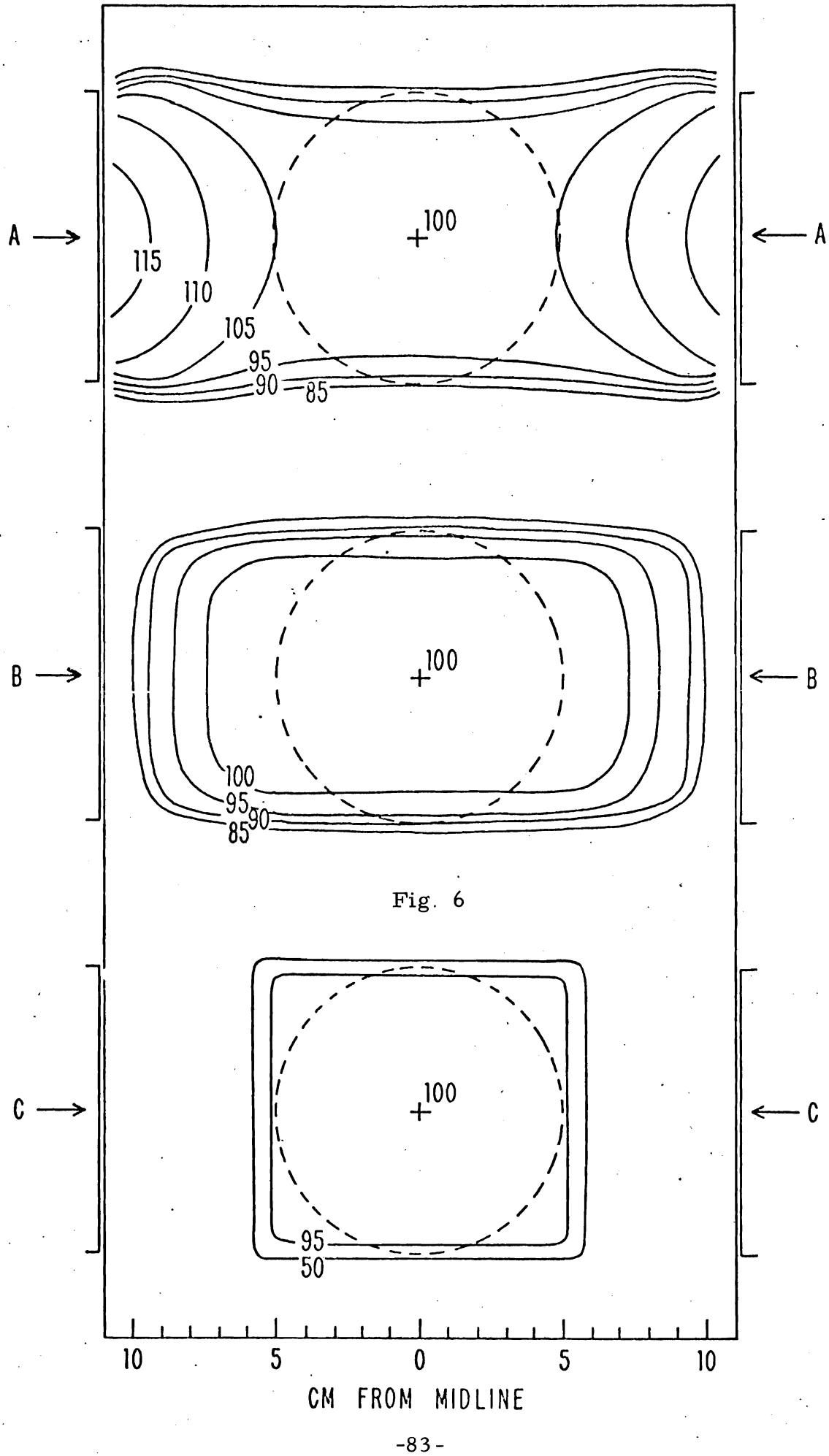
A
A
115
110
105
95
90
85
100
B
B
100
95
90
85
100
C
C
95
50
100
10
5
0
5
10
CM FROM MIDLINE

Fig. 6

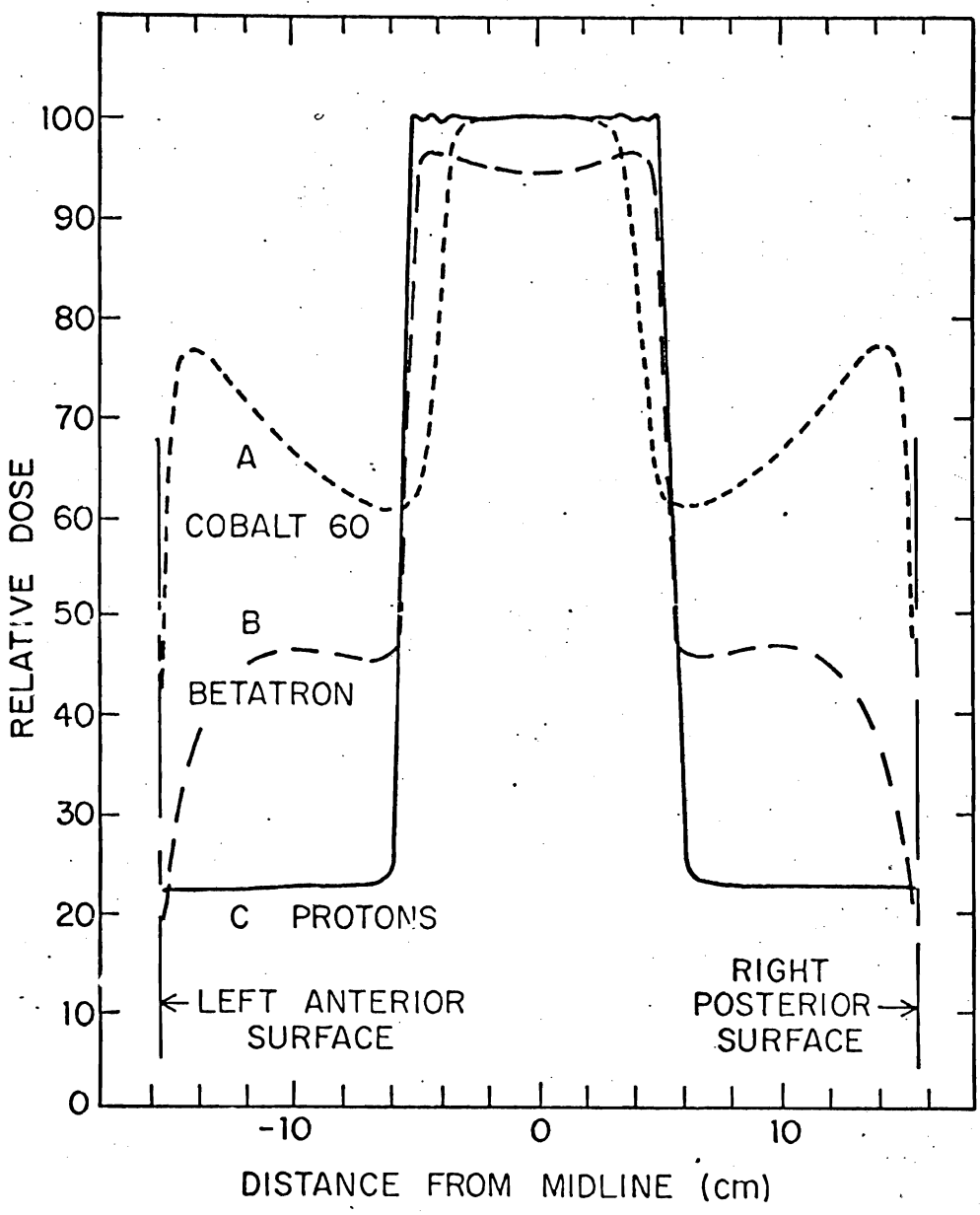
100
90
80
70
60
50
40
30
20
10
0
RELATIVE DOSE
A
COBALT 60
B
BETATRON
C PROTONS
LEFT ANTERIOR SURFACE
RIGHT POSTERIOR SURFACE
-10
0
10
DISTANCE FROM MIDLINE (cm)

Fig. 7

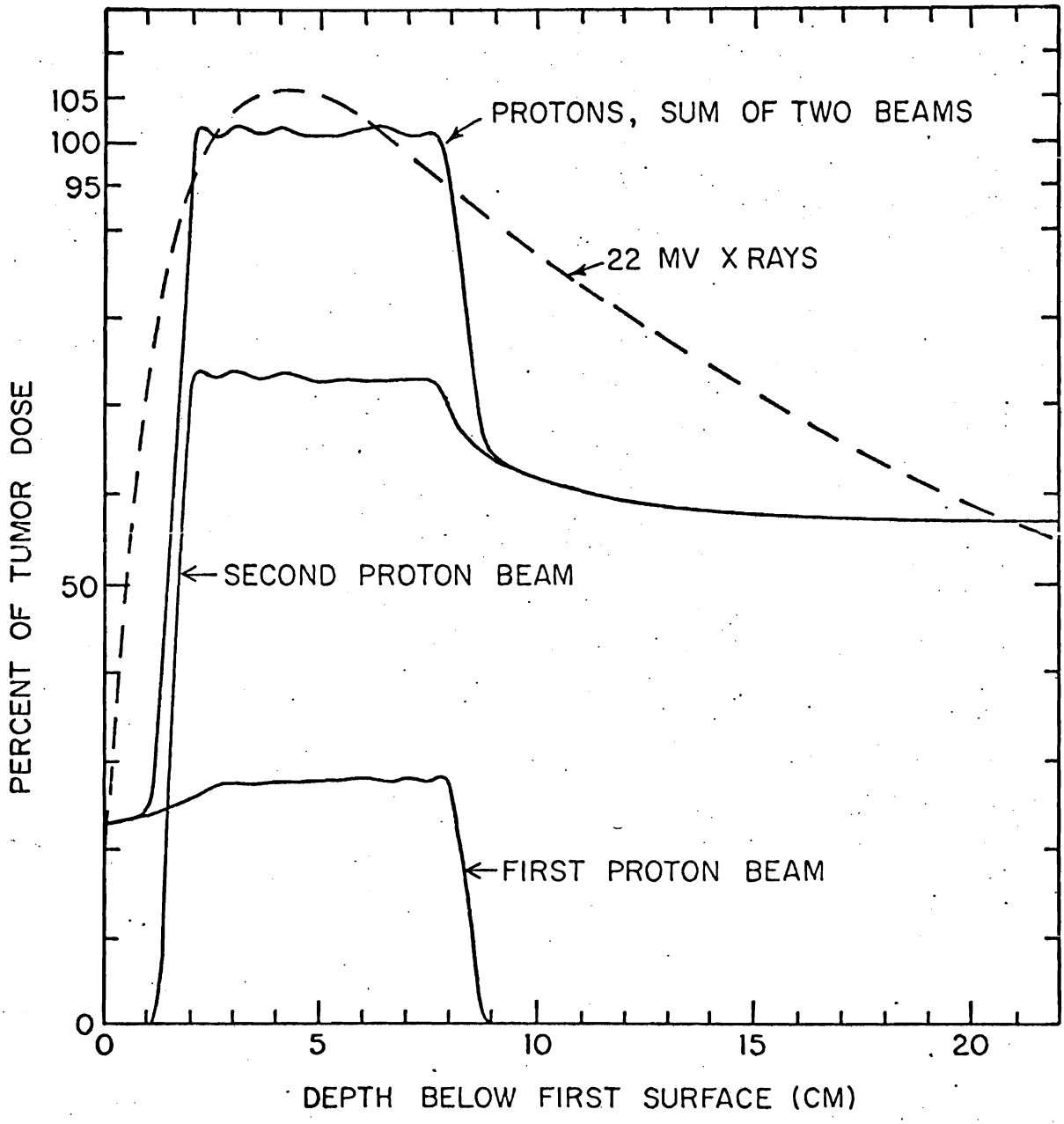
105
100
95
50
0
PERCENT OF TUMOR DOSE
PROTONS, SUM OF TWO BEAMS
22 MV X RAYS
SECOND PROTON BEAM
FIRST PROTON BEAM
0
5
10
15
20
DEPTH BELOW FIRST SURFACE (CM)

Fig. 8

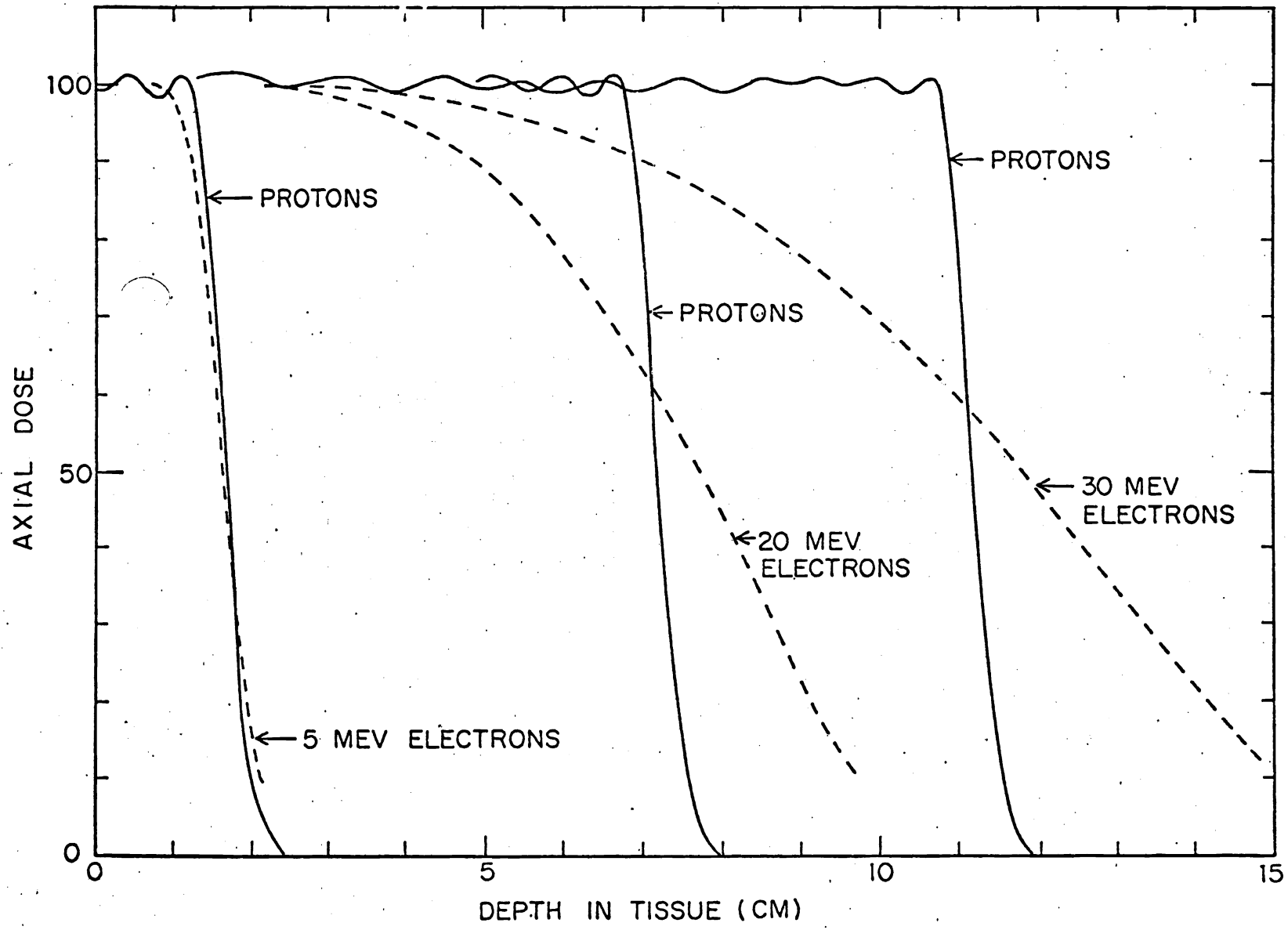
100
50
0
AXIAL DOSE
PROTONS
PROTONS
PROTONS
5 MEV ELECTRONS
20 MEV ELECTRONS
30 MEV ELECTRONS
0
5
10
15
DEPTH IN TISSUE (CM)

Fig. 9

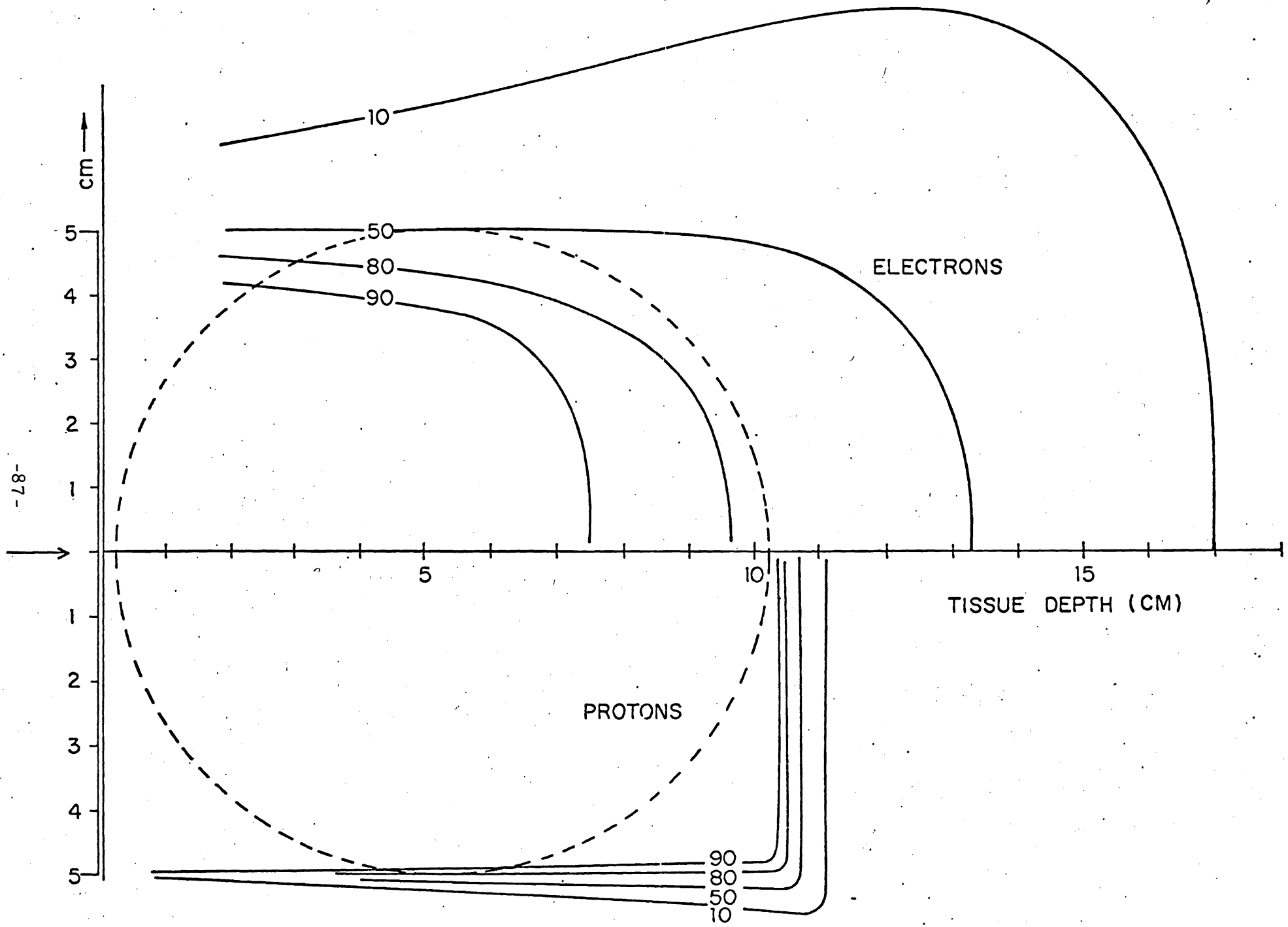
10
50
80
90
ELECTRONS
cm
5
4
3
2
1
5
10
15
TISSUE DEPTH (CM)
PROTONS
90
80
50
10

Fig. 10