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A COMPARISON OF PARTICLE-RADIATION-THERAPY MODALITIES

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ABSTRACT

The characteristics of dose distribution, beam alignment, and radiobiological advantages accorded to high LET radiation have been reviewed and compared for various "particle" beam radiotherapeutic modalities (neutron, Auger electrons, p, π^-, He, C, Ne and Ar ions). Merit factors were evaluated on the basis of effective dose to tumor relative to normal tissue, linear energy transfer (LET), and dose localization, at depths of 1, 4 and 10 cm. In general, it was found that neutron capture therapy using an epithermal neutron beam provided the best merit factors available for depths up to 8 cm. The position of fast neutron therapy on the Merit Factor Tables was consistently lower than that of other particle modalities, and above only ^{60}Co. The largest body of clinical data exists for fast neutron therapy; results are considered by some to be encouraging. It then follows that if benefits with fast neutron therapy are real, additional gains are within reach with other modalities.

A COMPARISON OF PARTICLE RADIATION THERAPY MODALITIES

INTRODUCTION

The 50% failure rate of cancer therapy is well-known. Despite the most sophisticated combinations of radiotherapy, chemotherapy, and surgery, the approximately 33% mortality due to recurrent primary tumor should make improvement of primary tumor therapy an important goal (1). An example would be the results obtained with gliomas; median survival time with supportive care only (no chemotherapy, radiation therapy) is ~3 months (2), while various combinations of radiation therapy, and radiation therapy combined with BCNU or CCNU produced median survival varying from 8-11 months (2,3). The tumors are inevitably fatal. A number of problems are associated with radiotherapy. These would include beam alignment (inclusion of tumor body as well as microscopic fingers of growth within the radiation field), and the radioresistance of hypoxic cells, as well as temporarily non-cycling cells in the so-called "latent pool" (4,5).

Particle* radiation therapy provides an alternative to conventional photon therapy, with potential advantages:

1. Better beam localization and/or alignment. Charged particles have reduced scatter and a definite range rather than exponential attenuation;
2. Increased biological effect. High LET radiations reduce or eliminate the variation in radiosensitivity between oxygenated and hypoxic cells, and phases of the cell cycle. Further, variation in response between tissues, and recovery from radiation damage is reduced.

*"Particle" is used here to denote neutrons, p, π^-, He, C, Ne, and Ar ions, and high LET electron distributions such as Auger cascades.

Through the use of the above modifications, either in combination or alone, it should be possible to enhance effective dose to tumor while restricting dose to normal tissues within the treatment volume to tolerable limits and minimizing damage to normal tissue surrounding the treatment volume.

The radioresistance of anoxic cells to conventional photon (low LET) radiation by a factor of 3 is a well-known radiobiological phenomenon. Clinically, x-ray therapy trials with hyperbaric oxygen and hypoxic sensitizers would appear to support the importance of hypoxia (6). Nevertheless, it may be that possible improved tumor response is a consequence of the fact that high LET radiations are impervious to ambient physical and radiobiological factors such as oxygen tension, cell cycle, and dose rate.

The problem of beam alignment is difficult to document. For benign (encapsulated) tumors whose location and extent is well-known, particle (proton) beams can be used with a precision sufficient to allow, for example, pituitary ablation (7). Since the major fraction of absorbed dose from the multi-portal treatment is confined to the pituitary fossa, tissue dose can be high enough to insure sterilization. Extreme care must be used in beam alignment and delivery of dose to minimize chance of damage to the optic nerves; the procedure is time consuming. In general, however, microscopic extensions (which exist by definition in malignant tumors) preclude precise definition of tumor extent. The radiation field must be opened up enough to include within its volume the region where such extensions are thought to exist. The absorbed dose is thus restricted to the tolerance of normal tissues within the field; to a large extent any enhanced radiation effect in tumor is restricted to the effects produced by differences in cell cycle time and growth fraction.

A significant source of error which is often ignored is the problem of human/machine error. Errors in the setting of parameters (field size, gantry angle, treatment time) affecting dose and dose distribution have been found to occur during the course of treatment to 2/3 of patients (8). Further, arithmetic error in treatment time calculation was found to be $\geq$5% in 10% of cases (9).

The above does not take into account the difficulty of precisely defining tumor location and extent. A study in 1960 showed that with small or medium volume radiation therapy of brain tumors, more than half of the tumors treated were either missed or had questionable coverage (10). Admittedly, modern techniques provide better tumor localization; yet best results for brain tumors (as described above) were obtained by irradiation of the whole head.

The poor prognosis for cancer therapy is due in part to the fact that tumors exhibit radiation sensitivities similar to normal tissues. Increases in median survival time noted above following radiation therapy is presumably a result of fractionated radiations which eventually gain access to what were originally hypoxic or nonproliferating compartments of the tumor, as well as to stimulate regrowth of normal tissues. Thus, any incremental tumor dose would be quite useful. For example, assuming a Do of $\sim$200 rem, and a normal tissue tolerance of 2000 rem (acute dose), a 10% increase in tumor dose would reduce the surviving fraction in the proliferative compartment by $\sim$60%. While tumor cell cycle times (median intermitotic time) are measured in hours, tumor doubling time is measured in months (4,5). Thus, useful life would be extended in the order of months. If the curative level of cell-killing had been reached, and assuming at least some cancers are monoclonal (11,12), the cure rate would be improved by almost a factor of 3.

From the above, it is clear that "small" (≈10%) errors can significantly affect local control, and why every effort should be expended in acquiring even fractionally increased effective doses to tumors.

In pursuit of these aims, various particle beams have been developed in an effort to improve dose distributions and effective dose to tumor. These include fast neutrons, protons, pions, and heavy charged particles (He, C, Ne, Ar). Fast neutrons provide a fairly good OER (Oxygen Gain Factor* ≈2), but dose distributions are analogous to γ-rays. Protons provide precise dose distributions, but an RBE and OER similar to γ-rays. Pions and heavy ions provide some advantages of both OER and dose distribution, with Ar ions yielding perhaps the best combination of Oxygen Gain Factor (1.8) and dose distribution, but no difference in RBE between peak and plateau.

Two modalities exist, however, which are evidently capable of giving an Oxygen Gain Factor (OGF) of >2, and a dose distribution providing automatic beam alignment with tumor on a cellular level. These two techniques are Neutron Capture Therapy (NCT) and Photoactivation Therapy (PAT). Neither are currently being investigated clinically within the U.S.

It is the purpose of this paper to present a comparison of the therapeutic modalities named above.

DISCUSSION OF THERAPY MODALITIES

A summary of experience and relevant physical and radiobiological parameters for the following beams is given below:

1. NCT
2. PAT

*Oxygen Gain Factor (OGF) = ratio of OER of standard radiation (x or γ rays) to OER of test radiation.

3. Protons

4. Fast Neutrons

5. Pions

6. Heavy ions

1. NCT

a. Principle; $^{10}B(n,\alpha)^{7}Li$ reaction. Boron must be selectively localized in tumor. Subsequent irradiation of the tumor with either thermal neutrons or epithermal neutrons releases energy via the $^{10}B(n,\alpha)^{7}Li$ reaction. Range of the densely ionizing particles is $\leq$10 μ (i.e., $\sim$1 cell diameter). An epithermal neutron beam may be used to obtain deeper penetration in tissue; the tissue itself is used to slow the epithermal neutrons down to thermal energies.

b. Experience - Initial trials were carried out in the United States, but clinical results were poor. Improvements in technique and in the vehicle for boron transport have led to renewed trials in Japan. So far 36 patients with glioblastoma have been treated, with some 5-8 yr "cures" and, on the average, extension of useful life by $\sim$3x (Ref. 13), relative to a random control group.

c. LET (of mixed field) (keV/μ)

γ's = low

$^{14}N(n,p)^{14}C \lesssim 50$

$^{10}B(n,\alpha)^{7}Li$

$\alpha \lesssim 150$

Li $\lesssim$ 200 (Ref. 14)

d. RBE

$B(n,\alpha)^{7}Li = 3.7$

protons from fast neutrons, and

$^{14}N(n,p)^{14}C$ reaction = 2.0

γ-rays = 1.0 (Ref. 15, 16)

RBE's summarized for NCT in Table I are for the mixed field.

e. OER

OER for the $^{10}B(n,\alpha)^{7}Li$ reaction = 1

(from OER of 2.5 MeV α; Ref. 17)

f. Dose Distributions

Two beams are available;

NCT(th) = thermal neutrons; Fig. 1 and 2

NCT(epith) = epithermal neutrons; Fig. 3 (Ref. 18)

For the purpose of evaluation of dose to tumor, ^{10}B concentration has been assumed to be 35 μg ^{10}B per gram tissue; normal tissue dose from ^{10}B was assumed to be 1/3 that of ^{10}B dose to tumor.

g. Fractionation - single exposure of 5-7 hours duration.

2. PAT

a. Principle; activation of Auger electrons in I through photoelectric absorption in I which has been substituted in DNA with iodinated deoxyuridine (IdUrd). This technique is described in detail in Ref. 19.

b. Experience - None

c. LET >100 keV/ (Ref. 20)

d. RBE

RBE = 9.1 due in part to location within nucleus in DNA (Ref. 21).

RBE's in Table I include effects of sensitization to low LET component of mixed field because of presence of IdUrd.

e. OER

OER = 1.4 (Ref. 22)

f. Dose Distribution

Activation photon energy = 40-70 keV

HVL $\overset{\sim}{=}$ 3.5 cm (Ref. 19).

Effective dose to tumor is summarized in Fig. 4 for various situations, which include hypoxia, and hypoxia plus fractionation. In this paper, the effects obtained for 5 and 25% replacement of thymidine (Tyd) with IdUrd are evaluated (PAT (5) and PAT (25)). Five percent replacement with halogenated pyrimidines has already been reported for tumor in man (19).

g. Fractionation; presumably could be fractionated on a conventional schedule (6 weeks, 30 fractions).

3. Protons

a. Principle - 160-200 MeV protons from cyclotrons/linear accelerators allow access to any organ within the body (23,24).

b. Experience

Therapy facilities exist in:

Moscow, Dubna, and Leningrad, Soviet Union

Uppsala, Sweden

Boston, U.S.A.

A facility is currently under construction at BNL, Upton, N.Y., USA.

Since 1961, more than 1000 patients have been treated at the Harvard Cyclotron for diseases of the pituitary gland. Since 1973, 144 cancer patients have been treated (24). Results: for same anatomic sites, dose distributions were judged to be superior to those obtainable with photon beam techniques. The small number of patients and short-time span to date precludes judgment on clinical efficacy.

c. LET

Fig. 5 shows the Bragg peak for monoenergetic protons which has a high LET (>50 keV/μ) only within the last 3-10μ of range (14). For clinical application, it is necessary to spread out the Bragg peak, which results in a low LET beam with no radiological advantage (Fig. 5; Ref. 23).

d. RBE $\lesssim$ 1.0 (Ref. 23,24)

e. OER $\lesssim$ 2.5-3 (same as γ-rays)

f. Dose Distributions

Shown in Fig. 5 for a tumor at ~6 cm depth. Peak-to-plateau dose ratio $\lesssim$ 1.4. At end of particle range, dose decreases from 80 to 20% of maximum dose in 4 mm (lateral fall-off the same) (24).

g. Fractionation - conventional (24).

4. Fast Neutrons

a. Principle - charged particles (deuterons) accelerated onto Be or ^{3}H targets by cyclotron or linear accelerator.

b. Experience:

A number of facilities exist within the United States, and in England. These include:

Medical Research Council Cyclotron, Hammersmith, Eng.

TAMVEC (Texas A & M Variable Energy Cyclotron) (Oct. '72)

Univ. of Washington at Seattle (Sept. '73)

MANTA (Middle Atlantic Therapy Assn.)

Using NRL (Naval Res. Lab.) Cyclotron (Oct. '73)

Fermi Lab Cyclotron (initiated recently).

Between the starting dates listed above and Sept. 1976, more than 700 patients had received fast neutron therapy at cyclotron facilities within the U.S. (25). Results: Normal tissue reactions have been maintained at levels similar to the effects of photon irradiation. Although some results have been encouraging, insufficient data exist to draw any firm conclusions re possible advantages of neutron therapy over photon therapy (25).

At Hammersmith Hospital facility, clinical trials have been going on since 1965. Between 1971 and 1975 a randomized clinical trial on advanced head and neck tumors was carried out; on the basis of 134 patients it was concluded that local control rates were significantly higher in the neutron irradiation group (25). In the years between 1970 and 1978, effects were observed on a wide variety of tumors in 800 patients. "In the great majority of cases, treatments resulted in the complete regression of tumors with very few recurrences. Successful treatments were particularly noteworthy in advanced tumors of the following sites: oral cavity, salivary glands, paranasal sinuses, breast, and anus. Sarcomas of soft tissue also regularly disappeared and the recurrence rate was much lower than those previously obtained with other forms of treatment" (Ref. 6).

c. LET

The spread of mean neutron energy used in fast neutron therapy is rather wide (see Fig. 6; Ref. 25). Neutron energy spectra associated with the limits of bombarding deuteron energy (16-50 MeV) are shown in Fig. 7 (Ref. 26). LETs associated with these neutron energies are given in Ref. 6. The effective LET would be $\sim$40-50 keV/μ.

d. RBE

RBE is again difficult to define uniquely for the various mixed energy neutron beams. Nevertheless, not too much variation is observed over the energy range in question. A good discussion of this problem is given in Chap. 4 of Ref. 6. A representative value of RBE may be obtained from Fig. 8 (Ref. 6); RBE = 3.

e. OER

The OER has been measured in a number of systems in the region between 1 and 15 MeV (27,28). OER = 1.6, so that OGF = 1.6 (Ref. 6).

f. Dose Distributions

Fast neutron depth-dose curves are similar to Co-60 (see Fig. 9; Ref. 26). The scattering of fast neutrons is analogous to the scattering of high energy γ-rays; isodose curves are rounded, with rather wide penumbra. Half value layers for various neutron therapy beams vary from 9-14 cm. For the purpose of these calculations, an HVL = 10 cm (the same as Co-60) will be used.

g. Fractionation

Two to 4 fractions/week (25).

5. Pions

a. Principle: Cyclotron produced pions traverse tissue, ending their range in spallation reactions with elements in tissue, producing high LET charged particles and neutrons (see Fig. 10; Ref. 29). The physical characteristics are: mass = 140 MeV = 273 x mass of electron = 0.15 x mass of proton; charge = charge of electron; mean lifetime = 2.6×10^{-8} sec. (Ref. 30).

b. Experience: Three facilities capable of testing pion beams for radiotherapy now exist:

LAMPF (Los Alamos Meson Physics Facility) in New Mexico (31)

TRIUMF (Tri-University Meson Facility) in Vancouver, British Columbia (30)

SIN (Swiss Institute for Nuclear Research), Villigen, Switzerland (32)

Patient treatments are already underway at LAMPF, and will start shortly at the other two facilities.

As of June 1979, 108 patients have been treated (31). This series was designed in part to evaluate tolerance of normal tissues. Fifty-three of the 108 treatments were in excess of 2700 peak pion rads, the level at which tumor regression is observed. It is thought that at these levels regression occurs more rapidly than with conventional treatment, with less normal tissue reaction. No definite conclusions were drawn.

c. LET

As with protons, OER and RBE of the peak as shown in Fig. 10 is fairly high (OER = 1.8, RBE ≈ 3) (Ref. 26). However, the peak must be broadened to accommodate a larger irradiation volume. Consequently, much of the peak to plateau ratio is lost and average LET goes down. The bulk of a modulated beam in the tumor volume has an LET <10keV/μ, while ~25% of the dose has an LET >10keV/μ (30).

d. RBE

A number of measurements in a variety of mammalian cell systems gives an average peak RBE of ~1.4 (Plateau RBE = 1.0) (30).

e. OER

The OER is such that the average OGF ≈ 1.25 (30,33).

f. Dose Distribution

The distribution of a beam modulated to provide a uniform dose over ~5 cm has a plateau which is ~80% of the peak. An exit dose equal to ~20% of the entrance dose is noted, due in part to the election and muon contamination in pion beams (30,33). A pion dose distribution is compared to other radiations in Fig. 11 (Ref. 34).

g. Fractionation:

100-125 rads daily

6. Heavy Ions:

a. Principle: Accelerated He, C, Ne and Ar ions.

b. Experience

Since July 1975, 157 patients have been treated at the Berkeley Laboratory. Although follow-up is short, control appears at least as good as with conventional therapy. The availability of He, C, Ne and Ar ions makes it possible to compare the effects of improved dose distribution (He ions) with the combined benefits of dose distribution and improved radiobiological parameters (OER and RBE) (Ref. 35).

c. LET:

LET is, of course, variable; for monoenergetic charged particle beams, the high LET portion is concentrated within the very narrow Bragg peak. For protons, LET approaches ~70 keV/μ at the peak so that for the heavier ions (He, C, Ne, Ar) LET should be well above the value necessary for low OER and high RBE. This has been observed for nearly monoenergetic C and Ne beams, where with increasing depth RBE reached a maximum near the Bragg peak, and then decreased. For Ar, RBE was found to decrease due to saturation effects. OER values were near unity for Ne and Ar at the Bragg peak (33). As with other charged particle

beams, the Bragg peak must be modulated to accommodate tumor volume. LET at various depths is given in Ref. 36, for beams with the peak spread over a depth of 10 cm. The average values of LET at the field center (10 cm depth) are:

He = 4.6 keV/μ

C = 27.3 "

Ne = 59.3 "

Ar = 183 "

For each case, LET at the distal side of the field was significantly greater than the proximal side (36).

d. RBE

Differences in RBE between peak and plateau (entrance) are not very large when the peak is broadened to 10 cm. RBE values are given in Ref. 37 for beam entrance (plateau), peak center, and distal peak. Average RBE values for peak center and entrance are:

	Peak	Plateau
He	1.2	1.0
C	1.25	1.0
Ne	2.33	1.95
Ar	2.15	2.18

Argon ion RBEs, particularly at the distal peak, are lower because of saturation effects.

e. OER

OER values for the same positions as described above are also given in Ref. 37. Oxygen Gain Factors (OGF) at peak center are given in Ref. 33, which summarizes most of the available experimental data. Oxygen Gain Factors have a

range of values, being lower at the proximal side and higher at the distal end of the modulated peak.

OGF's for peak center are:

He = 1.2

C = 1.2

Ne = 1.5

Ar = 1.8

f. Dose Distributions

The dose distributions for modulated charged particle beams are quite similar (34,36) (see Fig. 11). Dose localization with heavy ions is reduced somewhat with increasing charge; protons give the best dose localization, with Ne and Ar retaining favorable localization characteristics up to ranges of ~15 cm (36). Diminished usefulness beyond ~15 cm is a consequence of scattering and nuclear interaction before reaching the Bragg peak. For example, the percent of particles lost per cm travel in water are 1.5, 1.5, 2.0, 3.0, 4.0 and 5.0% for π^-, p, He, C, Ne and Ar ions, respectively. Lighter secondary particles (protons, neutrons) have deeper penetrations, producing an exit dose (see curve for Ne, Fig. 11).

Depth dose distribution will depend to some degree on the peak width. For intercomparison of depth dose distributions here, peak width will be assumed to be 5 cm at a mean depth of 10 cm.

Peak-to-plateau ratios will then be (34,35):

He = 1.4

C = 1.4

$$Ne = 1.25$$

$$A = 1.10$$

EVALUATION OF MERIT FACTOR

In 1975, a review of high LET facilities was carried out by Hall (26) in which up to 5 "stars" were awarded to neutrons, protons, pions or heavy ions, according to their value of OGF, and again separately, for their capacity to localize dose in tumor. In the present comparison, a merit factor M will be evaluated on the basis of effective dose to tumor relative to that delivered to normal tissues in the incident beam. The ratio of effective doses (D) is obtained by multiplying the ratio of RBEs (R) (peak/plateau, or tumor/normal tissue) times the ratio of absorbed doses (A) (peak/plateau, or tumor/normal tissue), so that

$$M(1) = D = R \times A$$

A second merit factor will be evaluated incorporating the effects of high LET radiations, as represented by the Oxygen Gain Factor (O).

$$M(2) = R \times A \times O$$

The Oxygen Gain Factor O is used here to represent the potential gain to be derived from radiation insensitivity to ambient physical and radiobiological parameters such as dose rate, oxygen tension, and cell cycle.

A third merit factor will be evaluated incorporating a factor representing the ability of the radiation to restrict dose to tumor volume. This dose localization factor will be called L. A maximum value of L=3 will be assigned to NCT and PAT, both of which have the potential ability to automatically localize dose

on a cellular (10μ) level. The magnitude of 3 assigns a value to cellular beam alignment which is the same as is given to an OER of 1 (i.e., OER and beam alignment are each weighted equally). Neutrons, which are difficult to collimate and give dose distributions similar to photons, are assigned L = 1, (i.e., given the same value as conventional photon beam irradiation). Protons, heavy ions, and pions will be given an intermediate value of 1.5. Thus,

$$M(3) = R \times A \times O \times L$$

The plethora of parameters make the determination of a unique merit factor difficult and probably not desirable. Different situations will require or permit application of different therapy beams. Depth dose is accounted for in the ratio of absorbed doses A. Yet this is not an overall determinant, as a poorly-penetrating beam may still be potentially useful in cases where tumors are accessible. In order to retain the ability to illuminate such situations, merit factors have been evaluated for depths of 1, 4, and 10 cm. Dose distribution data are used to evaluate A. The factor A is the ratio of oxygenated tumor tissue dose to surface normal tissue dose (or maximum normal tissue dose, whichever is greater). For charged particles, A will be ≥ 1; for exponentially attenuated radiations (photons, fast neutrons, thermal neutrons), $A \leq 1$.

The relevant parameters are gathered together for the various beams in Table I; merit factors are given in Tables II, III and IV, for 1, 4 and 10 cm depth, respectively.

It is understood that the quantification of merit factors is somewhat arbitrary, and that their use would be for an estimation of relative worth, rather than in an absolute determination of value. Thus small fractional changes may

not be meaningful, while factors of two should reflect real differences in potential.

In particular, the assignment of a factor of 3 to physiological alignment of dose at cellular dimensions might be considered arbitrary. Several facts bear on this:

1. The clinical finding that with small to medium volume radiation fields, more than ½ of tumors were suspected of receiving inadequate coverage.
2. Significant benefits to be gained from fractional (10%) increases in tumor dose, and
3. the fact that normal tissue tolerance to radiation increases as the volume of irradiated normal tissues decreases.

Therefore the magnitude of 3 would not appear to be frivolous. In any case factors have been presented with and without high LET effects as represented by "0", and the effects of enhanced beam localization and alignment "L", so that relative merit may be obtained without these factors if desired.

DISCUSSION

1. Fractionation Effects

The effects of fractionation have been ignored in the calculation of merit factors. They have been ignored even though the effects are suspected of being quite profound, because of the difficulty of quantitation. Fractionation is thought to exert its effects through:

a. Greater effect on cells with relatively fast cycling times.
b. As cells in the rapidly cycling "leading edge" of tumors are killed and removed, more centrally-located hypoxic or "latent" cells become better vascularized and rejoin the proliferative pool.

c. Repair of normal cells is enhanced relative to that of tumor, because a "bio-feedback" mechanism in normal tissue stimulates regrowth.

It is assumed that even with high LET radiations such as Ar, fractionated therapy will be used in order to take advantage of enhanced regrowth in normal tissues. Also, where LET of incident radiations is low, and peak (tumor) radiation is high, fractionation would be uniquely advantageous as repair would be allowed selectively to normal tissues. The latter is true to a limited extent for π^-, He, C, and Ne ions, and to a large extent for NCT and PAT. It is estimated that fractionation would enhance the effect of photoactivation therapy by up to a factor of 3, since the LET of the activating incident radiation (~50 kVp x rays) is predominantly low (19). In addition, fractionation may be necessary for NCT and PAT as replacement of thymidine and perhaps boron transport will depend upon efficient vascularization.

2. Applicability of NCT

Neutron Capture Therapy is at present limited to use with brain tumors, as the blood brain barrier is used to exclude borated compounds used for boron transport, from normal brain. Nevertheless, its extension to other tumors is actively being investigated through the use of borated porphyrins, phenothiazines, various nucleosides, and antibodies.

Results in Japan where brain tumors are being treated with NCT appears to be extremely encouraging. Every effort is made to insure access of the thermal neutron beam to the tumor bed, through surgical techniques. From Tables III and IV (where NCT(th) has been omitted due to its inapplicability at depths greater than a few cm), and tables of merit factors for other depths (not included in this paper), it is clear that an epithermal neutron beam provides the best merit factor now available for depths up to 8 cm.

3. Applicability of PAT

Photoactivation therapy has not been evaluated in vivo. Nevertheless its position on the merit factor tables appears to justify its investigation. As with NCT, its application would be limited to situations where normal tissues within the radiation field do not demonstrate prohibitive IdUrd update. Again, brain tumors would appear to fit this category. Since PAT has a uniquely high ratio of tumor RBE/normal tissue RBE, potential benefits would be gained in implant therapy, where the benefits of fractionation would automatically accrue.

4. Fast Neutrons

By far, the largest body of experience exists with Fast Neutron Therapy (FNT). Clinical evaluations to date indicate significant benefits have been obtained (6). Yet the positions of FNT on the merit tables is consistently lower than that of the other particle modalities, and above only Co-60, irrespective of assumptions made (i.e., inclusion of O and/or L).

It then follows that if benefits with FNT are real, additional gains are within reach with other modalities.

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FIGURE CAPTIONS

1. Absorbed dose distributions in tissue from mixed field components of Thermal Neutron Beam, Brookhaven Medical Research Reactor (Ref. 18).
2. Same as Fig. 1, but including dose to tissue from 35 μg ^{10}B per gram of tissue (total +^{10}B curve).
3. Absorbed dose distributions in tissue from mixed field components of epithermal neutron beam, Brookhaven Medical Research Reactor (Ref. 18). "Total +^{10}B" curve includes dose to tissue from 35 μg ^{10}B per gram of tissue.
4. Effective dose to tumor from Auger electrons activated by an external photon beam. Thymidine replacement with IdUrd is assumed to be at a level of 5, 25, or 50%. From ref. 19.
5. Bragg peak from a monoenergetic proton beam and a modulated proton beam dose distribution, compared to ^{60}Co. Ref. 23.
6. Characteristics of fast neutron beams currently in use for therapy. From ref. 25.
7. Neutron energy spectra from representative fast neutron sources used in therapy. Ref. 26.
8. RBE of neutrons generated by 16 MeV D - Be, for various dose fractions (acute reactions in skin). From ref. 6.
9. Depth dose curves in tissue for various neutron beams, compared to conventional radiation sources. From ref. 26.
10. Depth dose curve in tissue for a beam of pure pions. Momentum 190 MeV/c ± 5%. From ref. 29.
11. Depth dose distributions for various modulated charged particle beams, compared with 14 MeV neutrons and ^{60}Co.

TABLE I

RELEVANT PARAMETERS FOR PARTICLE THERAPY BEAMS

RADIATION	LET (KeV/μ)	RBE Peak	RBE Plateau	OGF	Peak/Plateau Ratio (A)
NCT (Thermal)	150-200	3.1 (1cm) 2.7 (4cm)	2.6	3.0	1.6 (1cm) 0.6 (4cm)
NCT (Epithermal)	150-200	2.3 (cm) 2.6 (4cm) 2.4 (10cm)	2.1	3.0	1.4 (1cm) 1.4 (4cm) 0.5 (10cm)
PAT (5)	$\geq$ 100	2.7	1.0	2.14	0.83 (1cm) 0.46 (4cm) 0.14 (10cm)
PAT (25)	$\geq$ 100	5.4	1.0	2.14	0.83 (1cm) 0.46 (4cm) 0.14 (10cm)
PROTONS	Low	1.0	1.0	1.0	1.4
FAST NEUTRONS	40-50	3.0	3.0	1.6	0.92 (1cm) 0.75 (4cm) 0.50 (10cm)
PIONS	75% $\leq$ 10 25% > 10	1.4	1.0	1.3	1.3
He IONS	4.6	1.2	1.0	1.2	1.4
C IONS	27	1.3	1.0	1.2	1.3
Ne IONS	59	2.3	2.0	1.5	1.3
Ar IONS	180	2.2	2.2	1.8	1.1
CO-60	Low	1.0	1.0	1.0	0.92 (1cm) 0.75 (4cm) 0.50 (10cm)

TABLE II

MERIT FACTORS FOR DEPTH IN TISSUE OF 1 CM

RADIATION	M (1) R x A	RADIATION	M (2) R x A x Q	RADIATION	M (3) R x A x Q x L
PAT (25)	4.5	PAT (25)	9.6	PAT (25)	29.
PAT (5)	2.2	NCT (th)	5.8	NCT (th)	17.
NCT (th)	1.9	PAT (5)	4.8	PAT (5)	14.
PIONS	1.8	NCT (epith)	4.6	NCT (epith)	14.
He IONS	1.7	Ne IONS	2.2	Ne IONS	3.4
C IONS	1.6	PIONS	2.2	PIONS	3.3
NCT (epith)	1.5	He IONS	2.0	He IONS	3.0
Ne IONS	1.5	C IONS	2.0	C IONS	2.9
PROTONS	1.4	Ar IONS	2.0	Ar IONS	2.9
Ar IONS	1.1	FAST NEUTRONS	1.5	PROTONS	2.1
FAST NEUTRONS	0.94	PROTONS	1.4	FAST NEUTRONS	1.5
CO-60	0.92	CO-60	0.92	CO-60	0.92

TABLE III

MERIT FACTORS FOR DEPTH IN TISSUE OF 4 CM

RADIATION	M (1) R x A	RADIATION	M (2) RxAxO	RADIATION	M (3) RxAxOxL
PAT (25)	2.5	NCT (Epith)	5.3	NCT (Epith)	16.
NCT (Epith)	1.8	PAT (25)	5.3	PAT (25)	16.
PIONS	1.8	PAT (5)	2.7	PAT (5)	8.0
HE IONS	1.7	Ne IONS	2.2	NCT (th)	5.8
C IONS	1.6	PIONS	2.2	Ne IONS	3.4
Ne IONS	1.5	He IONS	2.0	PIONS	3.3
PROTONS	1.4	C IONS	2.0	He IONS	3.0
PAT (5)	1.2	Ar IONS	2.0	C IONS	2.9
Ar IONS	1.1	NCT (th)	2.0	Ar IONS	2.9
FAST NEUTRONS	0.75	PROTONS	1.4	PROTONS	2.1
CO-60	0.75	FAST NEUTRONS	1.2	FAST NEUTRONS	1.2
NCT (th)	0.65	CO-60	0.75	Co-60	0.75

TABLE IV

MERIT FACTORS FOR DEPTH IN TISSUE OF 10 CM

RADIATION	M (1) R x A	RADIATION	M (2) RxAxO	RADIATION	M (3) RxAxOxL
PIONS	1.8	Ne IONS	2.2	NCT (epith)	5.3
HE IONS	1.7	PIONS	2.2	PAT (25)	4.9
C IONS	1.6	He IONS	2.0	Ne IONS	3.4
Ne IONS	1.5	C IONS	2.0	PIONS	3.3
PROTONS	1.4	Ar IONS	2.0	He IONS	3.0
Ar IONS	1.1	NCT (epith)	1.8	C IONS	2.9
PAT (25)	0.76	PAT (25)	1.6	Ar IONS	2.9
NCT (epith)	0.59	PROTONS	1.4	PAT (5)	2.4
FAST NEUTRONS	0.50	PAT (5)	0.81	PROTONS	2.1
CO-60	0.50	FAST NEUTRONS	0.75	FAST NEUTRONS	0.75
PAT (5)	0.38	CO-60	0.50	CO-60	0.50

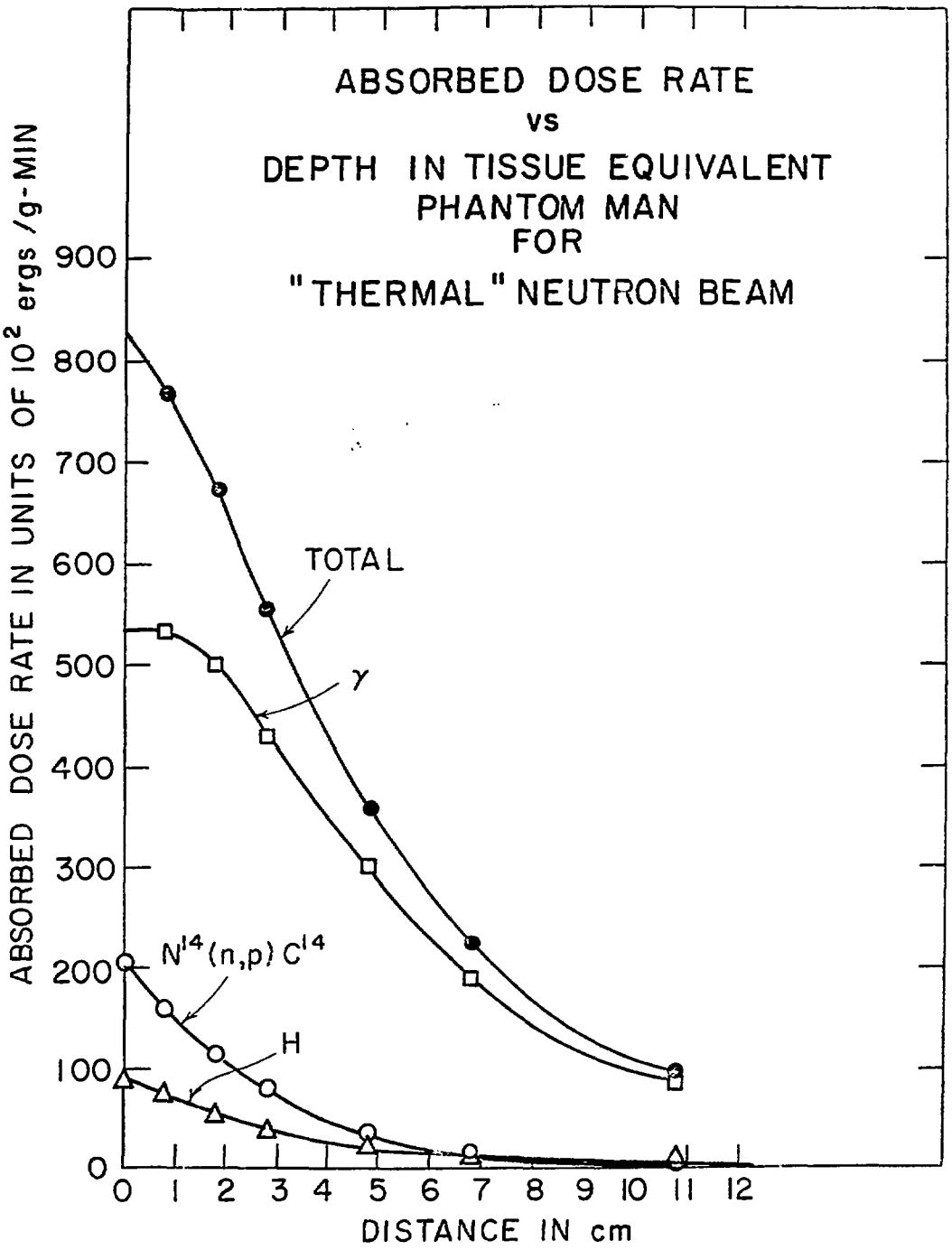

ABSORBED DOSE RATE
vs
DEPTH IN TISSUE EQUIVALENT
PHANTOM MAN
FOR
"THERMAL" NEUTRON BEAM
ABSORBED DOSE RATE IN UNITS OF 10^2 ergs /g-MIN
900
800
700
600
500
400
300
200
100
0
TOTAL
γ
$N^{14}(n,p)C^{14}$
H
0 1 2 3 4 5 6 7 8 9 10 11 12
DISTANCE IN cm

FIGURE 1

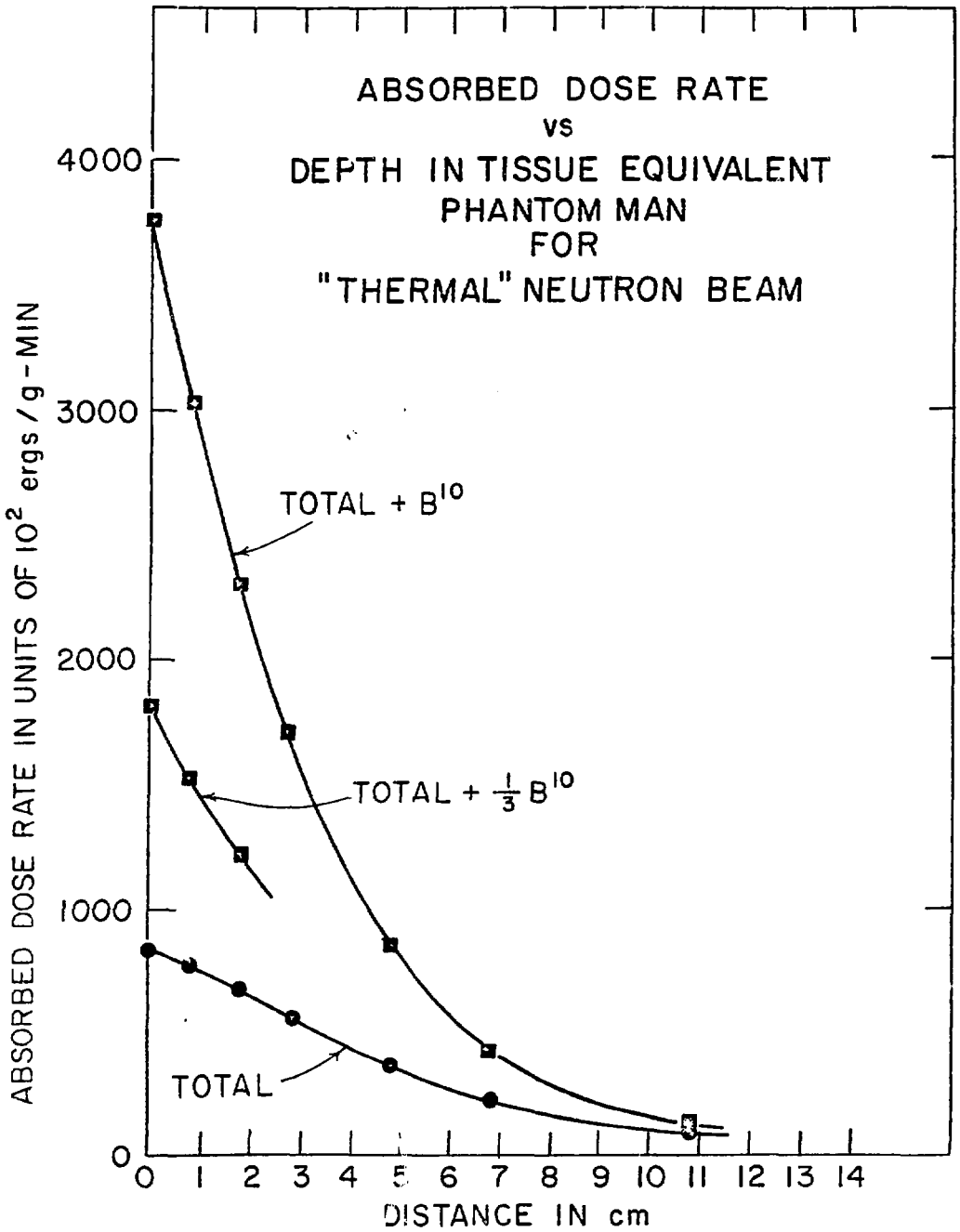

ABSORBED DOSE RATE
vs
DEPTH IN TISSUE EQUIVALENT
PHANTOM MAN
FOR
"THERMAL" NEUTRON BEAM
ABSORBED DOSE RATE IN UNITS OF 10^2 ergs / g - MIN
4000
3000
2000
1000
0
TOTAL + B^{10}
TOTAL + $\frac{1}{3}$ B^{10}
TOTAL
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14
DISTANCE IN cm

FIGURE 2

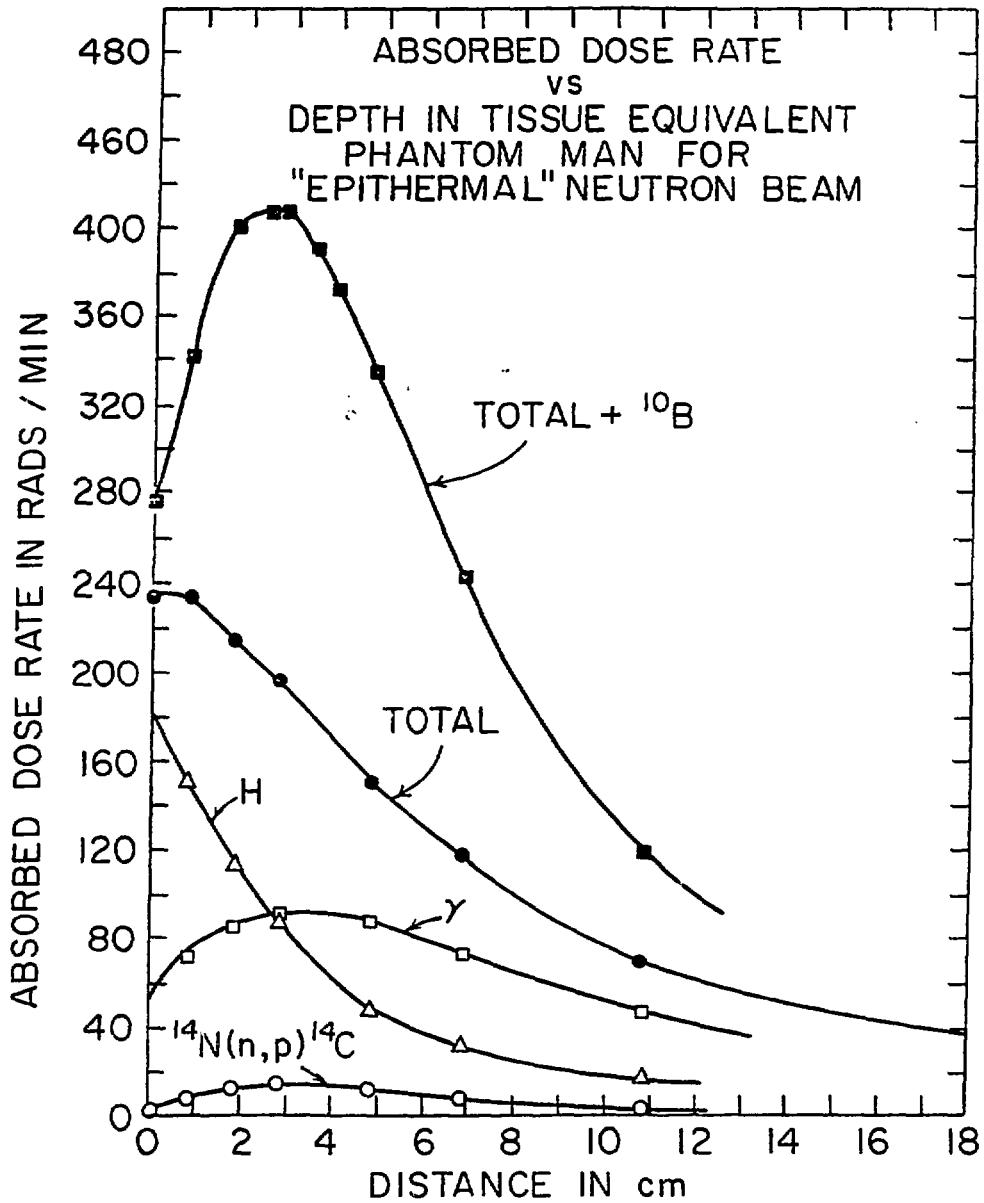

ABSORBED DOSE RATE
vs
DEPTH IN TISSUE EQUIVALENT
PHANTOM MAN FOR
"EPITHERMAL" NEUTRON BEAM
TOTAL + ^{10}B
TOTAL
H
γ
$^{14}N(n,p)^{14}C$
ABSORBED DOSE RATE IN RADS / MIN
DISTANCE IN cm
0
40
80
120
160
200
240
280
320
360
400
460
480
0
2
4
6
8
10
12
14
16
18

FIGURE 3

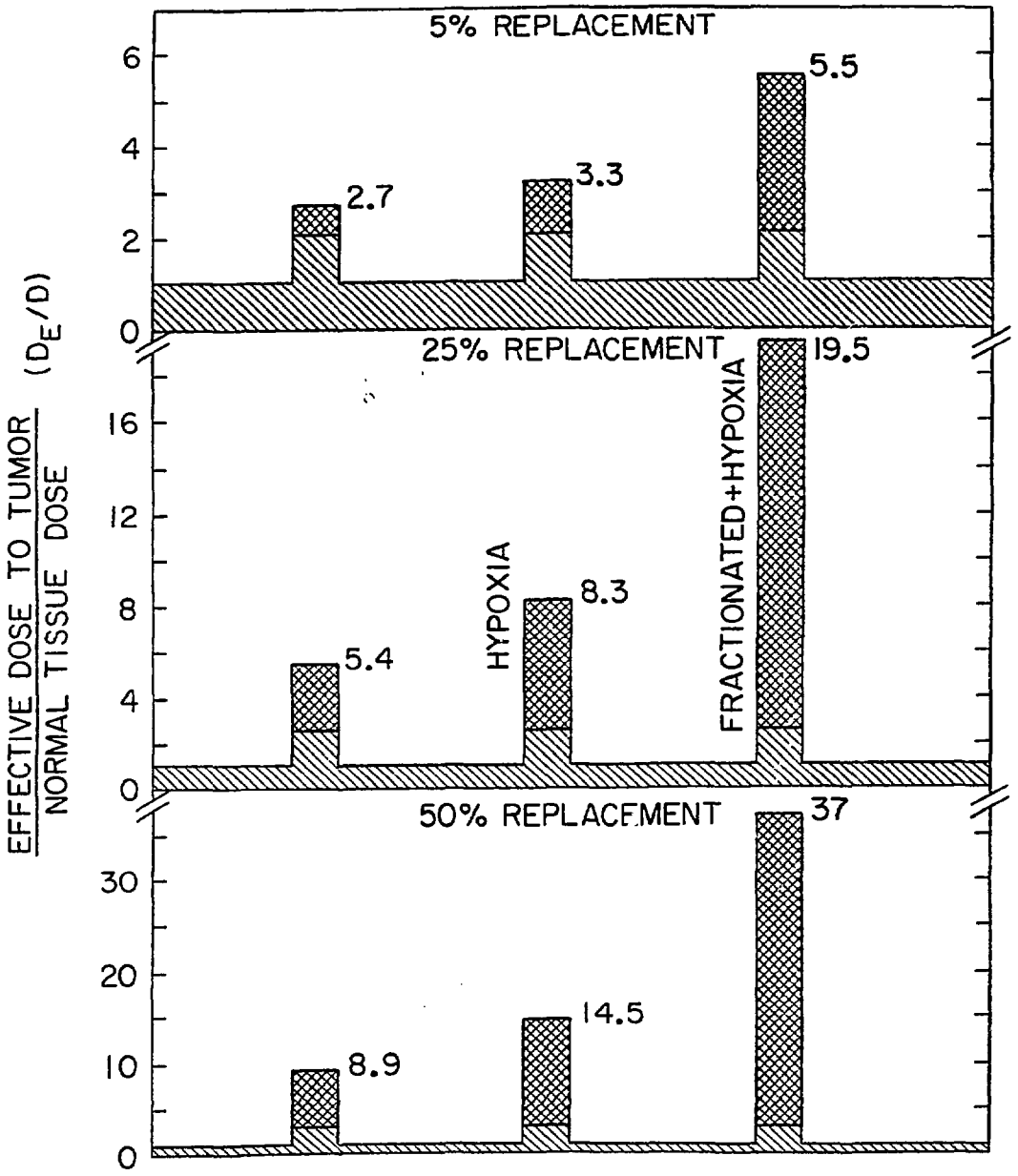

5% REPLACEMENT
6
4
2
0
2.7
3.3
5.5
25% REPLACEMENT
16
12
8
4
0
5.4
HYPOXIA
8.3
FRACTIONATED+HYPOXIA
19.5
50% REPLACEMENT
30
20
10
0
8.9
14.5
37
EFFECTIVE DOSE TO TUMOR / NORMAL TISSUE DOSE (DE/D)

FIGURE 4

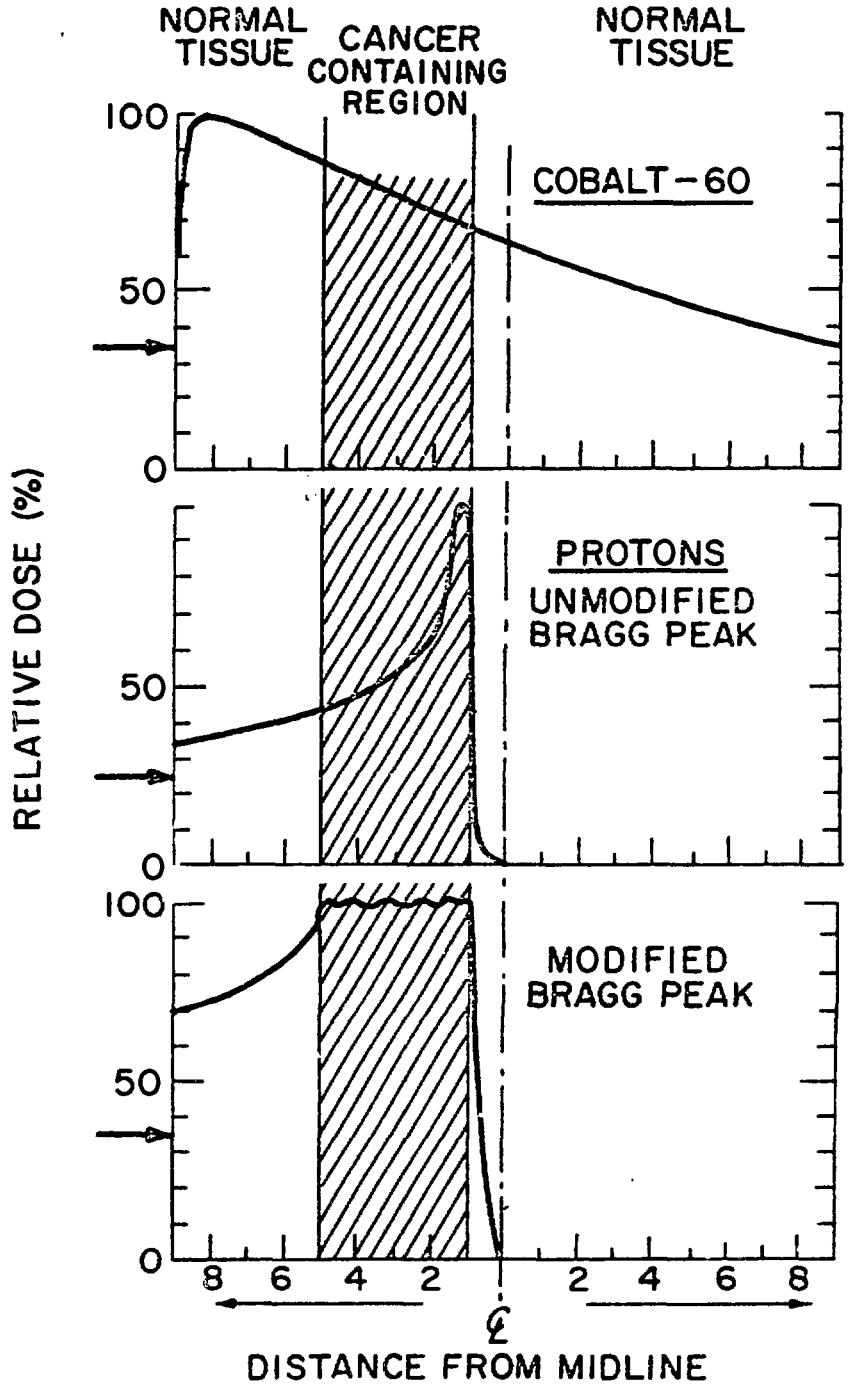

NORMAL TISSUE
CANCER CONTAINING REGION
NORMAL TISSUE
100
50
0
COBALT-60
PROTONS
UNMODIFIED BRAGG PEAK
MODIFIED BRAGG PEAK
RELATIVE DOSE (%)
8 6 4 2
2 4 6 8
℄
DISTANCE FROM MIDLINE

FIGURE 5

FACILITY	DEUTERON ENERGY (MeV)	MEAN NEUTRON ENERGY (MeV)	DEPTH OF 50% DOSE (cm)	DEPTH OF D MAX (cm)
Naval Research Lab	35	15	12.8	0.55
TAMVEC	50	21	13.8	1.07
University of Washington	25	8	10.2	0.30
Hammersmith Hospital	16	7.6	8.8	0.23

Comparison of beam characteristics

Figure 6

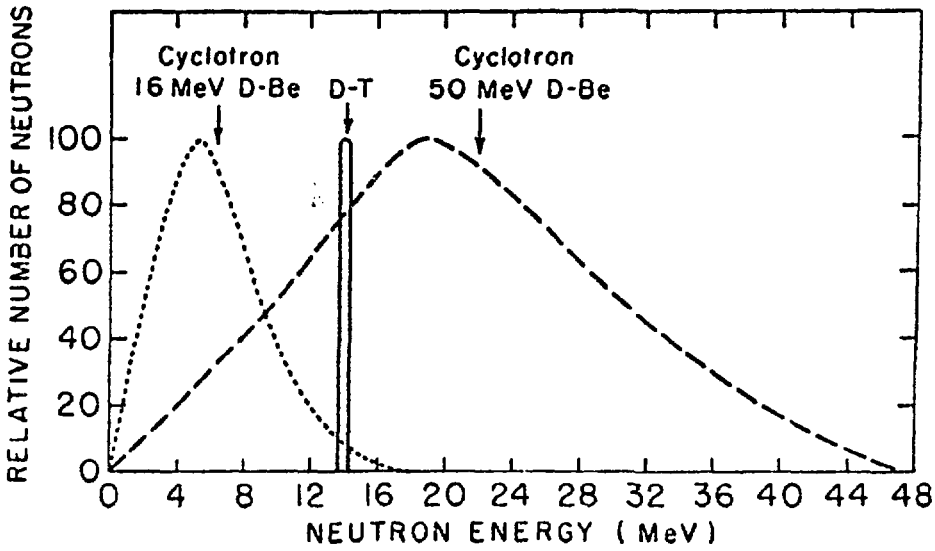

Cyclotron
16 MeV D-Be
D-T
Cyclotron
50 MeV D-Be
RELATIVE NUMBER OF NEUTRONS
100
80
60
40
20
0
0 4 8 12 16 20 24 28 32 36 40 44 48
NEUTRON ENERGY (MeV)

FIGURE 7

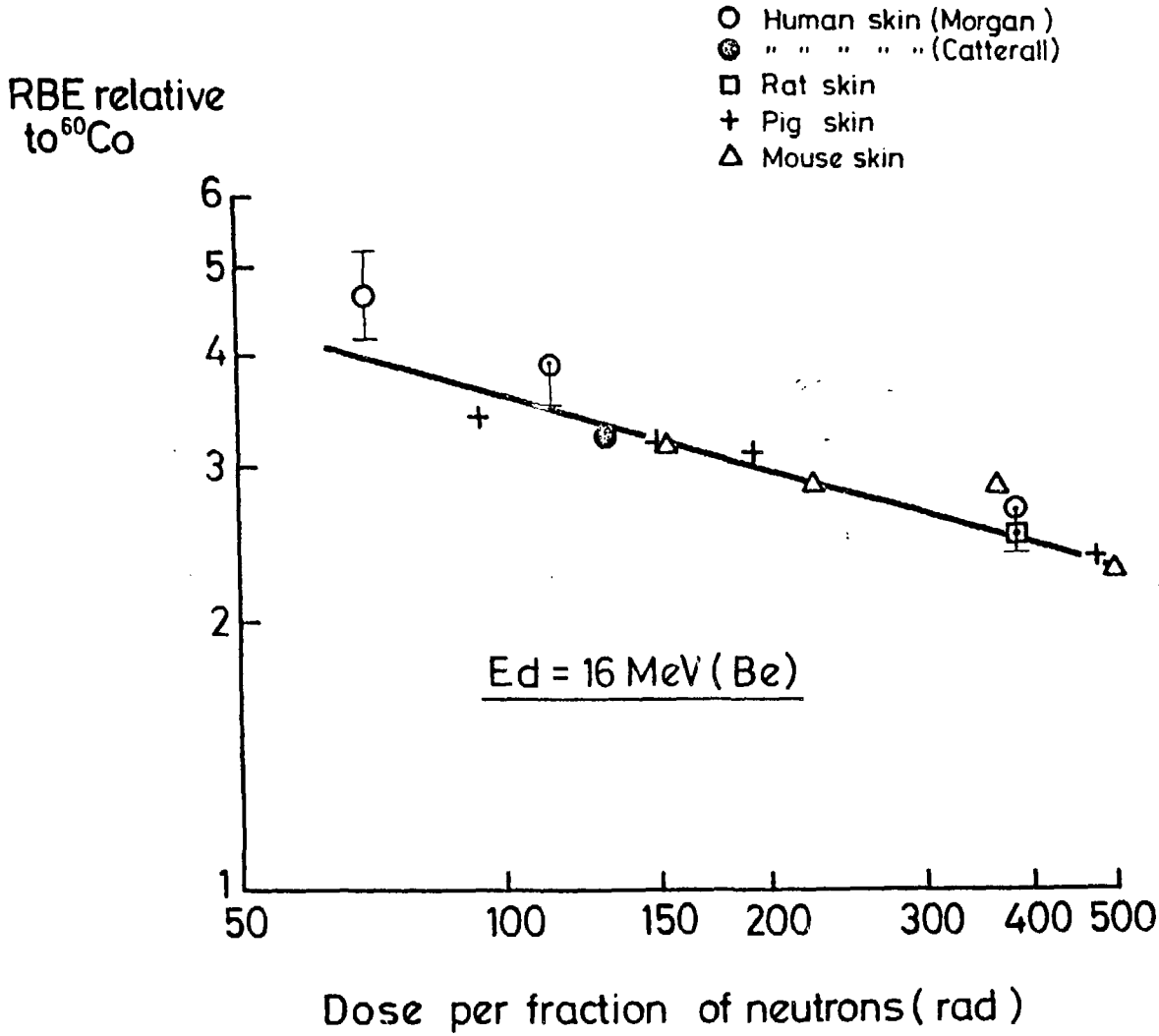

Human skin (Morgan)
" " " " " (Catterall)
Rat skin
Pig skin
Mouse skin
RBE relative to ^{60}Co
6
5
4
3
2
1
Ed = 16 MeV (Be)
50
100
150
200
300
400
500
Dose per fraction of neutrons (rad)

FIGURE 8

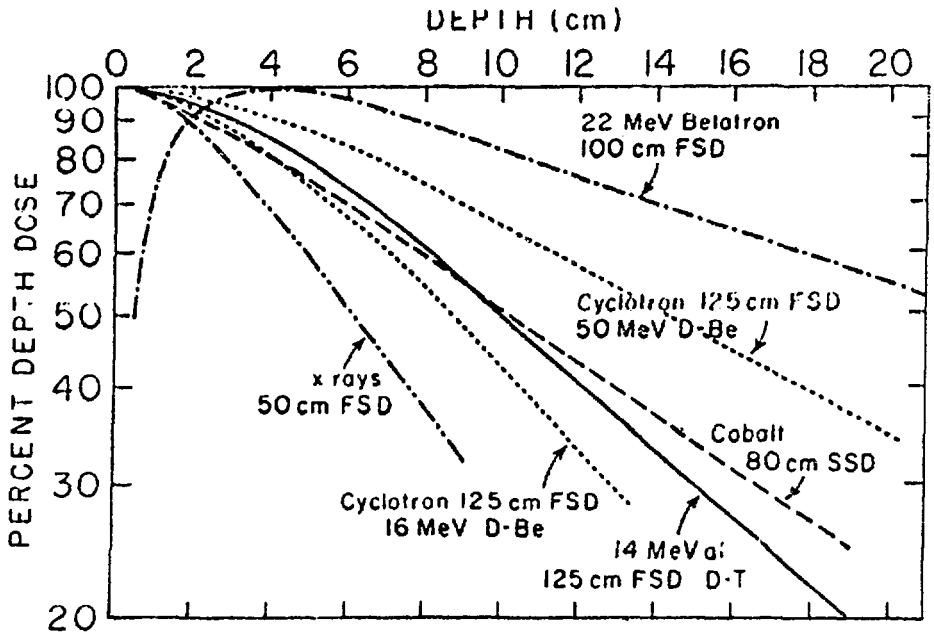

DEPTH (cm)
0
2
4
6
8
10
12
14
16
18
20
PERCENT DEPTH DOSE
100
90
80
70
60
50
40
30
20
22 MeV Betatron
100 cm FSD
Cyclotron 125 cm FSD
50 MeV D-Be
x rays
50 cm FSD
Cobalt
80 cm SSD
Cyclotron 125 cm FSD
16 MeV D-Be
14 MeV a
125 cm FSD D-T

FIGURE 9

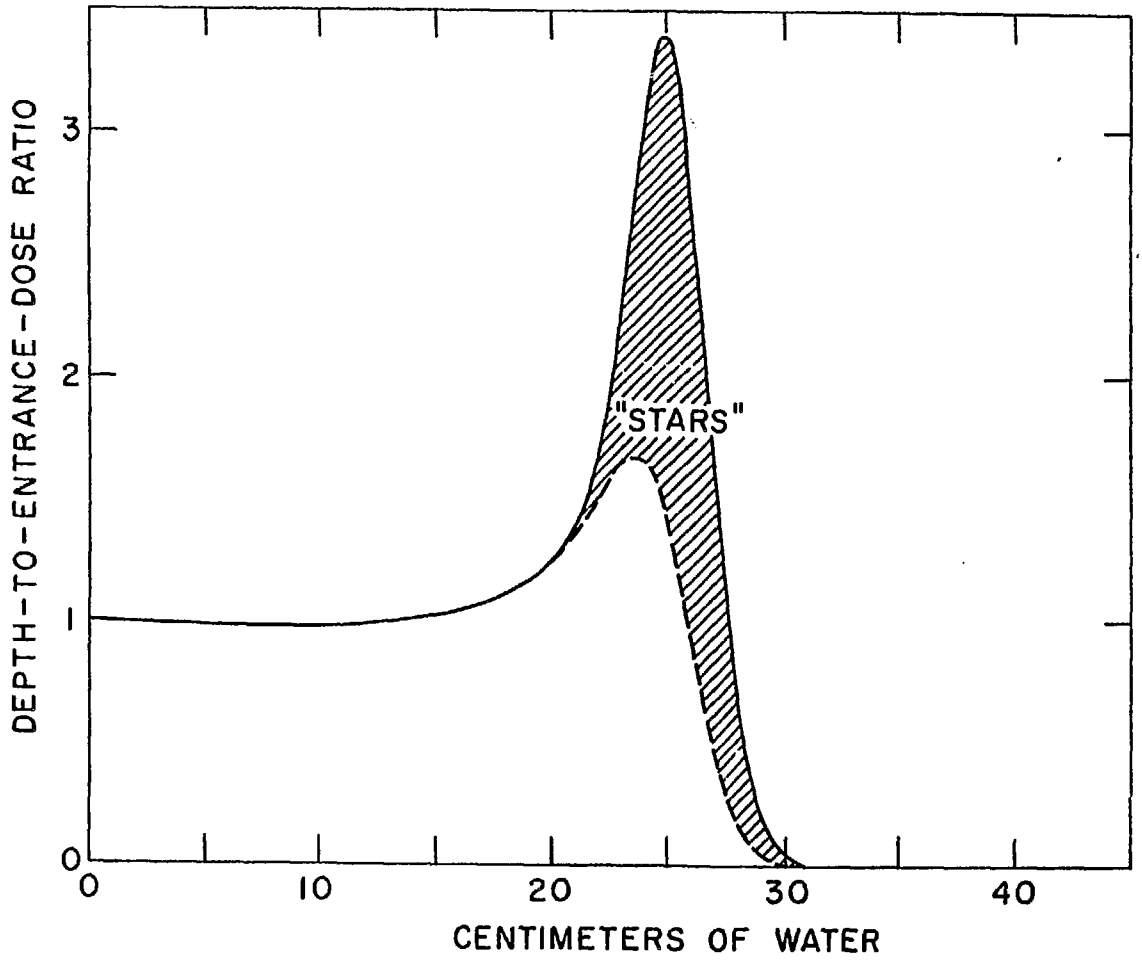
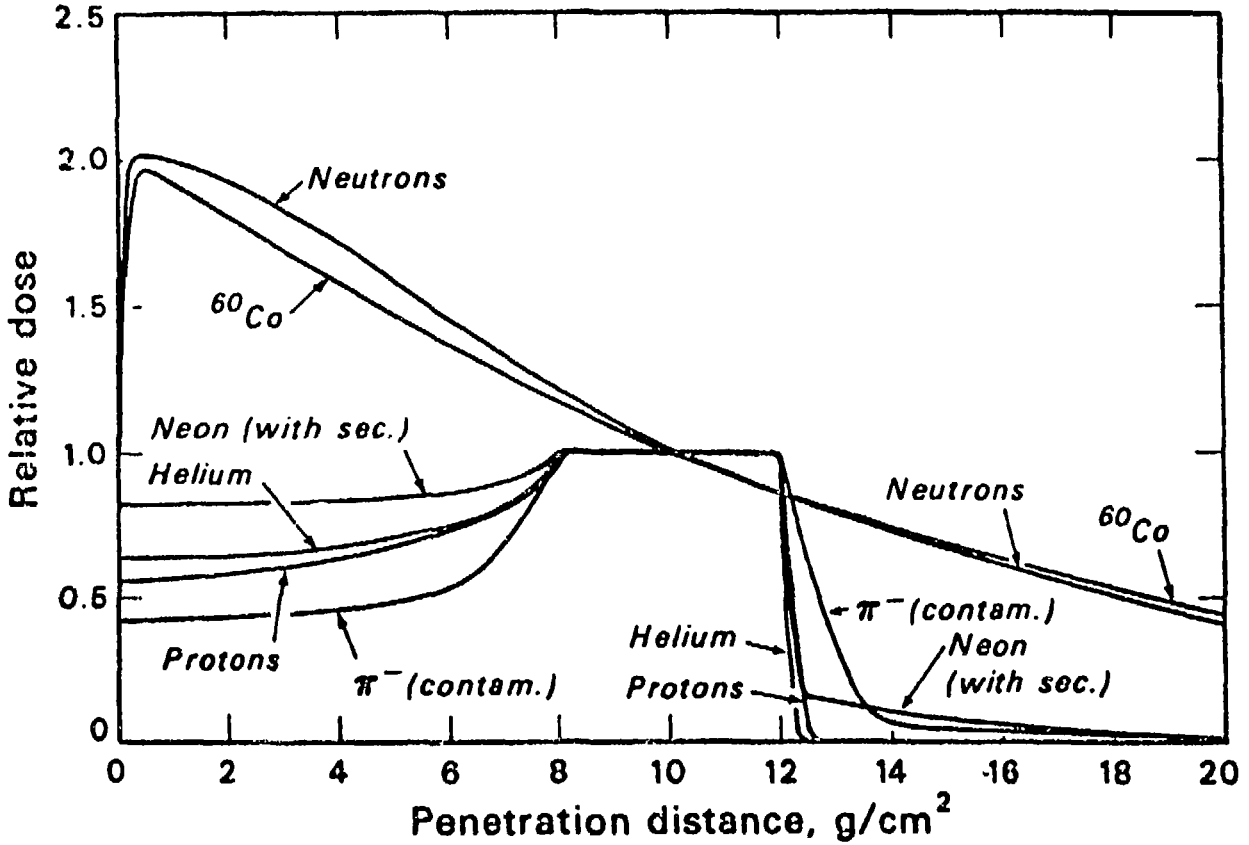


FIGURE 10



Central axis depth-dose distributions of ^{60}Co gamma rays, 14-MeV neutrons, protons, helium ions, neon ions, and negative pions.

FIGURE 11

Bond