PHYSICS OF OUR DAYS

Application of high-energy heavy charged particles in medicine

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This article treats the biological action of radiation, the methods and technology of irradiation by heavy charged particles, and the advantages to be gained by using heavy charged particles in radiation therapy and radioneurosurgery. Features of the dose distribution and of the biological action of different radiations are discussed. Estimates of the prospects for using heavy particles in medicine are given and the world data on performed studies are summarized.

One of the fundamental methods of treating malignant tumors is radiation therapy. X rays, γ rays, and electrons of energies up to 20 MeV are used for irradiation. It has recently been shown that irradiation by heavy charged particles (protons, α particles, etc.) permits one to get substantially better results, to avoid general overirradiation of the patient, and to perform bloodless surgical operations with thin beams of high-energy particles.

1. INTRODUCTION

At present, radiation and surgery, jointly or separately, are the most important methods of treating cancer patients. However, a considerable fraction of the patients that have undergone a course of radiotherapy cannot be completely cured. In most cases, this happens because of metastases that are not found in time or are too widespread. However, often the reason is that the existing means of radiation therapy prove to be insufficient for curing the patient. Hence, any improvement in the methodology of radiation therapy is of help to a vast number of cancer patients.[1)]

Up to now, γ rays and electrons have mainly been used in radiation therapy. Unfortunately, when one uses these types of radiation, the injury to healthy tissues is not small in comparison with the damage to the tumor. In 1946, Wilson[3] proposed using heavy charged particles in radiation therapy, in particular, protons. Interest in applying negative π^- mesons arose in 1961 after the first report of Fowler and Perkins[4] and Fowler's lecture[5] in memory of Rutherford (1964). More and more extensive experiments have been performed in recent years on clinical application of heavy charged particles: protons, deuterons, α-particles, and multiply-charged ions, and experiments with π^- mesons are being planned. These particles must have relatively high energies in order to penetrate deeply enough into the human body and to strike the tumor tissue: from several tens to several hundreds of megaelectron-volts. The widespread development of accelerator technology at these energies has recently given rise to a new field of medical radiology, the clinical use of heavy charged particles.[6-13]

Most often, radiation methods are applied in medicine for their action on the cells of malignant tumors. Another pathway is also projected: using radiations for bloodless surgery, i.e., for destroying certain regions of an organ or tissue in cases when it is desirable to avoid surgical intervention, e.g., in intracranial operations. Thus, radioneurosurgery has begun to develop, along with the radiation therapy of tumors.

As we know, one of the difficulties in using ionizing radiations for treating malignant tumors is that cancer cells multiply rapidly and are prone to form secondary foci, or metastases, in different organs. No methods have yet been found that permit one radically to affect the cancer cells without injuring healthy cells. Hence, modern medicine often proves to be helpless in cases of extensive metastatic processes. However, when no metastases are manifested clinically, the most radical means of treatment is surgical intervention. Only with certain localizations and forms of tumors does irradiation in itself cure the patient.

What is the position of radiation therapy in the modern clinic? As we have noted, irradiation is a radical means of treatment in certain cases, including, e.g., skin cancer, lip cancer, and cervical cancer. However, most often radiation therapy is applied in combination with surgical intervention.[14] When there is no assurance that the found tumor has not metastasized, the operation is combined with irradiation of the adjoining zone of possible metastasis, i.e., the corresponding lymph nodes.

The tumor itself is also irradiated. When irradiated, a tumor partially, or sometimes completely, regresses, and the edema of the adjacent tissues is diminished in cases that exhibit it. All of this reduces the volume of the operation, and often it opens up a possibility for surgical intervention.

In certain patients, radiation therapy is applied for so-called palliative purposes: the patient cannot always be saved, but one should always prolong his life and ease his suffering. Suppressing a tumor by irradiation and reducing the edema around it diminishes pain (which in itself is very important), and it improves the function of the affected organ.

The main aim of radiation therapy is to damage all the tumor cells enough to prevent new growth of the tumor. Here one must establish conditions that minimize injuries to the reproductive capacity of the surrounding healthy tissue. Unfortunately, this is not so simple to achieve. The radiation dose that can be applied to the focus is most often limited by the reaction of the skin in the radiation field, by general reactions of the organism (e.g., change in the composition of the blood), and by the need for sparing neighboring organs from damage. One cannot apply large doses in the usual methods of irradiation, especially when the tumor lies near organs whose overirradiation is inadmissible. Hence, success in radiation therapy essentially depends on how well localized the dose field is. As will become clear below, beams

of heavy charged particles permit one to create an incomparably better localized field than γ rays, electrons, or x rays.

2. THE BIOLOGICAL ACTION OF RADIATION

The biological action of radiation is determined by the ionization that it produces in the tissues. The unit of measurement of the dose is the "rad," or a dose at which 100 ergs are absorbed per gram of matter. Doses of 20—30 kilorads are required to suppress the vital activity of cells. However, marked changes set in, even at substantially smaller doses in tissues. In particular, surgical wounds cease to heal. Overall irradiation of the body beyond 15 rad can be dangerous to health, and it is simply inadmissible above 50 rad. At doses of overall radiation of the order of 700 rad, death occurs in two or three weeks because of damage to the organs of blood production (bone marrow). Rapid death occurs at doses above 1000 rad (several days). This mainly involves overirradiation of the brain and the mucous membrane of the intestine.

Radiation damage to cells can be manifested in different ways. First of all, cells lose their ability to divide, owing to damage to their hereditary mechanism (chromosome aberrations). Often these injuries are not manifested immediately: the irradiated cells can divide, but their next generation can no longer divide. The vital activity of the cells is itself damaged at large doses, and decomposition of the tissues sets in (necrosis).

The intensity of radiation expressed in rads determines the physical, but not the biological dose. The biological action depends not only on the amount of ionization, but also on its distribution. A dense ion track acts more strongly on tissue that several light tracks having the same total content of ions (with the same mean concentration of ions). The number of ions is proportional to the energy lost by the radiation in the tissue. The concentration of ions in a track is proportional to the amount of energy that the particle (or the secondary electron from a γ quantum) loses per unit path length, or as one says, proportional to the linear energy transfer (LET). X rays from a 200-kV tube give a LET of 3 keV/μm, protons of 130 MeV energy give 0.6 keV/μm, and recoil nuclei from fission neutrons give 30—50 keV/μm.

The difference in biological action of particles at the same physical dose is accounted for by the coefficient of relative biological effectiveness (RBE). In contrast to the physical dose or the LET, the value of the RBE is not defined in a single way: the RBE measured by the survival of cells differs from the RBE determined by chromosome aberrations or from the death of experimental animals. A new quantity has recently been used instead of the RBE: the quality coefficient (or factor), for which one chooses one of the experimentally obtained RBE values, most often the most pessimistic one. Table I[15] gives the currently accepted values.

The biological dose is measured in biological Roentgen equivalents (rems), and it is proportional to the product of the physical dose and the RBE. As we see from the above, the difference between the physical and biological doses is not significant in irradiation with x rays, γ rays, fast electrons, and protons. However, it is very important in working with neutrons, multiply-charged ions, and π^- mesons.[2)]

TABLE I. Relation of the quality factor to the LET

LET, keV/μm	Quality factor
3.5 or less	1
3.5—7	1—2
7—23	2—5
23—53	5—10
53—175	10—20

The biological effectiveness of irradiation depends not only on the dose, but also on the schedule of irradiation. Whenever enough time elapses between sessions (a day or several days), the tissues can regenerate, and the radiation damage proves to be less. The regenerative power of different tissues differs. Injuries to muscles and skin heal rapidly, whereas, e.g., nerve tissue hardly regenerates. Irradiation of patients with malignant tumors is usually carried out with small doses (200—500 rad), and it is continued for a prolonged period. This is the method of treatment that avoids damage to the skin and inflicts minimal damage on the healthy tissues.

Finally, we shall mention the oxygen effect. It has turned out that damage to tissues by γ rays or by particle radiation during oxygen lack (anoxia) is several times weaker than with a normal oxygen concentration. Increase in concentration above normal is not accompanied by any effects. Apparently, the point is that, when there is a lack of oxygen, the ions can recombine before their presence damages the cells. Owing to the oxygen effect, the central oxygen-poor parts of tumors prove to be more resistant to irradiation than their outer parts and the surrounding healthy tissues. The size of the oxygen enhancement ratio (OER), or the ratio of the biological effects for ordinary and oxygen-poor cells, depends on the LET. Figure 1, which is taken from Fowler,[5] illustrates this effect. It shows the relation of the RBE and the OER to the LET of α particles. The survival levels pertain to cells of a human-kidney tissue culture. We see from the diagram that the RBE and OER are almost constant at low LET (up to 5—10 keV/μm). The RBE reaches a maximum at 100—120 keV/μm (and then falls), while the oxygen effect vanishes. Thus one can overcome the oxygen effect by irradiating under conditions of high LET. This can involve using ions of heavy atoms (heavier than oxygen), which lose much energy in the tissues because of their large nuclear charges, neutrons with energies of the order of 10 MeV, which form short-range recoil protons, and π^- mesons, which cause nuclear "explosions" at the end of their ranges in

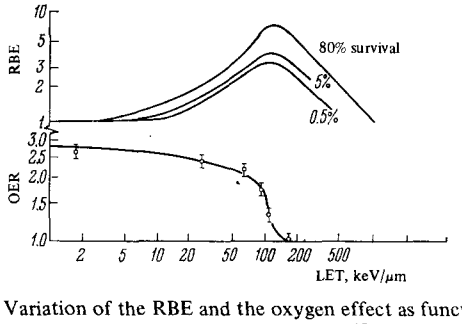

FIG. 1. Variation of the RBE and the oxygen effect as functions of the LET of particles. The data of Barendsen et al. [17] for survival of human kidney cells are given.

which nuclei emit slow, highly-ionizing fragments. Another way of overcoming the OER difference consists in decreasing the oxygen concentration by treating the tissues lying along the path of the beam outside the tumor with solutions of drugs.[18] On the other hand, one can saturate the patient's organism with oxygen by putting him in a special chamber having an elevated oxygen pressure or concentration in order to increase the oxygen concentration, even in the central part of the tumor.

3. LONGITUDINAL DOSE DISTRIBUTION

Figure 2 shows the dose distribution in tissues along the ray path for the ordinary types of radiation used in radiotherapy[15] and also for neutrons.[19] X rays (220 keV), whose absorption is described by a declining exponential, are characterized by a poor dose distribution. The dose applied to the parts of the body lying near the surface proves to be much larger than in the deep focus of the disease. The dose distribution from cobalt sources is substantially better. Irradiation is even better performed with electrons (betatrons with a diverted beam) and high-energy Bremsstrahlung γ quanta (from betatrons). In the latter case, an electron-photon cascade develops gradually in the patient's body, and the skin suffers insignificant damage. The distribution of the absorbed dose from a broad beam of 14-MeV neutrons declines exponentially, and it is very similar to the dose distribution from a γ quantum beam from a cobalt source.

All of the cited distributions have the general defect that the doses applied to the tissues lying in front of the tumor and behind it differ little from the dose to the tumor itself, or they even exceed the latter. The main method of combatting this defect is to irradiate the focus in different directions. This method is very effective, and it is no less applicable to proton beams than to γ-ray beams. The method of irradiating in different directions permits one substantially to avoid local reactions. However, the integral dose that the patient gets is not reduced. Consequently, the general reactions of the organism usually vary little. These include changes in blood composition, which often limit the dose that can be applied to the focus.

Figure 3 shows the longitudinal dose distribution in proton irradiation.[20] Monoenergetic proton beams (curve 1) have a clearly marked range, at the end of which all the particles are stopped. Deeper-lying tissues are practically not harmed. This makes it possible to work directly near important organs whose irradiation is inadmissible. There is a clearly marked peak on the dose-distribution curve (the Bragg peak) at the end of the range of the protons. Its height is several times higher than the initial part of the curve. Even when one irradiates in one direction, the dose at the end of the range proves to be substantially higher than the dose

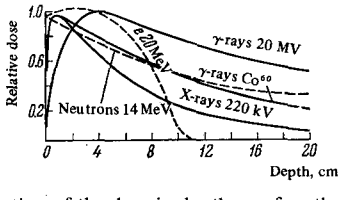

FIG. 2. Variation of the dose in depth as a function of the energy of electron, photon, and neutron radiation.

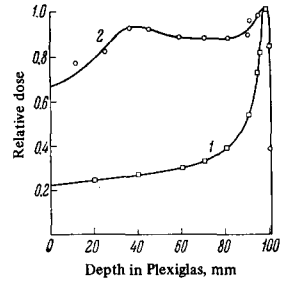

FIG. 3. The dose in depth in proton irradiation. 1—proton beam of 130-MeV energy, 2—the same beam passed through a ridge filter.

to the skin, and the total dose received by the organism is many times smaller than when one irradiates with γ rays or electrons.

Unfortunately, one can seldom apply monoenergetic proton beams because the dimensions of the focus to be treated usually appreciably exceed the width of the Bragg peak. In order to increase the width of the region receiving maximum dose, one must irradiate with a demonochromatized beam having a specially chosen spectrum. This is equivalent to superposing Bragg curves having their peaks lying at different depths. All of these curves add together in the surface regions, and the dose received by the skin is substantially increased. Figure 3 gives an example of such a distribution (curve 2). One usually demonochromatizes a proton beam with ridge filters, which consist of a set of plates of variable thickness.[8] Figure 4 gives a diagram of these filters. The width and profile of the filters are chosen to fit the extent of the region to be treated.

One can also attain a required dose distribution by selecting a momentum distribution of the charged-particle beam by using ion optics[21] or by varying the thickness of a supplementary absorber.[22] Finally, it has been suggested to scan rapidly a tumor of arbitrary shape with a narrow monochromatic beam.[22]

4. THE DOSE FIELD

Dose fields are usually depicted by means of isodoses, or curves that join points having equal absorbed doses. Figure 5a shows the dose field applied upon irradiating the body through a collimator having a round aperture with γ rays from a Co^{60} source (left) and with x rays (right). The curves show the relative value of the dose in percent. The 100% isodose lies near the surface of the body. The dose gradually declines with depth, and it proves to be substantially less at the focus than at the surface. The tissues lying beyond the tumor are not irradiated much more weakly than the tumor itself is. Attention is called to the spreading of the isodoses with depth. This spreading involves the angular divergence of the beams, and to a lesser degree, scattering

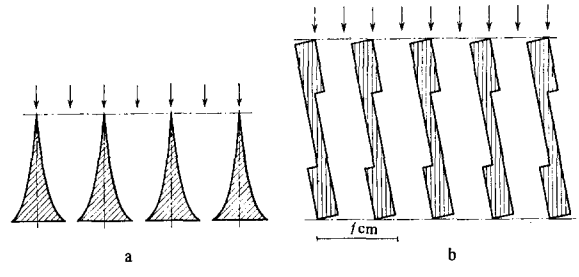

FIG. 4. Ridge filters. Two variants of the applied cross-sections of filters: for the proton beam at Uppsala [8] (a), and at the ITEP [20] (b).

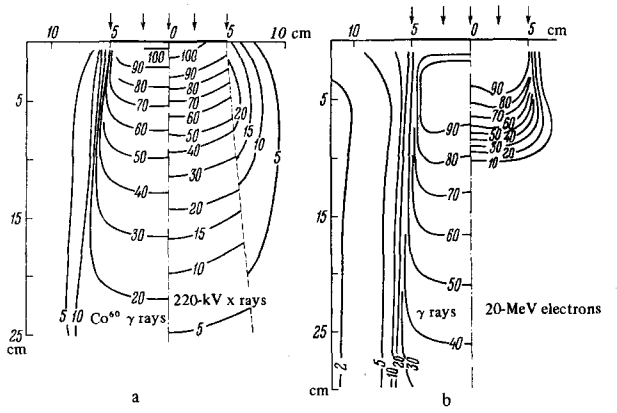

FIG. 5. Isodoses for different beams. [15] a–Co^{60} γ-rays (left) and X-rays with 220-kV tube voltage (right), 10 × 10 cm^2 field; b–20-MeV electrons and the Bremsstrahlung from these electrons (left), 10 × 10 cm^2 field.

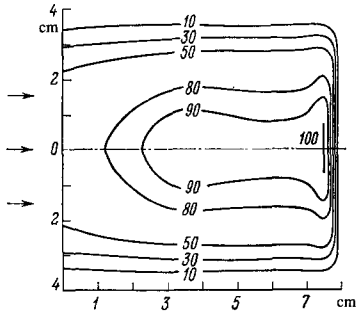

FIG. 6. Isodoses of a 100-MeV proton beam with a collimator diameter of 6 cm.

in the tissues. The dose declines slowly in the lateral direction. Hence the tissues lying alongside the focus suffer a heavy radiation load.

Figure 5b shows at the left the dose field from irradiating with bremsstrahlung γ quanta from 20-MeV electrons, and at the right, the dose field from the electrons themselves at this energy. Using bremsstrahlung permits one to shift the 100% isodose into the interior of the body, and hence, substantially to diminish the skin reactions. The dose field to the side of the focus is sharply improved. However, the longitudinal field distribution is poor. The tissues lying beyond the focus are irradiated not much less than the focus itself is.

The longitudinal dose distribution from the electrons in the initial region proves to be poorer than with the bremsstrahlung (since the 100% isodose for electrons lies at the very surface), while it is substantially better in the interior. Attention is called to the substantial spreading of the isodose curves in the deep part of the dose field. This spreading involves Coulomb scattering, which is very strongly marked for light particles, and especially for electrons.

Figure 6 shows the dose field received upon irradiating with 100-MeV protons through a collimator of 6 cm diameter.[20] The dose field has been shaped with a ridge filter. The field shows sharp drops at the sides and at the rear. This allows one to irradiate directly near vitally important centers. The 100% dose lies in the focus being treated. The dose applied to the outer parts of the body remains large, although it is substantially smaller than when one irradiates with γ rays or electrons. One can lessen the skin reactions by irradiating in different directions.

One can impart a complex shape at will to the dose fields obtained with protons (and other heavy charged particles). The field can be shaped with collimators of special form.[13,23] One can stop the protons at different depths in different regions of the dose field. These potentialities are as yet little used in clinical practice. The reason for this lies not so much in technical difficulties as in the fact that clinicians have not yet learned to use the potentialities that have been opened up.

Good geometrical definition of the dose field opens up new possibilities for radiation methods. As we know, surgical removal of a tumor, just like the amputation of affected extremities (e.g., for sarcoma), on the one hand rids the patient of the pathological focus, but on the other hand, it threatens him with spread of the disease. Cases can occur in which cancer cells break off at the time of the operation itself, and they are transported to other parts of the body. Thus the operation increases the danger of metastasis. The natural thought arises of whether one can treat the tumor cells with a fatal radiation dose (tens of kilorads) before the operation itself. Then the breaking-off of tumor cells during the operation would become harmless. (If the tumor is large, then one cannot avoid operating after such an irradiation, since necrosis of the irradiated tissues soon sets in, and it is accompanied by very serious general reactions of the organism.) The prospectives of such an irradiation are now being intensively studied.[24] The condition for it is a great fall in the dose level in the region adjoining the focus. We recall that the overall irradiation of the patient must not exceed several tens of rads. That is, it must amount here to tenths, if not hundredths of a per cent of the dose at the focus. Studying dose fields in the region of very low isodoses involves serious difficulties, since here one must attentively study the distribution of secondary particles that arise during irradiation.

5. SECONDARY PARTICLES AND THEIR DOSE FIELD

The primary beam generates secondary radiation in the tissues. In radiation therapy with electrons and γ quanta, the secondary radiation consists of quanta and cascade electrons that develop in the tissues. The effect from this radiation is not studied separately, and it is treated together with the effect from the primary beam.

When radiating with protons, α particles, and other light nuclei, one must account for the effect produced by recoil nuclei, nuclear fragments, and neutrons that arise from nuclear reactions. The recoil nuclei and fragments have exceedingly short ranges. Their contribution to the dose is concentrated in the region through which the primary beam passes. The amount and energy of the neutrons depends substantially on the energy of the primary beam. This contribution is small at proton-beam energies below 100 MeV, but it rises to 10% of the effect of the primary beam at an energy of the order of 200 MeV.

Figure 7 shows curves for the contribution of different components to the total dose. The curves are drawn from the calculations of Zerby and Kinney for a 200-MeV primary beam, and they illustrate the longitudinal distribution of the dose along the axis of the beam.[25] The

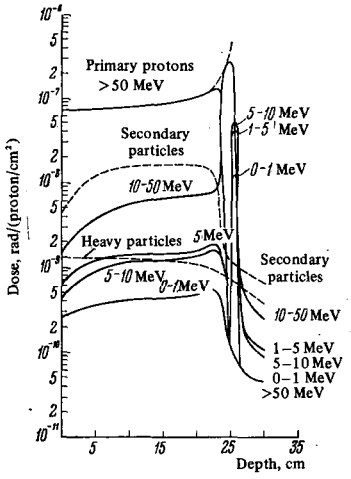

FIG. 7. Contributions of different radiations to the absorbed dose. Wide beam of 200-MeV protons (calculations from [25]).

dotted curves characterize: the contribution of the primary beam (the upper curve), the total contribution of the secondary particles (the middle curve) and the contribution of the heavy particles (the lower curve). The series of solid curves describes the contributions of secondary protons having different energies. We see from the diagram that the primary particles give the greatest contribution to the dose up to the end of their range. The dose received by the tissues lying beyond the stopping point of the primary beam amounts to several percent of the dose of the beam, and it declines rapidly with decreasing proton energy. The quality factor can differ appreciably from unity only at the very end of the range and in the region beyond it. At the usually applied energies, this has little effect on the dose distribution.

The pattern of the dose distribution varies little upon going from protons to α particles. Qualitative changes occur only upon going to heavier particles. Figure 8, which is taken from the lecture[5], shows the longitudinal dose distribution that arises upon irradiating with nuclei, as calculated with account taken of the RBE, that is, in rems. The dose distribution for α particles, just like that for protons, has a characteristic cutoff at the end of the range. However, for neon nuclei the tissues lying beyond the range curve already receive 10–20% doses, and this relationship becomes continually worse with increasing atomic weight of the bombarding nuclei (Ar, Fe). The reason for the effect is that heavy nuclei, when interacting with tissues, split into fragments that have a longer range than the original nuclei (we recall that the ionization losses at a given velocity are proportional to the square of the charge, and they rapidly decline when the nucleus is split into fragments). Thus, for neon nuclei having a range of 5 cm, the mean range for nuclear interactions is also 5 cm. For iron nuclei it is as low as 2.5 cm. Upon fragmentation, protons and α particles are produced with ranges up to 15 cm.[5] Fragmentation of the primary nuclei also causes the dose to decline with depth in the body instead of rising. This effect is clearly visible in Fig. 8 for heavy nuclei.

The contribution of secondary particles is most substantial when irradiating with π^- mesons. The therapeutic effect of π^- mesons involves their deceleration in the tissues as well as nuclear explosions that arise at the end of the range as the pions being stopped are captured

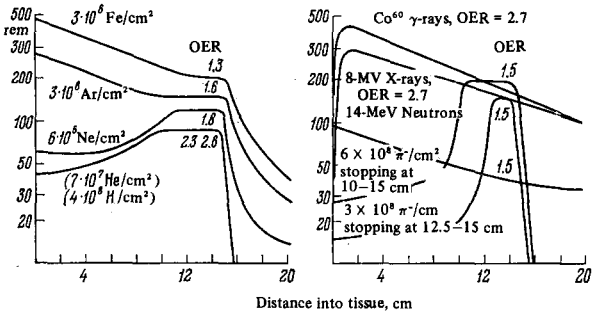

FIG. 8. Calculated dose distribution as a function of the depth of penetration into tissue for parallel beams. The value of the OER is given for a depth of 10–15 cm. The RBE values are taken for the 80% survival level. [5,17]

by nuclei. The ionization damage along the deceleration path is in no way specific for π^- mesons. The energy (140 MeV) liberated in the nuclear explosion in an oxygen nucleus is partitioned as follows. About 40 MeV is spent in overcoming the binding energy of the nucleons and fragments. This energy is lost. Neutrons carry away about 70 MeV, but they contribute relatively little to the part of the energy that is absorbed in the vicinity of the capture point of the π^- meson. Finally, about 30 MeV goes into kineitc energy of fragments, α-particles, and slow protons. All of this energy remains near the stopping point, and it gives rise to an appreciably elevated dose as compared with the surface of the body.

The dose distribution for a beam of π^- mesons from which electrons and muons have been removed is shaped in such a way as to give a uniform distribution in a tumor of dimensions $10 \times 10 \times 10$ cm, as shown in Fig. 9.[21] The contribution of neutrons was not taken into account in this distribution. It amounts to about 10% of the dose from charged particles in the tumor,[21] while the dose distribution from these neutrons matches the radiation conditions that would occur if an isotropic neutron source were located in the tumor itself.

6. SCATTERING OF CHARGED PARTICLES IN TISSUES AND THE "PENCIL" BEAM PROBLEM

When passing through matter, charged particles undergo multiple Coulomb scattering, with the result

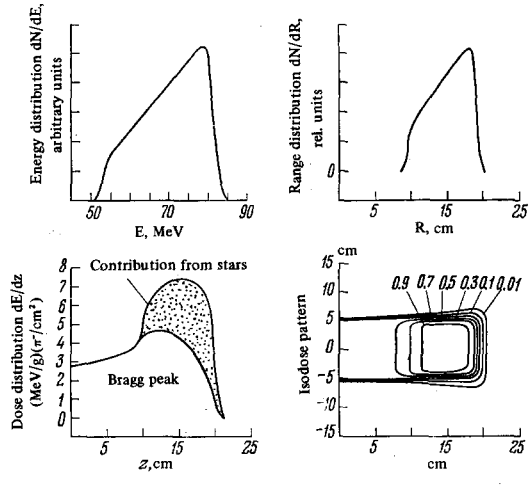

FIG. 9. Dose distribution of a pure beam of π-mesons shaped so as to give a uniform distribution over the region of a tumor of dimensions $10 \times 10 \times 10$ cm^3. [21]

that the dimensions of the beam gradually increase. The scattering is conveniently described by the "scattering radius" σ, which characterizes the root-mean-square radius of a beam whose diameter is negligible at the entrance into the scattering medium.

One can use the following formula[3)] for scattering in tissues:[23]

$$\sigma = 0.03\,(t/R)^{1.65}\,Rm^{-0.45}z^{-0.1}, \quad (1)$$

Here z is the charge of the particle being scattered as expressed in electronic charges, m is its mass (in proton masses), R is its range in tissue, and t is the depth for which σ is being calculated.

Let us consider particles that stop at a depth of 7 cm (a typical depth for intracranial intervention). We get

$$\sigma_\pi = 5 \text{ mm}, \ \sigma_p = 2 \text{ mm and } \sigma_\alpha = 1 \text{ mm}.$$

The scattering radius for heavier nuclei is even less than that for α-particles. However, this is not essential in clinical applications, since a typical target diameter for intracranial intervention amounts to 5—8 mm (the dimensions of the hypophysis). It makes no sense to strive for further decrease in the scattering radius after it has become substantially smaller than the beam dimensions. For the thin pencil beams required in intracranial intervention, the cited numbers show that π^- mesons are poorly suitable, protons are good enough, while α-particles are better than protons.

For a given depth t of the focus, fast particles give smaller scattering radii than the slower ones, since $\sigma \sim R^{-0.65}$.

Spread of the beam with depth distributes its energy over an ever growing area. The longitudinal dose-distribution curves (see Fig. 3) are valid only for wide beams whose dimensions are much greater than the scattering radius. The Bragg peak is substantially more weakly marked for pencil beams than for wide beams.

Scattering of particles considerably complicates dose-field calculations. The calculations prove to be simple only when the scattering radius is small in comparison with the dimensions of the beam. Then we can assume with good accuracy that the 50% isodose passes along the contour of the collimator, and the variation of the dose on both sides is determined by the error function:

$$P(x) = P_0\,[1 \pm \operatorname{erf}(x/\sigma)]/2, \quad (2)$$

Here x is the distance from the 50% isodose, and P_0 is the dose at the center of the field. The sign in Eq. (2) depends on the side of the collimator contour to which the point being treated lies. Eq. (2) holds when the beam is parallel and the radius of curvature of the boundary substantially exceeds the scattering radius. Calculating the dose field from γ-ray sources and electron beams is very complicated. Thus, heavy charged particles permit one not only to get a well-limited dose field, but also to calculate it easily.

7. COMPARISON OF THE CLINICAL EFFECT FROM VARIOUS TYPES OF RADIATIONS

As we showed above, application in radiation therapy of heavy charged particles instead of electrons and γ-quanta pursues a number of goals: 1) to improve the relationship between the doses absorbed in the focus and in the neighboring tissues and also at the surface of the body; 2) to improve the relationship between the dose at the focus and the integral dose; 3) to diminish the oxygen effect; and 4) to obtain narrow pencil beams. Let us consider the various heavy charged particles from this standpoint.

Figure 8 compares the depth distributions of the dose with account taken of the RBE for parallel beams of γ quanta, protons, heavy ions, and π^- mesons.[5] The calculated distributions of the absorbed dose (in rems) were chosen in such a way as to get as uniform a distribution as possible throughout the region of a tumor at a depth of 10 to 15 cm. The value of the OER is given for the depth 10—15 cm.

Protons and α-particles are relatively weakly ionizing particles over most of their range. Although they have no appreciable advantages over γ rays and electrons, either in terms of the RBE or the oxygen effect, the clear geometric definition of the beam and the existence of the Bragg peak give them a substantial advantage over γ rays and electrons because of their incomparably better dose distribution in the patient's body.

The relatively weak scattering of heavy charged particles in tissues permits one to form thin pencil beams from them that are suitable for neurosurgery. α-Particles permit somewhat thinner beams than protons do. Otherwise they are equivalent to protons. The insignificant advantage of α-particles for neurosurgical interventions is gained at rather high cost, since, for the same ranges, the energy and momentum of α-particles must be four times as great as for protons. This gives rise to substantially more expensive accelerators and more expensive ion optics.

As we mentioned above (see Sec. 6), it is not justified to go to nuclei heavier than α-particles from the standpoint of reducing the width of the beam. It might be reasonable to use them only if one could thus suppress the oxygen effect. Is this possible? There is an appreciable decline in the oxygen effect at an LET of ~ 100 keV/μm. One can conveniently calculate the linear energy losses from an empirical formula relating the energy of the particles to their range in tissue:

$$R = m^{-0.8}z^{-2}\,(E/32)^{1.8}.$$

In this formula, the range R is expressed in centimeters, the energy E in mega-electron-volts, the mass m in proton masses, and the charge z in electronic charges.

If we differentiate this expression, we find

$$dE/dx = 18m^{0.45}z^{1.11}/R^{0.45} \approx 25z^{1.56}/R^{0.45}$$

(the second half of the equation is valid when m = 2z, i.e., for nuclei heavier than hydrogen).

If we substitute dE/dx = 100 keV/μm = 10^3 MeV/cm and R = 5 cm (a reasonable estimate for the dimensions of a focus being treated), we find z = 17. However, even for z = 10 (neon), fragmentation of nuclei substantially impairs the dose field (see Sec. 5). Thus, suppressing the oxygen effect by going from proton irradiation to nuclei holds no great promise. In discussing this problem, we should also bear in mind the fact that accelerators for multiply-charged ions are many times more expensive than proton accelerators.

Let us proceed to discuss π-meson therapy. As we have shown (see Sec. 6), π-mesons are too light for intracranial interventions. On the other hand, π^- mesons have a number of important advantages. They traverse their entire pathway in tissue until final stopping almost

without nuclear interactions. At the end of their range, they are captured by nuclei of atoms of the tissue with 100% probability, and they cause these nuclei to split. Here neutrons, protons, α particles, and heavier ions are emitted.

The particles of charge $z > 1$ mostly have short ranges, they give a high concentration of ions, and they produce a large energy yield immediately near the capture site. The averaged RBE of these particles is close to 3, while the effective RBE of all the particles averaged over the region of a pathological focus of dimensions 5—10 cm is about 2. The mean value of the OER for the rays of stars is 1.4 according to Fowler,[5] while the OER averaged over the region of the focus is 1.57 (instead of 2.7 as in irradiation by protons, electrons, and γ quanta).

All of this taken together shows that, if a pion beam is sufficiently cleaned of accompanying particles, the ratio of the dose at the focus to the entrance dose proves to be 2.5—3 times greater for π^- mesons than for protons and α-particles. When the focus being treated is anoxic, we must also take account of the difference in OER for π^- mesons and protons. Both of these factors have the result that the ratio of the damage to the focus to that to the surface of the body can prove to be 4—5 times greater for π^- mesons than for protons and α-particles.

As for the neutrons that arise from nuclear splitting, they increase somewhat the integral dose absorbed in the healthy tissues. However, we must bear in mind the fact that these neutrons emerge isotropically from the tumor, and hence they cause the greatest damage in it. Absorption of the neutrons leads to an additional decrease in the dose received by the healthy tissues. The intensity of a parallel neutron beam declines by half in a path length of about 15 cm.[19] Hence, the dose from the neutrons outside the tumor declines more rapidly than the inverse square of the distance. The oxygen ratio for 10—20 MeV neutrons is the same as for π^- mesons. That is, it amounts to 1.5,[22] which is substantially better than for protons. Thus the neutron component that arises in π^- meson capture in tissue has both a favorable geometric distribution and a good OER.

Let us proceed to the total integral dose received by the healthy tissues in irradiation by protons and by π^- mesons. According to Fowler's calculations,[5] the ratio of the damage to a tumor saturated with oxygen having dimensions of 5 cm to that to the healthy tissues amounts to 0.76 for protons and α-particles, but 1.5 for π^- mesons. That is, π^- mesons prove to be twice as effective as protons and α-particles. When the tumor is anoxic, this gain increases to 3.2.

Figure 10 shows an estimate of the clinical effectiveness of different types of radiation.[26] The effectiveness is characterized by the ratio of the damage to a tumor lying at a depth of 10 to 15 cm to that to the healthy tissues in the path of the beam. The given estimates include the RBE and the OER, and they also take account of the secondary particles that arise in nuclear interactions. The curve demonstrates the clearly marked advantage of π^- mesons. It shows that the therapeutic effect is expected to be 12 times greater for π^- mesons than for heavy ions, α particles, and protons. Consequently, π-meson therapy may prove to be the next important step in radiation therapy.

At present, π-meson medical laboratories are being

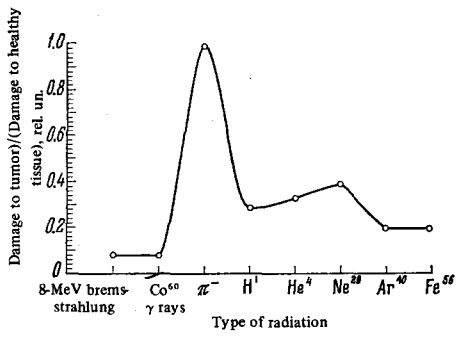

FIG. 10. An "evaluation" for various types of radiation based on the relative damage to a tumor and to healthy tissue. [26]

planned in meson factories being built at Los Alamos (USA), Vancouver (Canada), and Zürich (Switzerland).[22,26-28] It has been proposed to create a clinical pion beam from the 680-MeV synchrocyclotron at Dubna as well, after a high-current phasotron has been installed there.[29]

8. CLINICAL NEEDS AND THE POTENTIALITIES OF ACCELERATORS

In ordinary radiation therapy, a complete course of treatment requires doses of the order of 6×10^3 rad over an area of about 25 cm^3. If we assume that the depth of the lesion is 10 cm, we find that a complete course of treatment requires a total absorbed radiation energy of

$$E = 6 \cdot 10^3 \text{ rad} \cdot 1 \text{ g/cm}^3 \cdot 25 \text{ cm}^2 \cdot 10 \text{ cm} \cdot 100 \text{ erg/g} = 1.5 \times 10^8 \text{ erg}.$$

If we assume the proton energy to be 115 MeV, we find that the total number of protons needed for the course of treatment is

$$N = 1.5 \cdot 10^8 \text{erg} (115 \cdot 10^6 \text{ eV} \cdot 1.6 \cdot 10^{-12} \text{ erg/eV}) = 0.8 \cdot 10^{12} \text{ protons}.$$

Intracranial interventions require doses of the order of 25×10^3 rad with a volume of the region under treatment of the order of several cm^3. This leads to an even smaller value of the absorbed energy. Depending on the type, the intensity of modern proton accelerators amounts to 10^{11}—10^{13} protons per second. Thus, with the appropriate utilization, each accelerator can provide radiation therapy for several hundred persons per day. This corresponds to the requirements of the largest cities, or even of small countries. An accelerator built specially for proton therapy (with an energy of the order of 200 MeV) will cost several million rubles. Hence the introduction of proton therapy into medical practice for treating cancer is currently quite possible from the economic standpoint. α-Particle accelerators are several times as expensive as proton accelerators. Consequently, as we see it, it is harder to count on widespread application of α-therapy in the near future. Widespread application of heavy charged particles in therapy is being impeded not so much by technical and economic factors as by quite other factors: insufficient experience, lack of trained cadres, complexity of reorganization of oncological establishments from decentralized to highly centralized, insufficient understanding of how necessary such a reorganization is, etc.

The prospects for widespread application of π^- mesons in medicine involve to a large extent the possibilities for building cheap enough meson factories. There are currently some encouraging estimates for this type of ap-

paratus that show that the cost of a meson factory based on a linear accelerator having a proton energy of 500 MeV at low duty ratio is about five million dollars.[30]

Several words on the choice of type of accelerators for proton therapy. Several paths can be taken here. Since one can accelerate protons to 200 MeV energy most simply and cheaply in instruments having a d.c. magnetic field, one might consider cyclotrons having separated orbits that use a spiral field variation. They permit one to release particles having practically any energy up to the maximum. Linear accelerators with regulated proton energy are also suitable for these purposes. It is apparently no less suitable to use for acceleration proton synchrotrons in which the particles move over the same trajectory throughout the acceleration cycle. The energy of the beam is determined by the instant of time at which the beam is ejected from the accelerator. This method of extracting the beam has been tested on the synchrotron of the Institute of Theoretical and Experimental Physics (ITEP), and it fully justified itself.[31]

Recently, the working proton accelerators have continually more often been used for medical purposes. Thus, for example, a medical proton beam has been created with the accelerator at Carnegie Technical Institute.[32] A linear accelerator—the injector of the gigantic accelerator at Batavia—will yield a 200-MeV beam for irradiation of patients in the intervals between cycles.[33]

9. TECHNIQUE OF PROTON IRRADIATION

The technique of radiation therapy using proton beams substantially differs from that of x-ray or γ-ray irradiation. High-energy protons are generated in accelerators that are complicated and large in size, whose cost amounts to the bulk of the cost of the therapeutic complex. These instruments cannot move around the patient—the patient himself must move.

The advantages of proton beams consist to a considerable extent in the fact that they can be accurately shaped, both in dimensions and in energy. If one does not do this, then going to proton irradiation loses sense. Hence the equipment must necessarily include special devices for conveying, focusing, and shaping the beam. We shall describe the technique of proton beams with several examples.

The energy of the proton beam must be appropriately chosen. When one uses the Bragg peak, the energy is determined by the depth of the focus to be treated, and it must be chosen individually. When working in full penetration, this isn't strictly necessary, but the energy of the beam must be great enough to pass through the body of the patient. At the same time, it must not be too large because the neutron background increases rapidly with increasing beam energy.

In neurosurgical irradiation with full penetration, as a rule, proton beams are used without preliminary deceleration. Their energies amount to 160 MeV at Harvard, and 185 MeV at Uppsala. At Berkeley, irradiation can be performed with 910-MeV α-particles. A 200-MeV proton beam is used at the ITEP.

At a number of accelerators, Bragg-peak is performed with preliminary deceleration of the beam. Figure 11 shows a diagram of the extraction and transport of the therapeutic proton beam constructed in 1967 from the 680-MeV synchrocyclotron of the Laboratory of Nuclear Problems (LNP) at Dubna.[34] The 680-MeV proton beam extracted from the vacuum chamber of the accelerator is focused by a pair of magnetic quadrupole lenses into a water moderator of thickness about 160 g/cm^2. The decelerated protons are rid of subsidiary particles with a deflecting magnet, and they are then transported for a distance of about 30 meters into the clinical suite, which is situated behind a thick concrete shield. Seven focusing magnetic quadrupole lenses are set up along the path of transport of the beam. The beam passes through a vacuum conduit throughout its path to the patient. The clinical suite consists of several rooms. Room 1 is the treatment room, which is designed for positioning the patient under treatment and for the necessary dosimetric equipment. The dosimetry of the proton beam is performed from room 2, the console room. Room 3 is designated for medical checking of the patient. The suite on the lower floor lying below rooms 1 and 2 is provided with x-ray equipment for comparative study of the radiobiological actions of photons and protons.

Figure 12 shows an overall plan of the arrangement of the dosimetric, adjustment, and auxiliary equipment designed for controlling the course of irradiation in the medical proton beam of the Laboratory of Nuclear Problems of the Joint Institute of Nuclear Research. A Faraday cylinder and plane-parallel ionization chambers

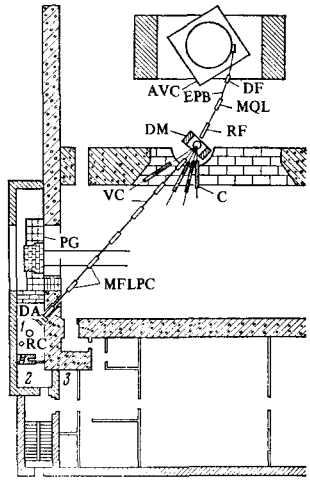

FIG. 11

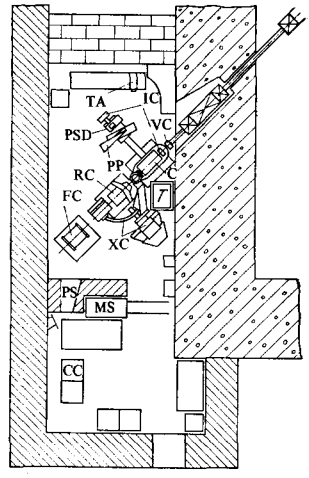

FIG. 12

FIG. 11. Overall diagram of the shaping of the therapeutic proton beam and the arrangement of the clinical suite in the synchrocyclotron building of the Laboratory of Nuclear Problems of the Joint Institute for Nuclear Research. AVC—accelerator vacuum chamber, DF-deflecting fittings, EPB—extracted 680-MeV proton beam, MQL—magnetic quadrupole lens for focusing the primary beam, RF—retarding filter, DM—deflecting magnet, C—collimators, VL—vacuum conduit, MFLPC—magnetic focusing lenses for the proton channel, PG—protective gate, DA—dosimetric apparatus, RC—rotating chair, 1—treatment room, 2—console room, 3—room for medical checking of patients.

FIG. 12. Overall diagram of the arrangement of the dosimetric, adjustment, and auxiliary apparatus in the clinical suite of the synchrocyclotron bulding of the Laboratory of Nuclon Problems of the Joint Institute for Nuclear Research. VC—vacuum conduit, C—collimator, IC—ionization chambers, PP—movable Plexiglas phantom, PSD—profile-determining semiconductor dosimeters, RC-rotating chair, FC—Faraday cylinder, PS—periscopic system for observing the object being irradiated, MS—movable concrete shield, XC—X-ray centerer with television apparatus (T), TA—television apparatus for watching the patient, CC—control console.

are used to measure the intensity of the proton beam. The dose distribution in a Plexiglas phantom is determined with movable, small-clearance silicon detectors. In a number of cases, the dose to the tumor is measured directly with silicon dosimeters introduced into cavities of the human body. These detectors permit one to bring the Bragg peak precisely to the focus to be treated. On and off switching of the accelerator and release of the assigned dose are performed automatically from the console room. The cross section of the beam is chosen in accordance with the shape of the tumor, and it is regulated with a special collimator that consists of a set of movable plates. During irradiation, the patient is fixed in a chair that can be moved in the horizontal and vertical planes, and is automatically rotated over a chosen angular range about the vertical axis. The patient is adjusted to the axis of the beam with optical centerers and with an x-ray apparatus having an electron-optic converter. The patient is observed during the irradiation with a television setup and a mirror periscopic system.

In order to extract the beam from the proton synchrotron of the ITEP[31] at the necessary instant of the acceleration cycle, the current is turned on in a pulse coil. During one revolution, the magnetic field of the coil ejects protons from the accelerator chamber, and directs them into the vacuum channel. The beam is deflected by a magnet into the treatment suite, and it is focused by magnetic lenses. A ridge filter (see Sec. 3) gives the beam the necessary scatter in energy. Special measures are taken to ensure that the beam will be uniform at the focus. The beam first passes through a thin scatterer, and then the central, most uniform part of the beam isolated by a collimator is used for irradiation. The instant of extraction of the beam brings about a coarse proton energy selection. Thin plexiglas absorbers are introduced for smoother selection of the beam energy. The intensity of the beam is 1.5×10^{10} protons/sec throughout the irradiation field.

Figure 13 shows an overall view of the treatment suite at the ITEP. The patient is placed in a chair that can be rotated about the vertical axis and shifted across the beam. The chair is attached to an elevating platform. The patient is kept under remote observation with a closed television system. An optical centerer whose light ray is directed along the axis of the proton beam serves for positioning the patient in the beam. An x-ray apparatus is set up alongside the patient. An image arises on the screen of the electron-optic converter, and after amplification, it is transmitted to the console. A stand with a beam monitor (a current transformer whose primary winding is the beam), a ridge filter, and Plexiglas absorbers is set up in front of the patient. The front part of the room contains an apparatus for intracranial interventions using the proton beam (not shown in the diagram).

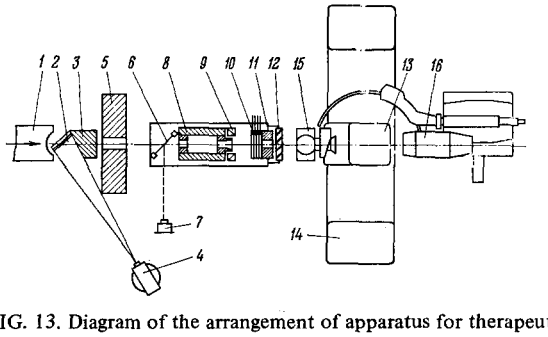

FIG. 13. Diagram of the arrangement of apparatus for therapeutic irradiation with the proton synchrocyclotron of the Institute of Theoretical and Experimental Physics. 1—end of the vacuum channel, 2—scintillator, 3—shutter for covering the beam, 4—transmitting television tube, 5—biological shield, 6—Mylar-film mirror, 7—optical centerer, 8—collimator, 9—induction transducer, 10—composite absorber, 11—exit collimator, 12—ridge filter, 13—rotating chair, 14—chair elevator, 15—x-ray tube, 16—electron-optic converter.

The beam is not scattered in order to get a uniform distribution over the focus in the proton beam at Uppsala (Sweden), as it is at the ITEP, but is scanned by crossed magnetic fields. The ray of an electronic oscillograph on the console in front of the operator follows the motion of the proton beam.[37]

Figure 14 shows the arrangement of the apparatus with the patient in place in Berkeley for intracranial interventions.[38] The patient lies on his back, and his head is fixed with a mask that is specially prepared for each patient. During the irradiation, the table with the head-holder is rotated by $\pm 35°$ about the vertical y axis. In addition, the patient's head is rotated by the same angle about the longitudinal x axis of the body. The trace of the beam in the patient's body amounts to the two joined sheets of a cone that meet at the focus under treatment. The cones have a thick connector whose width is approximately the diameter of the beam to the 50% isodose. This isodose has the shape of a dumbbell, as is shown in Fig. 15a (proton irradiation with full penetration[7]). Figure 15b shows the dose field obtained in Bragg-peak irradiation from several opposite directions (with α particles).

Neurosurgical operations with the proton beam require special caution, since vitally important centers and large blood vessels lie directly near the focus being treated. In irradiation of the hypophysis, a displacement of the beam by 2—3 mm could cause it to strike the crossing of the optic nerves (the chiasma) and consequently lead to loss of vision. Before the operation, the focus to be treated is brought under x-ray control to the intersection of the vertical and horizontal axes of rotation of the patient's head with an accuracy of no worse than 1 mm.

A fixation system is used for immobilizing the patient's head in Uppsala and Harvard, in which the inner frame of the rotation mechanism is rigidly attached to the patient's head by drill rods that make direct contact with the skull. At the ITEP, holders are used for fixing the head that rest against the jaw, the back of the head, the temples, and the bridge of the nose. As a rule, irradiation of intracranial targets is performed under anesthesia, most often total. The clinical beam at the

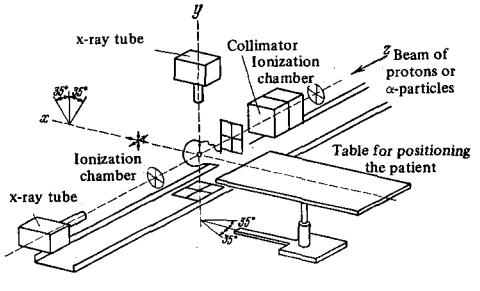

FIG. 14. Diagram of the arrangement of apparatus for irradiating the hypophysis with the stereotactic setup at Berkeley.

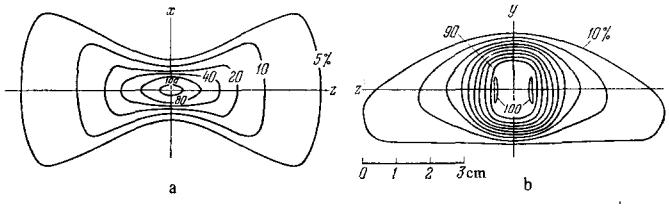

FIG. 15. Isodoses of the beam used for irradiating the hypophysis at Berkeley. a) Rotating irradiation by protons with full transmission; b) α-particle irradiation in different directions with the Bragg peak brought to the hypophysis.

ITEP, where it has been possible to avoid this, is an exception.

10. SOME STATISTICAL DATA

Proton irradiation was first performed in Berkeley in 1954. From that time until March, 1972, the world statistics counts about 1000 patients that have undergone proton and α-ray therapy. Irradiation has been applied for malignant neoplasias in different locations (the esophagus, lungs, mammary gland, larynx, and female sex organs) and for suppressing the function of the hypophysis (Cushing's disease, diabetic retinopathy, and metastatic cancer of the mammary gland).

Table II gives the parameters of the accelerators used for clinical studies on irradiation by proton and α-particle beams.

In the Soviet Union, the Institute of Experimental and Clinical Oncology of the Academy of Medical Sciences of the USSR under the direction of Academician N. N. Blokhin and Professor A. I. Ruderman began to conduct clinical application of protons in 1967 at Dubna, and in 1969 in Moscow. A medical beam may also be set up in a few years at the accelerator at Gatchina (near Leningrad).

It is as yet difficult to judge fully the results of treatment, since it was often applied in the terminal stage of an illness in the first experiments. It is still early in many cases to speak of a successful cure, since the five-year period accepted for estimating the results has not yet elapsed. An appreciable fraction of the patients are elderly people who have died of other diseases during this period. For all these reasons, the statistics is still clearly insufficient. Nevertheless, study of the results undoubtedly shows that proton irradiation gives no poorer medical results than the currently widely used γ-ray irradiation. At the same time, it is not accompanied by the general reactions that are almost unavoidable in γ-ray irradiation. Proton irradiation opens up a number of new, important possibilities that are completely unattainable in the usual methods of irradiation (bloodless

TABLE II. Parameters of the accelerators being used for clinical studies

Accelerator	Particles and their energy	Current (or current density in the beam)
Phasotron of the Lawrence Radiation Laboratory, Berkeley, USA	p, 340 MeV α, 910 MeV	2×10^8 sec^{-1} cm^{-2}
Phasotron at Harvard University, Cambridge, USA	p, 160 MeV	2×10^9–5×10^{10} sec^{-1}
Phasotron at the Gustaf Werner Institute, Uppsala, Sweden	p, 185 MeV	10^7–5×10^{10} sec^{-1}
Phasotron of the Laboratory of Nuclear Problems of the United Institute of Nuclear Studies, Dubna, USSR	Accelerator: p, 680 MeV; beam: p, 90–200 MeV	5×10^7 sec^{-1} cm^{-2}, 10^9 sec^{-1}
Strong-focusing synchrotron of the Institute of Theoretical and Experimental Physics, Moscow, USSR	Accelerator: p, 7.2 GeV; beam: p, 70–200 MeV	1.5×10^{10} sec^{-1}

TABLE III. The numbers of patients that have undergone a course of treatment with wide proton beams

Disease	Start of irradiations	Number of observations	Reference
Uterine cancer	1957	7	Uppsala, 1959 [37]
	1959	10	Uppsala, 1964 [39]
Metastatic mammary cancer	1960	1	Berkeley, 1963 [40]
Brain tumors	1961	6	Harvard, 1962 [9], 1970 [41]
	1961	3	Berkeley, 1963 [42]
	1964	7	Uppsala, 1967 [43]
Nasopharyngeal tumors	1964	10	Uppsala, 1964 [44]
Cancer of the larynx, esophagus, and lungs	1967	58 *)	Dubna, 1971 [13]
Uterine cancer, superficial skin tumors, metastases to regional lymph nodes, bone and joint tumors	1969	144 *)	Moscow, 1971 [13]

*Data for mid-1972.

neurosurgery, preoperative irradiation with large doses, irradiation near vitally important centers, etc.).

Questions involving features of treatment of different forms of illness are outside the scope of this article. We shall limit ourselves to listing the number of patients that have been treated with beams of heavy charged particles. Unfortunately, we do not have complete data on the foreign laboratories. The numbers given in Tables III and IV are taken from the reviews[6,18]. The data for the two therapeutic proton beams in this country are given for mid-1972.

The tempo of clinical studies is being retarded by the fact that the accelerators work mainly for physics, and only rarely for medicine. Only at the ITEP accelerator are special "medical" acceleration cycles intercalated among the main cycles, whereby the physicists and doctors work independently. The synchrocyclotron at Harvard has used a larger part of its time in recent years for radiation therapy.

11. CONCLUSION

Clinical application of proton beams (and α-particle beams) for treating malignant tumors has passed through its period of initial testing. Just like all other methods known at present, irradiation with these beams cannot radically solve the whole problem of combatting such an insidious and grave disease as cancer. However, since radiation therapy must still be used, we should distinctly report that proton and α-particle irradiation are always better than γ-ray irradiation. The heavy charged particles permit one to shape the dose field in depth and in cross-section with an accuracy unattainable with the other methods. The absence of overall over-irradiation permits one to apply much larger local doses and to attain more radical results. These beams permit one to perform bloodless surgical operations, and they open up new prospects for preoperative irradiation. Irradiation with π^- mesons will apparently also be very effective. However, this problem still requires study.

The level of development of accelerator technology is sufficient for starting now to equip clinical complexes to permit treating a large fraction of the patients suitable for irradiation. The cost of these establishments is not too great. Thus, it is not so much technical barriers that block the path of clinical application of heavy charged particles as historical and psychological barriers.

Widespread development of the proton-ray methods requires reconstruction of the system of radiation treat-

TABLE IV. The numbers of patients that have undergone treatment with narrow beams of protons and α-particles

Disease	Start of irradiations	Number of observations	Reference
Metastatic mammary cancer	1954	150	Berkeley, 1969 [7]
	1962	4	Harvard, 1965 [45]
	1972	19	Moscow, 1972 [46]
Diabetic retinopathy	1958	166	Berkeley, 1969 [7]
	1962	23	Harvard, 1968 [47]
Acromegaly	1958	102	Berkeley, 1969 [7]
	1963	163	Harvard, 1968 [47]
			Harvard, 1971 [41]
Cushing's disease	1959	17	Berkeley, 1969 [7]
	1967	28	Harvard, 1971 [41]
Parkinson's disease	1958	14	Uppsala, 1967 [43]
	1962	2	Harvard, 1964 [48]

ment for oncological disease. One cannot have proton accelerators in every regional polyclinic. On the other hand, proton accelerators make it possible to supply the necessary doses in a period of several seconds, if not fractions of a second. Most of the time here is spent in preparing the patient, rather than in therapy. An accelerator will be used correctly only if several treatment suites are installed around it, with the idea that the beam will be switched from one to another as the patients become ready. Under these conditions, each accelerator can provide treatment for patients from an entire geographical region, and large medical centers designed to serve these regions must be built.

No matter how great this work is, the advantages of proton (and also π^- meson, when attainable) irradiation are so weighty that this path seems to us to be necessary.

In conclusion, the authors find it their pleasant duty to thank Professor A. I. Ruderman, whose collaboration made possible the publication of this article, and also I. G. Zhakov and E. I. Minakova, who have read this work in manuscript and have made a number of important remarks. We honor the memory of Academician I. Ya. Pomeranchuk, whose initiative played a great role in the development of proton therapy in the USSR.

[1)]Thus, for example, about 320,000 person die of cancer every year in the USA alone. [1] According to approximate estimates, [2] 58,000 of these patients per year could be saved from death by improving the existing methods of radiation therapy.

[2)]The reserve assumed in defining the quality factor is not small, and it is poorly known. It gives rise to uncertainity in calculating biological doses in working with strongly ionizing radiation. [16]

[3)]The error in Eq. (1) for 70–200 MeV protons does not exceed 3% of $\sigma_{t=R}$.

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