ACCELERATORS FOR THERAPY

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Abstract
In the past decades circular and linear electron accelerators have been developed for clinical use in radiation therapy of tumors with the aim of achieving a high radiation dose in the tumor and as low as possible dose in the adjacent normal tissues. Today about one thousand accelerators are in medical use throughout the world and many hundred thousand patients are treated every day with accelerator-produced radiation. There exists, however, a large number of patients who cannot be treated satisfactorily in this way. New types of radiations such as neutrons, negative pions, protons and heavy ions were therefore tested recently. The clinical experience with these radiations and with new types of treatment procedures indicate that in future the use of a scanning beam of high energy protons might be optimal for the treatment of tumors.

1. INTRODUCTION

Soon after the discovery of X-rays by Conrad Wilhelm Roentgen in 1895 it became obvious that this new type of radiation was able to damage living tissues. The radiation reactions were observed first in the skin of scientists and technicians and led soon to regulations for a careful use of ionizing radiations in all fields of application. At the same time X-rays were used to destroy tumors in patients.

Today, from a region with a population of about one million, about 6000 patients per year need treatment for cancer. Half of them are treated by surgery, the other half with ionizing radiation. About two thirds of these patients can be cured. That means the life threatening tumor is destroyed by the treatment and the patient may die only much later at a normal age. This situation today, that 2000 of 3000 patients can be cured per year in such a population, is a result of using particle accelerators in radiation therapy. On the other hand, at present about 1000 patients cannot be treated successfully. This is an unsolved clinical problem where future accelerators may play a crucial role. It will be explained here how tumor therapy has been improved during the last decades using accelerators and what developments are being proposed for the future.

2. DEVELOPMENT OF PRESENT TUMOR THERAPY

2.1 Tumor therapy with X-rays

The central problem of tumor treatment with ionizing radiation is depicted in Fig. 1. A beam of X-rays is directed to the tumor which usually is located deep in the patient's body. The radiation dose D decreases as a function of depth as indicated in the lower part of Fig. 1 with the result that a tumor situated 10 cm deep receives only about 25 percent of the surface dose. Later it will be explained in detail how the destruction of tumor cells is related to radiation dose. But it is already obvious from Fig. 1 that radiation damage in the skin of the patient would be much larger than in the tumor.

In order to increase the dose in the tumor more radiation beams can be used successively as shown in Fig.1. With three beams the dose in the tumor region can already be increased in this way to about 75 percent of the skin dose. This principle of using multiple beam iradiation

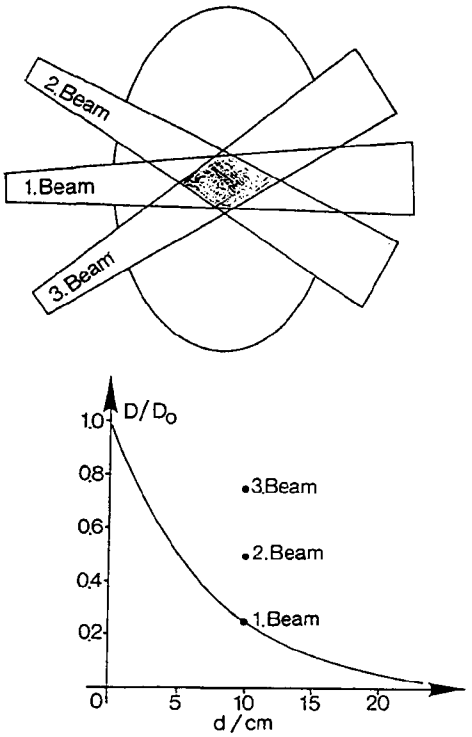

Fig. 1 Decrease of X-ray dose with depth in water (below). Use of multiple beam crossing in the tumor region for increasing the dose in the tumor (above).

for increasing the dose in the tumor was most important in the beginning of radiotherapy and it will be shown later how this principle was developed further during the last decades. Nevertheless, the steep decrease in the depth dose curve of 100 kV X-rays as shown in Fig. 1 was a serious physical draw back. It led to intense efforts by physicists to increase the energy of X-rays and produce more penetrating radiations.

As shown in Fig. 2, the relative radiation dose at 10 cm depth can be increased by about a factor of two using 1 MeV photons. Such high energy photon radiation was available at the beginning of our century only from radioactive sources such as radium. In fact, sources containing many grams of radium were manufactured at that time for tumor irradiation. However, these sources were extremely expensive and only very few hospitals in the world were able to purchase one of them. Therefore, a high-voltage installation for producing one million Volt was constructed in our institute in Frankfurt by Friedrich Dessauer in 1920. I think this was the first time in the world that such a high-voltage generator with a current of many milliamperes was installed. During the worldwide financial crisis in the early twenties the whole equipment had to be sold to a Japanese institute.

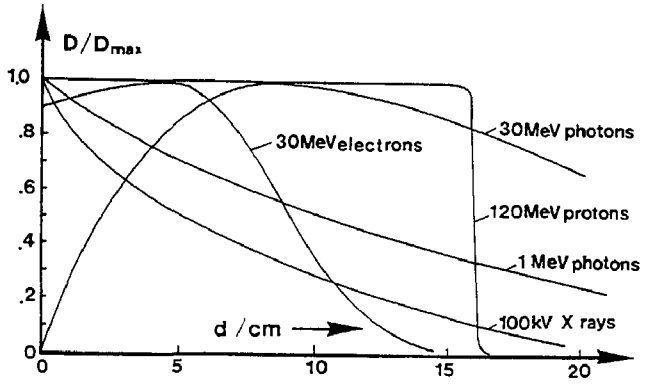

Fig. 2 Relative dose as a function of depth d in water for various types of radiations

In 1940 a cascade generator for three million Volts and 10 mA current was constructed in our institute with the aim to produce high energy photons and fast neutrons. This equipment had to be moved because of safety reasons to a salt mine in eastern Germany during the second world war and was shifted from there to Russia after the war.

2.2 Tumor therapy with high energy photons

A big step forward was the invention by Rolf Wideröe, a Norwegian physicist, who in this year (1992) celebrated his 90th birthday in Switzerland. He is well known in accelerator physics for his ideas of multiple acceleration of ions in linear tubes, which were formulated in his doctoral thesis at the Technical High School at Aachen. These ideas were later used by Lawrence for the construction of the cyclotron. Wideröe worked also at this time on the acceleration of electrons by the induced electric field of an increasing magnetic field, the so-called betatron. He formulated the basic equations for a particle beam, the well known 1:2 condition between the accelerating inductive magnetic field and the magnetic field being responsible for the Lorentz force of circular movement of the electrons. The physical conditions for stable beams in such an accelerator were formulated much later by Steenbeck in Berlin working for the Siemens Company at that time. Finally, for obtaining a high beam current, a suitable electron injector was developed for the betatron by Kerst in USA. He finally succeeded in obtaining a photon beam with an intensity equivalent to many grams of radium and a photon energy of around 20 MeV.

As shown in Fig. 2, with photons of such a high energy, a completely different rate of the radiation dose with depth can be achieved. The relative dose in the skin is very low and in a depth of about 10 cm a broad maximum exists. This can be explained easily as follows: It is shown schematically in Fig. 3 that high energy photons enter from the left side into solid matter and induce secondary electrons, mainly Compton electrons, emitted in the forward direction. In Fig. 3 it is assumed that in each layer of matter one of these electrons is emitted. Radiation dose is defined by the energy imparted by directly ionizing particles to matter. Therefore radiation dose is proportional to the number of electrons traversing the layers in Fig. 3. In the first layer one half electron path is contributing to the dose. In the second layer there are one and a half electrons and so on. The maximum dose is reached at about the range of the electrons. For a spectrum of bremsstrahlung with a maximum energy of 30 MeV the mean photon energy is around 15 MeV and the corresponding electrons with $dE/dx = 2$ MeV/cm have a range of about 7 cm in water. The decrease of radiation dose behind the maximum is due to the attenuation of the photons in matter which was neglected for the sake of simplicity in the explanation given above.

This expected advantageous depth-dose curve in the irradiated body of a patient was the main reason for us to construct a 35 MeV betatron for tumor therapy around 1950 (see Figs. 4 and 5). But when we applied this new type of radiation in clinical trials, other more-or-less unexpected advantages were observed. If a bone is situated in front of a tumor then with 100 kV X-rays a 'shadow' exists in the irradiated tumor due to the strong attenuation of photons by the photo effect in the calcium atoms. The influence of a bone was much less with the high energy photons from the betatron since the attenuation by Compton effects is independent of the atomic number of the material.

The most important advantage of high energy photons, however, was really a surprise for the radiologists. The treatment of a tumor needs a radiation dose of about 60 Gy which is given usually in daily fractions of one to two Gy. If X-rays of some hundred kilovolts are used for such a treatment, the patients feel very ill a few days after the beginning of the treatment. They have to stay in bed and suffer severely from nausea and vomiting. These very unpleasant symptoms in the patients did not appear during the treatment with the high energy photons from a betatron. The reason is the very small angle of Compton scatter of high energy photons as indicated schematically in Fig. 6. In the treatment with 100 kV X-rays the whole body of the patient receives a rather high dose of radiation leading to the above mentioned symptoms. Whereas with high energy photons the radiation dose is restricted to the primary beam.

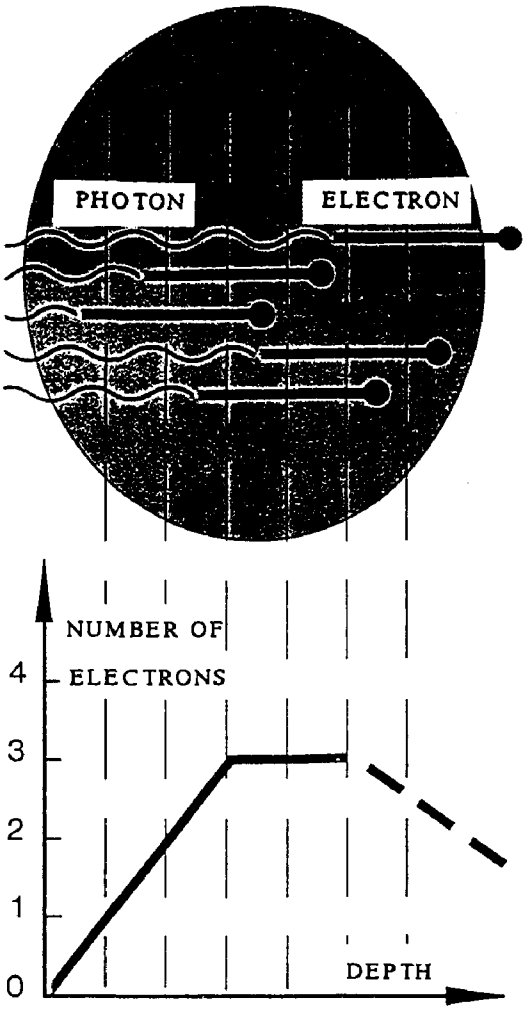

Fig. 3 Relative dose as a function of depth for high energy photons

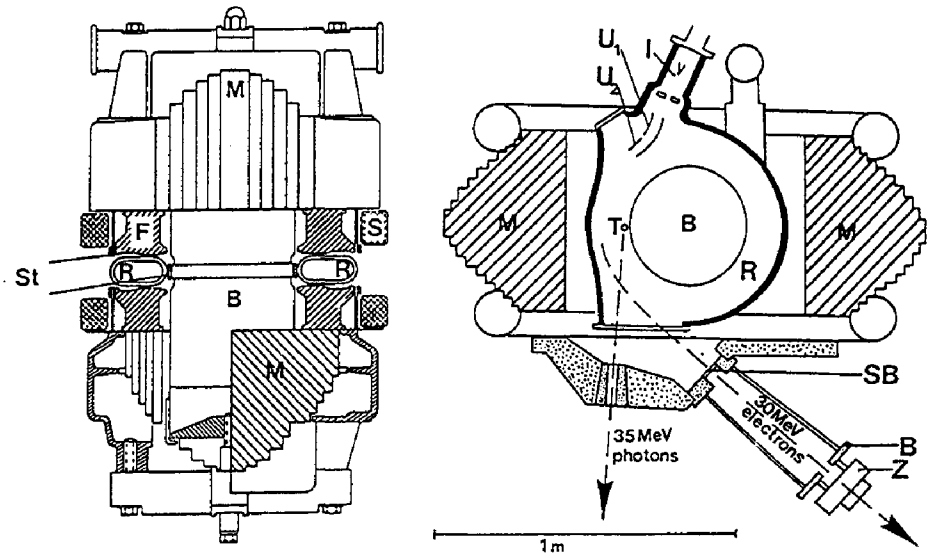

Fig. 4 Section of the 35 MeV betatron of the Institute of Biophysics in Frankfurt, Germany, constructed around 1950 together with Siemens.

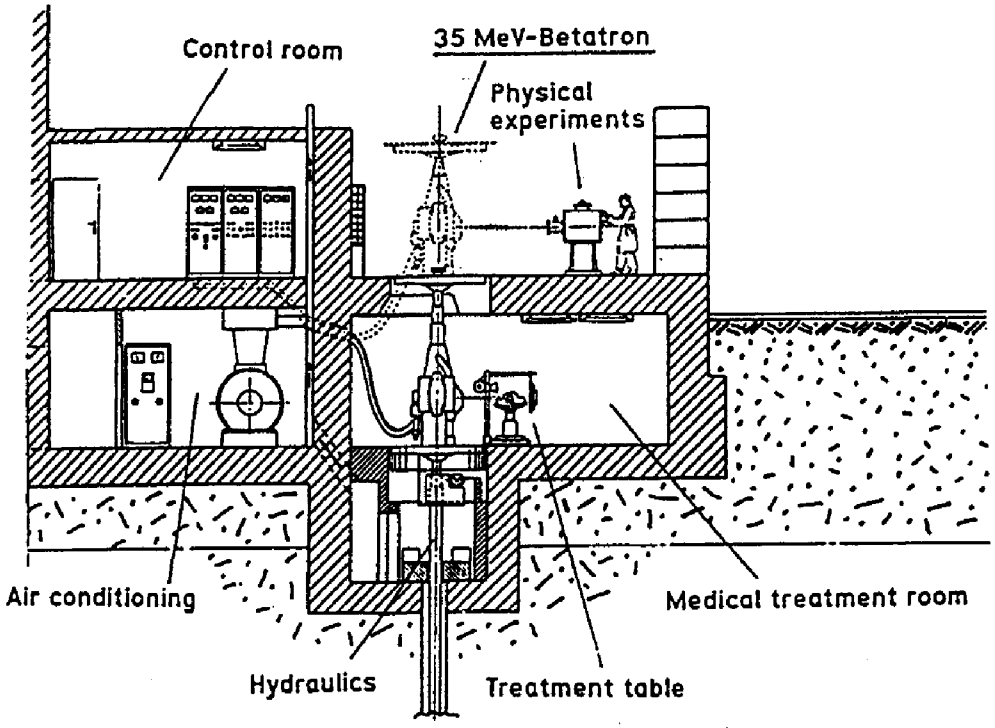

Fig. 5 Installation of the 35 MeV betatron in the Institute of Biophysics in Frankfurt, Germany, for nuclear physics experiments in a large experimental hall on the ground floor and clinical treatment of tumors in the basement.

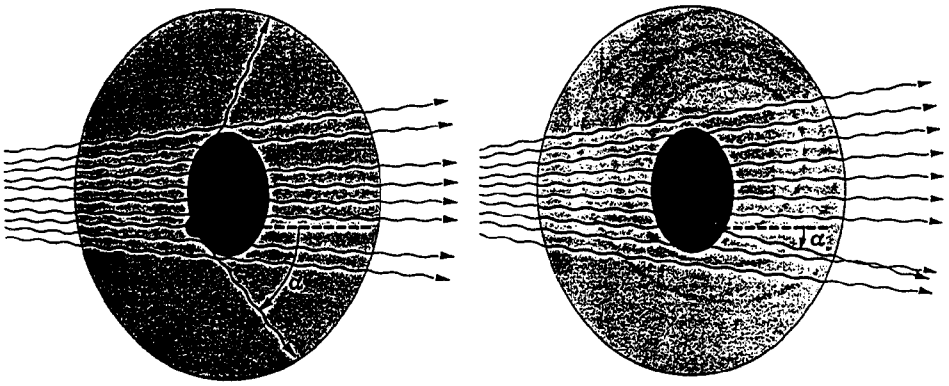

Fig. 6 Scheme of Compton scattering of 100 kV X-rays (left) and 30 MeV photons (right)

This is an example of the often observed effect that a certain procedure is proposed for clinical application having in mind a certain advantage. In the case of high energy photons this was the favourable depth-dose curve as depicted in Figs. 2 and 3. In practice, however, another effect then turns out to be much more important. Here it was the unexpected positive influence of the small angle of scattering on the general health condition of the patient. The avoidance of radiation sickness, as these symptoms were often called, therefore seems to be the most important advantage of high energy photons in tumor therapy.

In Fig. 2 a dose profile for 30 MeV electrons is also shown. The radiation dose stays more or less constant from the surface up to a certain depth, e.g. 6 cm for 30 MeV electrons. Then a steep decrease of the dose follows caused by the range of electrons modified by the large scattering and energy straggling of the electrons. The normal tissue behind the tumor in this way receives only a relatively small dose. The energy of the electrons used has to be adjusted to the spatial extension of the tumor.

Today most of the cancer patients are treated either with high energy photons or fast electrons. The circular electron accelerators, the betatrons, are replaced mostly by electron linear accelerators. These machines are easier to handle, are smaller and deliver a higher dose rate. It is estimated that altogether nearly one thousand of these accelerators are now in medical use throughout the world.

3. DEVELOPMENTS FOR FUTURE RADIATION THERAPY OF TUMORS

As mentioned already in the introduction about two thirds of the patients can be treated satisfactorily nowadays using accelerator-produced high energy radiation. On the other hand, a large number of patients, who come to the clinic for a tumor treatment cannot yet be cured today. Their tumor cannot be treated by surgery because of the presence of essential normal tissues in the neighbourhood of the tumor. If these tumors are treated with ionizing radiation, only a tempory relief can be achieved by the destruction of the tumor. The unintentional radiation reactions in the normal tissues adjacent to the tumor, however, very often lead to the death of the patient. In the last decades many attempts were made, therefore, to treat these patients using other types of radiations and new modalities of treatments. To understand the basic problems which have to be solved in tumor therapy, some important fundamental biological facts will now be explained.

3.1 Radiobiological effects in living cells

In Fig. 7 a living cell is shown schematically. The organisation of such a cell can be compared with that of a large chemical factory, the cell nucleus being the leading directorate. Here all the information necessary for maintaining life processes in the cell and for cell reproduction is stored in a double-stranded macromolecule, called deoxyribonucleic acid (DNA). The information is presented here in a text of about 10^9 bits using an alphabet consisting of only four different letters (A = adenine, C = cytosine, G = guanine and T = thymine) as shown schematically in the middle and right of Fig. 7. The DNA molecule is made of two opposite strands and the pairs of letters A-T and C-G fit together by hydrogen bonds as shown to the right of Fig. 7. In this way the second strand in the DNA is just a negative copy of the first strand.

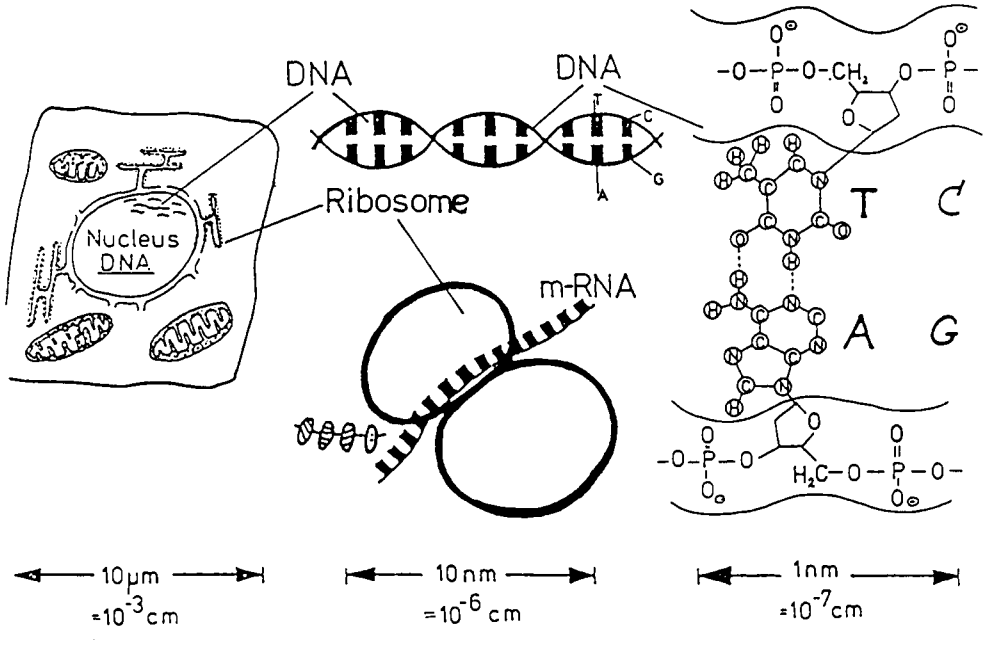

Fig. 7 Scheme of a living cell and DNA structure

This information in the DNA is used by the cell in the following way: A small part of the

DNA of about 300 to 500 letters is copied by the cell from the DNA. This molecule is called messenger-RNA since it leaves the cell nucleus and transports information to the cytoplasm of the cell. There, this text is translated into a sequence of amino acids, called a protein or an enzyme. The living cell is using an alphabet of 20 different amino acids for this purpose. Therefore a triplet of RNA letters is always coding for one amino acid in the enzyme molecule. There is much redundancy in this genetic code of a living cell. But in general, one letter in the DNA decides on a certain amino acid being put in a distinct position in an enzyme.

Due to the specific sequence of the amino acids in the enzyme this molecule gets a special spatial structure. It is then able to recognize and bind selected substrates, e.g. a glucose molecule. Another part of this enzyme may, for example, bind an energetic molecule with a phosphorus group, such as adenosine triphosphate (ATP). Both reactive partners have lost by this binding most of their freedom of statistical movement in space and consequently the entropy is reduced in this system. In this way the enzymes in a living cell act like the well known 'Maxwellian demons' reducing the entropy of the system. In a next step, the enzyme brings together both reactants and in this way the biochemical reaction of this binding procedure is accelerated by a factor of 10^6 to 10^8. Each biochemical reaction in the living cell is catalysed by a special specific enzyme and it is obvious that destroying one letter in the DNA may lead to the death or inactivation of a complete cell.

In experiments measuring the inactivation of living cells by irradiation with ionizing particles a very important discovery was made: If the cells were tested for their vitality immediately after irradiation, a large number of dead cells was registered at a certain radiation dose. If this test of vitality was done, however, several hours later, a smaller number of cells suffered from the irradiation and most were vital as if unirradiated. This was an indication of the repair of radiation damage in living cells. The biochemical mechanism of repair of radiation damage should be explained here briefly using a simple example (see Fig. 8).

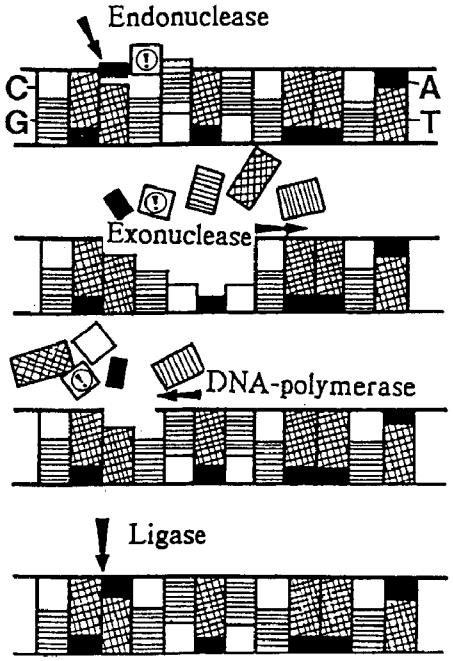

Fig. 8 Repair of a single base damage in the DNA by four different repair enzymes

If a letter in the DNA is destroyed by the passage of an ionizing particle, this can be recognized by a special enzyme molecule which moves up and down the DNA. This enzyme makes a cut into the backbone of the DNA at the position of the damage and is called therefore 'endonuclease'. Then a second enzyme cuts out the damaged DNA letter and some more adjacent letters. It is called therefore 'exonuclease'. A third enzyme, the DNA polymerase, fills the existing gap with new DNA letters using the opposite strand of the DNA as a template.

Finally an enzyme, called 'ligase' closes the gap in the DNA backbone and the radiation damage has vanished. This is only one example of an enzymatic repair in a living cell. We know from our experiments that this repair system is able to repair about 1000 lesions per minute in each cell. The repair enzymes mentioned above have been isolated and can be purchased as biochemical tools for molecular biological experiments in cells today.

From the molecular mechanism of repair in the DNA explained above, it can be understood that this system may not operate perfectly. If during the time necessary for the repair more damage takes place in the DNA in the same region of the DNA but in the opposite strand, then a correct repair of the original sequence of letters by the DNA polymerase is not possible due to the lack of information from the template. Such a double base damage in the DNA is irreparable.

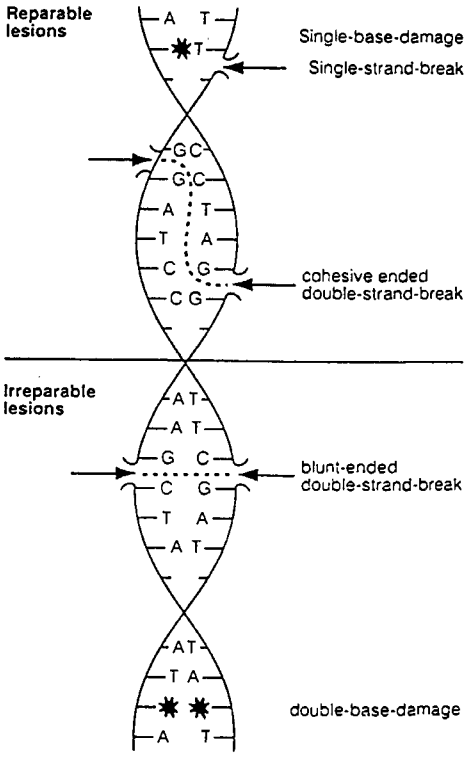

Fig. 9 Reparable and irreparable radiation lesions in the DNA

In Fig. 9 the most important radiation lesions in the DNA are shown, some being reparable, the others irreparable. By the passage of an ionizing particle lesions in the DNA letters as well as in the backbone of the DNA may occur. Breaks of covalent bindings in the DNA backbone are called 'strand breaks'. Single strand breaks are reparable lesions. They can be closed by the enzyme ligase as explained already. Double strand breaks (dsb) are also reparable if they stay together for a sufficiently long time. This is the case if the two opposite strand breaks are diagonal in the DNA. Such a double strand break is called staggered-ended dsb. The ends of a blunt-ended double strand break, on the other hand, diffuse away from each other very quickly and therefore are irreparable.

It can be understood from the pattern of energy depositions along a particle track of ionizing radiation in matter that the reparable DNA lesions i.e. single-base damage and single-strand breaks and also the staggered-ended double-strand breaks are induced mainly by sparsely ionizing radiation such as high energy photons and electrons. Densely ionizing radiations, such as alpha particles or protons of a few MeV, in contrast, induce preferentially the irreparable lesions: blunt ended dsb and double-base damage. This is, by the way, the reason that densely ionizing radiation is considered to be more dangerous than sparsely ionizing radiation in the field of radiation protection.

In general, a more densely ionizing radiation is more effective in the inactivation of living

cells. This can be expressed by the relative biological effectivenes, RBE which is defined as follows:

$$RBE = D_r/D_i$$

where D_i is the dose which is necessary to get a certain radiation effect with radiation type i (e.g. densely ionizing radiation) and D_r is the dose of a sparsely ionizing reference radiation, necessary to obtain the same biological effect. In general, more densely ionizing radiation induces a larger number of irreparable lesions per dose as compared with sparsely ionizing radiation. Therefore the RBE for densely ionizing particles is larger than one for many biological reactions.

An optimal radiation for the treatment of tumors should consist of particles which are sparsely ionizing as long as they penetrate the normal tissue and induce there mainly reparable lesions. In the tumor these particles should be densely ionizing inducing mainly irreparable radiation lesions. Such a particle exists indeed: the negative pion. A negative pion with an energy of about 80 MeV penetrates about 12 cm of water with sparse ionization and small scattering. At the end of its track it is captured by an atomic nucleus and densely ionizing particles are set free in a nuclear spallation reaction (see Fig. 10).

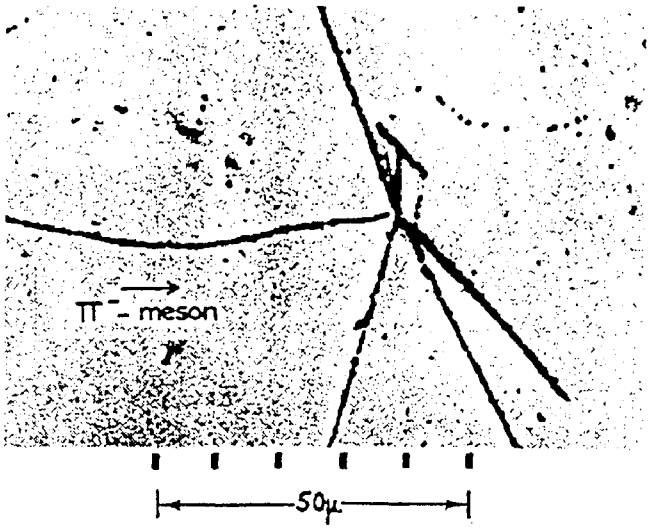

Fig. 10 Photoemulsion showing a nuclear spallation by a negative pion

3.2 Tumor therapy with negative pions

The idea to use negative pions for tumor therapy was first mentioned by the physicist Fowler in 1961. At that time negative pions could already be produced with some accelerators which delivered beams of protons of more than 600 MeV. The current in these accelerators, however, and consequently the particle fluence of the negative pions, was so small that they could not be used for tumor therapy. Since that time, three accelerators in the world are able to deliver enough negative pions for medical tumor treatment: Los Alamos, USA; Vancouver, Canada; and the Paul Scherrer Institute (PSI) in Villigen, Switzerland. The installation at the PSI is the most dedicated one and we have worked there from the beginning, more than ten years ago, on the development of tumor therapy with negative pions.

The first experiments with suspensions of hypoxic tumor cells proved the basic assumption that at the track ends of negative pions densely ionizing radiation with a high RBE of about 2.4 was present. With the financial help of the Swiss cancer league a small clinic and a special applicator for pion tumor therapy was constructed and is shown in Fig. 11.

A beam of 590 MeV protons (current 20 μA) hits a beryllium target. The resulting negative pions are picked up by sixty superconductiing coils and are bent into a direction

parallel to the proton beam. All sixty pion beams are then bent by 90° coils and impinge concentrically on the patient as indicated in Fig. 11. There, in the center, a spot of spallation products exists with a volume of about 30 cm^3 and a dose rate of about 1 Gray per minute. The patient is protected from the target radiation by a 3-m thick iron plug.

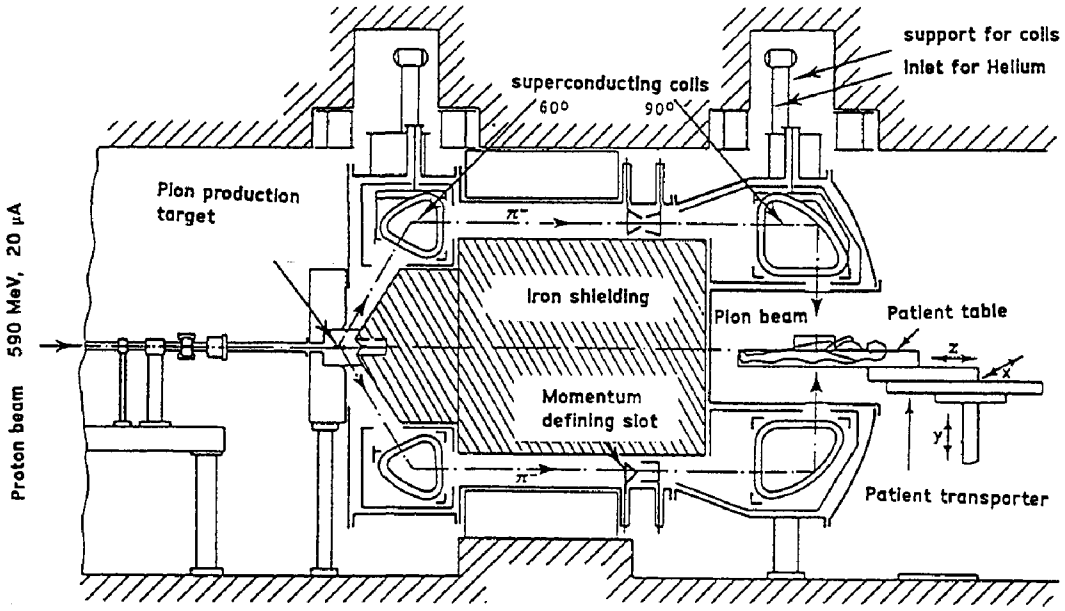

Fig. 11 Installation for irradiation of patients with negative pions, PIOTRON, at the Paul Scherrer Institut, Villigen, Switzerland

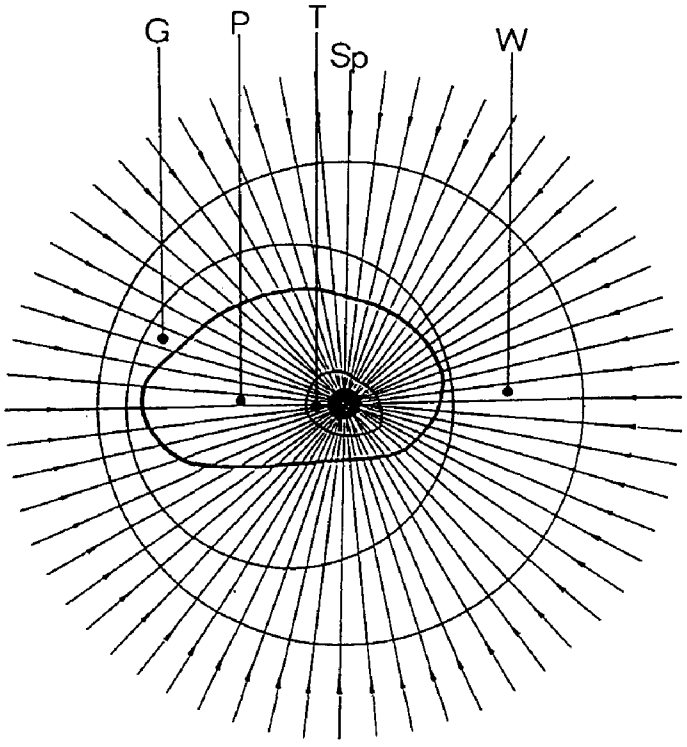

Fig. 12 Scheme of the spot scan for irradiation of tumors with negative pions
For the irradiation of a tumor (T) which is larger than the small pion spot (Sp) and has an irregular shape, the patient (P) is embedded in solid material (G) to obtain a cylindrical contour

as shown in Fig. 12. With this cylinder the patient is inserted into a circular water filled ring (W) with rubber side walls. The patient can be moved by computer control relative to the spot of stopped pions which stays always at the same fixed position in space. In this way the radiation dose can be distributed homogeneously in the irregularly shaped tumor and the adjacent normal tissues can be spared. A few hundred patients have been treated in this way during the last years with negative pions at the PSI. The clinical experience can be summarized as follows:

a) Negative pions were thought to be advantageous due to the induction of a large fraction of irreparable radiation lesions in the tumor. This advantage is reduced, however, by the fact that the tumors are much larger than the small spot of densely ionizing spallation products and must be treated by the scanning procedure explained above. As a consequence, each part of the tumor is irradiated for a certain time with densely ionizing radiation from the spot and the rest of the irradiation time with sparsely ionizing radiation from the pions in flight. Instead of an RBE of 2.4 as determined from cell suspensions and from irradiation of small mouse tumors, an RBE of only 1.7 can be achieved in large tumors in the patients.

b) The clinical trials indicated that the most important advantage of the pion treatment is related to the scanning procedure taking into account the unregular shape of the tumor and sparing as much as possible the adjacent normal tissue. This important advantage, however, is reduced by the fact that neutrons are produced also by nuclear spallation and are scattered out of the treatment volume. The RBE of this densely ionizing radiation is high and this is in contrast with the initially expected advantage of negative pions that they would traverse normal tissue with sparse ionisation.

This clinical experience which has been proven by further systematic and more precise experiments led to the proposal to use protons in radiation therapy. The disadvantages of negative pions mentioned above can be avoided and all important advantages can be used with even higher efficiency.

3.3 Tumor therapy with high energy protons

With high energy protons a high dose rate can be achieved easily with a relatively small proton current. With a current of one nanoampere a volume of one liter can be irradiated with a dose of one Gray in about one minute. Therefore a single beam of protons can be used for tumor therapy. For reaching every point in the human body a proton energy of about 200 MeV is neccessary. As was shown in the previous chapter, the most important advantage in the clinical use of negative pions was the conformal irradiation of the tumor with the spot scan method. With high energy protons the irregular shape of the tumor can also be taken into consideration as is explained in Fig. 13. A proton beam with a small diameter of about 5 mm is scanned over the tumor and the energy is continuously modulated by absorbers in such a way that the proton range coincides with the edge of the tumor. The first irradiation would be done e.g. from the direction indicated with (a) in Fig. 13. The next day the irradiation is given from direction (b) and so on. In this way the tumor can be irradiated with a homogeneous distributed dose. By selecting a suitable set of beam directions a very sensitive and essential normal tissue, indicated by "S" in Fig. 13 can be spared completely. It should be mentioned that such a sharp dose gradient from the tumor (T) to an essential senisitive normal tissue (S) can only be obtained with protons. Other types of particles, such as light or heavy ions would always result in a considerable dose behind the range of these particles due to densely ionizing secondary particles from nuclear reactions.

The development of a suitable scanning procedure for a 200 MeV proton beam is very advanced at the PSI. The construction of a small proton accelerator dedicated to medical use, however, still is an open technical problem to be solved in the near future. It seems that the use

of high energy protons will be a big step forward in tumor therapy, comparable with that of using high energy photons and fast electrons thirty years ago.

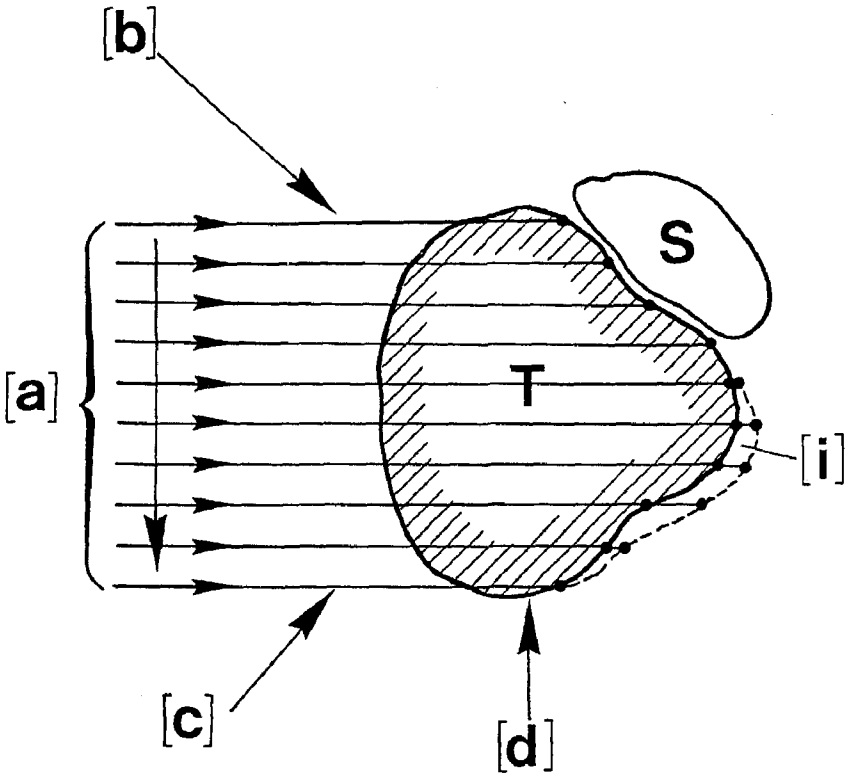

Fig. 13 Multiple beam scanning procedure for irradiation with high energy protons

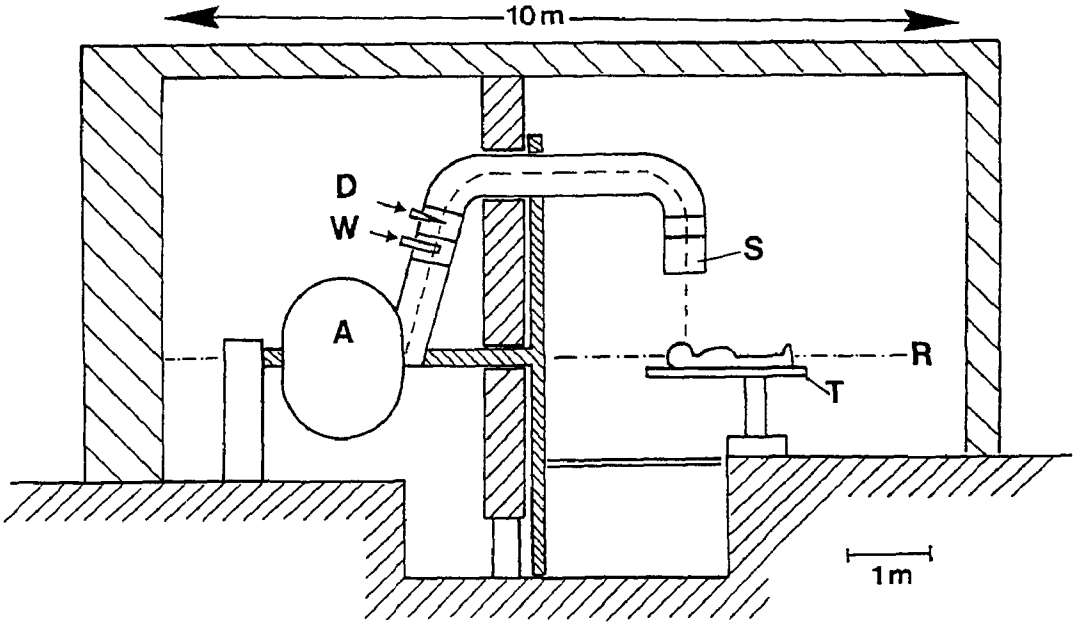

Fig. 14 Scheme of a clinical setup for tumor therapy with high energy protons