Medical ion radiography

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The aim of this review is to acquaint the reader with the principles and methods of ion radiography—a method of studying the inner structure of an object by using heavy charged particles. Along with the refinement of the traditional x-ray method of diagnostics and the development of a number of new methods, such as positron tomography and nuclear magnetic resonance, and in spite of the great advances attained in x-radiography in recent years, a persistent search continues for new, refined methods. First of all, efforts are directed toward seeking effective methods of early diagnosis of tumor lesions with less danger than in x-radiography. Studies have been conducted in a number of countries in the past decade on the possibility of applying heavy charged particles of relatively high energies for these purposes. Ion radiography enables one to obtain a higher contrast image than x-radiography at lower doses of irradiation, and to differentiate soft tissues and to detect in them anomalies of small dimensions. It opens up the possibility of obtaining new diagnostic information. Theoretical studies in the field of ion radiography and experiments on animals, on human tissues, and in a number of cases, on patients, have shown the promise offered by using ions for diagnosing not only tumors, but also a number of other serious lesions. This new field of study has incorporated the experience of particle and nuclear physics and widely employs its variety of investigational methods. This article also treats problems involving the application of accelerators for ion radiography and specifications for the beam parameters and for the particle detectors. This review gives an account of the advances in this new field of studies and the prospects for its development and the difficulties on the pathway of introducing it into practice.

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CONTENTS

1. INTRODUCTION

The human race has been employing electromagnetic radiation and sound for diagnostic purposes for a long time. The x-ray method of diagnostics is continually being perfected. However, it has almost exhausted its possibilities, which are limited by the physical laws of interaction of x rays with matter. Everywhere in the world the search is being conducted for new, more effective and safe methods of medical diagnosis: positron tomography, nuclear magnetic resonance, etc., have been developed. The main efforts are directed toward seeking methods of detecting tumor lesions in early stages.

In the past decade heavy charged particles accelerated to relatively high energies have begun to be applied for diagnostic studies—ion radiography has begun to develop.

The possibility of using fast protons to study the inner structure of an object was first pointed out in 1946 by R. Wilson,[1] whose idea was later developed by H. And-

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erson.[2]

On what principles is ion radiography based? In passing through matter heavy charged particles lose energy in ionizing the atoms of the medium. Their tracks in the material are nearly rectilinear, with ranges strictly related to the energy of the particle and the density of the material. This property of ions has found application in the residual-range method. By recording the flux distribution of monochromatic particles upstream and downstream from the object being studied, one obtains information on its integral density distribution in the direction of the beam. The residual-range method has been developed further and has served as the basis for ion tomography—a method of studying the spatial density distribution of an object from the integral density distribution in several directions.

The pioneers in applying protons in medical radiography were V. W. Steward of the University of Chicago and A. M. Koehler of Harvard.[3-10] A number of studies have shown theoretically and experimentally the advantages of ion radiography over x-ray methods in terms of the contrast limit of the image and of the radiation doses. These advantages stem from the difference in the physical laws of interaction of ions and photons with matter. Images of unusually high contrast with relatively low radiation doses have been obtained with beams of accelerated ions.

Yet another method of ion radiography has been developed in recent years. It employs the property of fast protons of undergoing nuclear interaction with matter. The distribution of nuclear interaction events in the object yields information on its density distribution. The coordinates of the events are determined with modern position-sensitive charged-particle detectors.

This review treats the physical principles of ion radiography, its methods, and the results of studies of animals, human tissues, and patients. The experiments have shown the promise offered by ion radiography in diagnosis not only of tumors but also of other serious lesions.

The development of ion radiography is based on using accelerators. The prospects of ion radiography are directly connected with the design of accelerators whose beam parameters correspond to appropriate specifications. This article discusses the variants of projects for such accelerators.

In ion radiography one employs the traditional charged-particle detectors that are applied in physical studies; however, certain features exist in their utilization in ion radiography. Therefore this review will cast light on some problems of the application of detectors.

We also discuss the potentialities of ion radiography and the prospects of its development.

2. THE RESIDUAL-RANGE METHOD

a. Physical principles

1) *Energy losses spent in ionization in matter; range (residual).* In passing through matter, a heavy charged particle interacts electromagnetically with the electrons of the atoms with consequent steady loss of its energy. The deceleration of the particle continues until its energy has fallen to the thermal energy of the atoms of the retarding medium. The retardation process is statistical in nature. The Bethe equation is used for a quantitative description of the energy losses of heavy charged particles in passing through matter. This equation allows one to determine the energy losses due to ionization and excitation of the atoms of the material along the element of path length dx. For particles having energies up to ~200–250 MeV per nucleon (these are precisely the energies employed in the residual-range method described below), these losses are expressed as follows[11]:

$$-\frac{dE}{dx}=\frac{4\pi\rho e^4 z^2 N_0 B}{Amv^2}, \tag{2.1}$$

Here we have $B=Z[\ln(2mv^2/I)-\ln(1-\beta^2)-\beta^2]$ and A, Z, and ρ are respectively the mass number, the atomic number, and the density of the retarding material, and e and m are the charge and rest mass of an electron. Further, N_0 is Avogadro's number, c is the speed of light, v is the velocity of the particle, ze is its effective charge, $\beta=v/c$, and I is the mean excitation energy of an atom of the material. The quantity B is called the stopping power of the material, since it contains the characteristics of the retarding medium. For protons of energy ~200 MeV we find $B=0.5$. We can see from Eq. (2.1) that the energy losses are proportional to the density ρ, to the square of the charge of the particle, and to the ratio Z/A of the material. The ratio Z/A is about the same for most of the elements comprising the tissues of the human organism. We see also that the energy losses dE/dx increase as the energy of the particle declines. This result is expressed in the well-known maximum of energy losses near the endpoint of a beam of monochromatic particles that is known as the Bragg ionization peak.

In decelerating in a homogeneous medium, a heavy charged particle has a definite range. Therefore the flux of monoenergetic particles declines sharply toward the end of the path. If a density inhomogeneity lies in the path of the particles, then their range is altered, and correspondingly the flux of particles near the stopping point is altered. The residual-range method in ion radiography is based on this property of heavy charged particles.

X rays interact with matter in a different way from ions: they undergo Compton scattering and photoelectric absorption. Consequently the x-ray flux declines exponentially with increasing thickness of the absorber (Fig. 1). Here the functional dependence of the extinction coefficient of the beam on the Z of the material lies in the range from Z^2 to Z^3. Owing to the difference in physical properties of the interaction with matter of x rays and protons, x-ray images differ qualitatively from proton images.

In order to put the method into effect, one must know the relationship between the range of the particles and their energy in tissues. The range-energy relationship in water, which resembles tissues in density and com-

position, is described by the following simple empirical formula to an accuracy of ~10% for the range of particles and energies of interest for radiography:

$$\frac{E}{A}=29.5\left(\frac{z^2R}{A}\right)^{0.604}.$$

Here z is the atomic number, A is the atomic mass number of the particle, R is its range in cm, and E is the energy in MeV.[12] The parts of the human body most difficult to penetrate are equivalent in stopping power to a layer of water 30–40 cm thick. Hence, for radiographic study of the human organism, one must use protons of energy ~230 MeV or α particles of energy ~900 MeV.

2. *Straggling, longitudinal resolution of the method.* The fundamental characteristics of each radiographic method are the longitudinal, transverse, and volume resolutions and the radiation dose.

Figure 1 demonstrates the difference in physical properties of ions and of x rays using the example of 137-MeV protons and 100-kv x rays. We see from the diagram that the actual curve for protons does not fall off vertically. This involves a number of factors. The existence of a spread of ranges, which is due to the statistical nature of the energy losses, and which is called straggling, is one of the major ones. Straggling limits the longitudinal resolution of the method, or its sensitivity to changes in density. Under real conditions, the longitudinal resolution of the method and the shape of the curve for protons in Fig. 1 depend on a set of factors: straggling, energy spread of the beam, shortened ranges caused by multiple scattering in the material, and errors in the range introduced by the detector. As a rule, the first two factors play the major role. The longitudinal resolution of the method is determined by the quantity $\Delta p/\Delta m$ when protons are used and by $\Delta x/\Delta m$ when x rays are used (see Fig. 1). Thus we obtain a qualitative picture of the advantage of protons over x-rays in the sensitivity to density changes of the material. Indisputably this is the main advantage of charged particles over x rays. Yet it can be exploited only if the irradiation doses to the patient in ion diagnostics prove acceptable. As we shall show below, the irradiation doses accompanying ion radiography are lower than the doses experienced in x-ray radiography.

Which ions ensure the best longitudinal resolution? Whenever we can neglect the spread of ranges involving nonmonochromaticity of the beam, the longitudinal resolution depends mainly on the magnitude of the straggling σ_R—the standard deviation of the longitudinal distribution of the points at which the particles have been brought to rest.

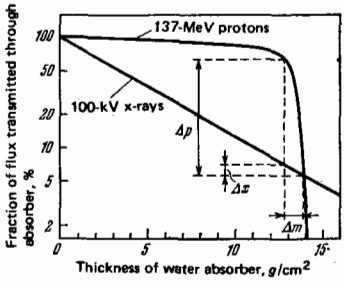

FIG. 1. Dependence of the fraction of the flux of protons and x-rays transmitted through an absorber on the thickness of the homogeneous absorber.[5]

Benton *et al.*[12] have given the empirical dependence of the magnitude of the straggling σ_R of the range R in water and on the atomic mass number A of the particle:

$$\sigma_R=0.0120R^{0.951}A^{-0.5}\ \text{cm}.$$

At a depth of 30–40 cm of water, the straggling of protons amounts to ~1.0% of their range, which is about twice as large as for α particles and four times as large as for carbon nuclei. This means that heavy ions yield better longitudinal resolution than protons.

3. *Multiple scattering of particles in matter; transverse resolution of the method.* In passing through matter, a charged particle is not only decelerated, but is also elastically scattered in the Coulomb field of the nuclei of the atoms. Consequently it suffers small deflections from its original trajectory, on being scattered in each individual interaction event by a very small angle, while practically losing no energy thereby. The overall effect of the large number of small deflections is called multiple scattering. It leads to a spread in the stopping points in a plane perpendicular to the beam, and it limits the transverse resolution. Thus multiple scattering prevents one from detecting, using protons,[13a] a mammary tumor of diameter less than 1–2 mm, or a brain tumor of diameter less than 2–3 mm. The standard deviation of the transverse distribution of stopping points of various ions having the same range in water is described by the following approximate empirical formula[12]:

$$\sigma_x=0.0232z^{-0.207}A^{-0.396}R^{0.896}Z_s^{0.963}A_s^{-0.5}.$$

Here Z_s and A_s are the atomic number and the mass number of the retarding material, while z and A are the atomic number and mass number of the particle (R and σ_x are in cm). For a given range, we see that heavy particles are scattered less than light ones. Thus the use of ions (^{4}He, ^{12}C, ^{14}N, ^{16}O, etc.) instead of protons allows one to obtain a higher transverse resolution. We note in passing that the effect of multiple scattering that arises when the particles move along the boundary between two media can be used *per se* to obtain a radiographic image of an object of small thickness.[14]

4) *Radiation doses.* One can use the curves[12] shown in Fig. 2 to determine the radiation doses accompanying a radiographic procedure.

5) *Stopping power, density, and elemental composition of human tissues.* The study of the physical properties of human tissues is one of the most important aspects of the entire problem. To elucidate the potentialities of ion radiography, we need exact and complete data on the stopping powers of both normal and pathological tissues. At the same time, their experimental determination involves great difficulties. Therefore the published data are far from complete. Reference 15 presents calculated values of the stopping powers of brain tissues and of one of the varieties of tumor tis-

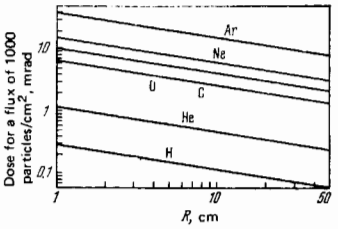

FIG. 2. Radiation dose given by different ions as a function of their mean residual range in water.[12]

sues. The stopping powers were measured for various biological objects, such as blood, muscle and fatty tissue, and also for a number of other materials that play an auxiliary role in radiography: paraffin, plexiglas, polyethylene, and salt solutions. Information on the stopping power of the bone tissue of the human skull can be found in Ref. 16. Analysis of the data on the densities of tissues, especially soft tissues, that have been published during the past 100 years has shown that they do not satisfy modern requirements.[8] One can find information on the densities of normal tissues and of certain types of pathological tissues in Refs. 8, 10, 17–19. The density of tumor tissues differs from that of the surrounding normal tissues by about 3%. There are indications that the density of hemorrhagic foci in the brain exceeds that of normal brain tissue by 2–3%, while the density of necrotic tissues arising from embolism of the cerebral blood vessels is about 5% lower than the density of healthy brain tissue.[8] There are as yet no systematized data on the properties of pathological tissues. In order to obtain data adequate to the demands of radiography on the densities of tissues and on their changes in lesions of various types, a group of American pathological anatomists and physicists has developed an extensive program of studies that has been realized through broad cooperation of specialists in various research centers. Systematization of density measurements to an accuracy of the order of 10^{-5} g/cm^3 is being planned.

b. Results

The first experiments on proton radiography were performed on specimens of human tissues.[3-10] In the studies of Steward and Koehler,[4,6,7] a monoenergetic proton beam from the Harvard 160-MeV cyclotron was employed for proton radiography of brains having various types of lesions (Fig. 3).

This is the design of the experiment (Fig. 4). A proton beam extracted from the accelerator is deliberately scattered to obtain a broad beam uniform over its area. Then it is brought to the needed energy with an absorber. At a distance of 3 m from the absorber, the particle beam is uniform over a radius of ~10 cm from the axis of the beam. The object under study is placed at this site in a special plexiglas vessel having parallel walls that is filled with an immersion liquid of density equivalent to the tissue. A photographic film is placed immediately behind the object in the region of decline of the Bragg peak. This method can be called "contact radiography", since it resembles the method of contact printing from a negative.

In spite of the screening effect of the skull bones, the very first experiments reliably detected brain tumors, found intracranial hemorrhagic foci and regions of necrosis of brain tissues, and also numerous sclerotic lesions. Analogous experiments have detected small tumor satellites in the mammary gland that were not found by x-radiography.

The differing degrees of dependence of the attenuation of an ion beam and of x rays on charge Z of the atoms of the retarding medium gives rise to a qualitative difference between ion and x-ray images. Thus, on an x-ray image the bone tissues appear with a much greater degree of contrast than the soft tissues and they strongly obscure the latter. Whereas proton images yield a lower degree of contrast of the bone tissues against the background of the soft tissues, so that the structure of the soft tissue is better visible. A tumor tissue can practically not differ in Z from the surrounding medium, but can differ in density. Then it is quite visible in an ion image but not on an x-ray image.

The most refined scanning apparatus has been developed at the Argonne National Laboratory.[13a,20,21] One such system employs four proton beams of 1 mm^2 cross-section. The stopping power of the material in the pathway of one of them remains invariant during the experiment. This beam serves as the reference: both intensity and energy are monitored with it. The specimen to be studied is displaced in two mutually perpendicular directions in 1-mm steps. A scan over an area 254×254 mm^2 takes 18 min. Application of the method of scanning with a system of narrow beams made it possible to increase substantially the sensitivity to changes of density and to reduce the radiation dose as compared with the ordinary "contact" method. Regions of tissue are detected that differ in density from their environment by 0.2–0.5%.

The described series of studies showed that soft tis-

FIG. 3. Proton radiographic image of a head containing a brain tumor (arrow). The dose at the front surface is less than 0.5 rad.[7]

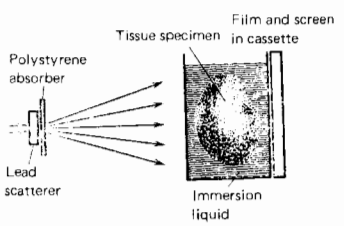

FIG. 4. Diagram of a radiographic experiment employing the residual-range method.[6]

sues are better differentiated by using protons than by using x rays and that the radiation doses in ion radiography are considerably lower than in x-radiography for the same quality of image. Thus, in the simplest "contact" proton radiographic procedure, one of the forms of tumors (mammary carcinoma) is detected with a dose at the front surface of somewhat less than 0.3 rad (it is even smaller when the scanning method is employed), while the corresponding image obtained in x-ray mammography corresponds to a dose of 6–15 rad, or in xeromammography to ~3 rad.[10] Theoretical calculation[21] has shown that a brain tumor of dimensions $3 \times 3 \times 3$ mm^3 can be detected by proton scanning with a dose of 0.09 rad. Probably the existing x-ray apparatus cannot detect such small neoplasms, even with a radiation dose of 1 rad.

Radiographic studies employing ^{12}C, ^{16}O, and ^{20}Ne ions have been performed in the beam of the bevatron of the Lawrence Laboratory at Berkeley.[12,15,22-26] Studies were begun in 1976 of patients with tumors of the mammary gland (Fig. 5) and of the soft tissues of the extremities.[15] The pattern observed in Fig. 5 is asymmetric. Presence of a tumor in one of the patient's glands was suspected from this fact. Subsequent examination of the glands confirmed the existence of the tumor. Under actual conditions in ion scanning the radiation doses have been rather small (0.1 rem). Ion-radiographic images are of greater contrast than proton images. This fully agrees with the theoretical predictions: both straggling and multiple scattering are smaller for ions than for protons.

An apparatus has been built at the Joint Institute for Nuclear Research (Dubna) for radiographic studies with α particles from a synchrophasotron with an energy of 200 MeV per nucleon.[27] In this case the radiographic information on the object under study is taken from a color television monitor.

c. Proton-ion tomography

The method of obtaining a spatial picture of the density distribution of an object under investigation from data on the integral density distribution of the object in several directions is called tomography. Apparatus for the spatial reconstruction of an object by computer employing a series of two-dimensional x-ray images obtained by irradiating the object at different angles has already been employed in medical practice for a number of years. As practice has shown, modern x-ray tomographic apparatus enables one to detect a difference in density of soft tissues of ~1% in the localization of features of dimensions of several millimeters. The question arises of how much more effective ion tomography will prove to be than x-ray tomography in connection with the difference in the physics of interaction of protons and x rays with matter. The high contrast of the image obtained in contact radiography and the low level of radiation doses give assurance of the promise offered by ion tomography.

What has been done in this field? Experiments have been designed and a number of theoretical calculations has been performed[22,28-32] to ascertain the competitive power of ion tomography over x-ray tomography. Proton experiments have shown that, after reconstruction, one can localize regions of dimensions of the order of several millimeters that differ in density from the surrounding material by about 0.5%. The calculations show that the advantages of protons and ions over x rays increase with increasing thickness of the object under study. Martin[20] considers that the radiation-dose advantage in using protons as compared with x rays in tomography of the head amounts to about 15. The calculations of Hanson and his experiments[29] performed at Los Alamos with the LAMPF accelerator under the same conditions give a value ~8. And with identical radiation doses, proton scanning yields an advantage in density resolution no less than twofold.[30]

Crowe *et al.*[22] have performed tomographic studies with α particles using the 184-inch cyclotron of the Lawrence Laboratory at Berkeley. An α-particle beam of 900-MeV energy was directed into an apparatus including a system of detectors made of three proportional chambers and a telescope made of 13 scintillation counters 1–2 mm thick designed to measure the residual range (Fig. 6). The object could be rotated about an axis by using a special chair, and the irradiations were performed over a certain angle of rotation. The operation of the entire apparatus was controlled by a PDP-15 computer. The data on the residual range, the rotation angle, etc., were accumulated on magnetic tape for subsequent reconstruction of the density distribution of the object of study. Study of the mathematical methods of reconstruction and methods for the most pictorial

FIG. 5. Ion radiograph of mammary glands of a patient.[15]

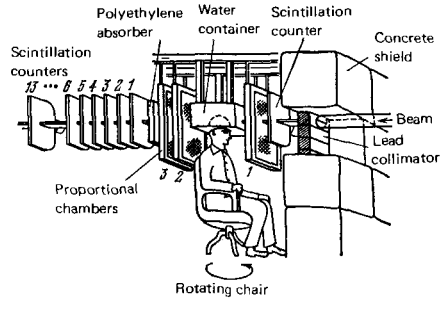

FIG. 6. Diagram of apparatus for α-tomography.[22]

and simple display of the information on the spatial density distribution has shown that the best results are given by Goitein's[31] iterative method of three-dimensional reconstruction from a series of two-dimensional distributions.

A tomographic image of the human head has been obtained on the above-described apparatus (Fig. 7), and study of patients has begun. The tomographic procedure takes several minutes. Motion of the patient and of his internal organs during the exposure reduces the contrast of the image. Hence one of the fundamental problems is to increase the speed of action of the detecting apparatus. One of the major conclusions from this work is that α particles give a smaller radiation dose in the diagnostic procedure than do x rays.

Reference 32 gives the calculated values of the radiation doses in ion and x-ray tomography of the head. Employment of hydrogen and helium ions gives the greatest advantages in doses, whereas the heavier ions allow one to attain higher image contrast.

3. THE NUCLEAR-SCATTERING METHOD

a. Physical principles

The residual-range method discussed above, which is outstanding in its flexibility in its various modifications has a general feature: it yields the integrated density of the object along the path of the particle beam and does not give local measurements directly: three-dimensional reconstruction of the object requires multiple irradiation of the object in different directions.

The nuclear-scattering method (NSM), which the authors have called the "protoscopy" method, yields a three-dimensional picture of the object directly in the course of a single exposure, and it provides supplementary, independent information on the content of hydrogen nuclei in the object of study. It is based on using the phenomenon of nuclear interaction of the particles with the material. At present the method is at the stage of studying tissue specimens. It consists of the following.[33] A proton beam of energy 600–1000 MeV passes through the target object under study and undergoes nuclear interaction with the material of this object. A particle that has undergone interaction is scattered at a large angle. Position-sensitive detectors placed in front of the object and behind it give information on the

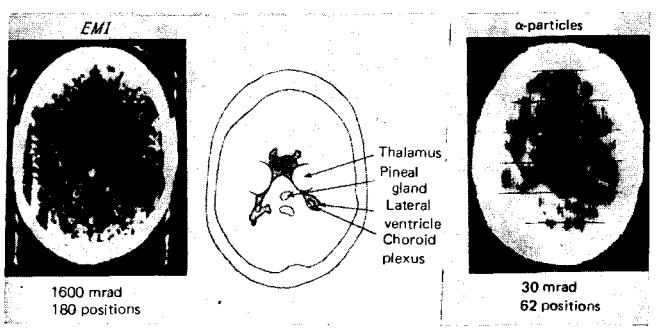

FIG. 7. Tomograms (reconstructed images) of the brain. Left—x-ray tomogram; right—tomogram with 900-MeV α-particles.[22]

coordinates of passage of the primary and secondary particles (for more details, see below in the section *Experimental scheme*). This information enables one to determine the site of the points of interaction. The number of recorded interactions from a volume element $V=ST$ is expressed as follows:

$$N_s = N_I S N_a \int_\Omega \frac{d\sigma}{d\Omega}\, d\Omega, \tag{3.1}$$

Here S is the area of the cross-section in cm^2, T is the thickness in cm, N_I is the flux of particles per 1-cm^2 area of the object, N_a is the number of atoms per 1 cm^2 of the volume V, Ω is the solid-angle subtended by the detectors in steradians, and $d\sigma/d\Omega$ is the differential nuclear scattering cross-section for the given interaction expressed in cm^2 sr^{-1}. The latter is a function of the scattering angle θ known from Refs. 34–37.

If ρ is the density of the material in the volume element V, and A is the atomic weight, then $N_a = 6 \times 10^{23}\rho T/A$, and Eq. (3.1) transforms into

$$N_s = \frac{0.6 N_I V \sigma \rho}{A}. \tag{3.2}$$

Here the cross-section $\sigma = \int_\Omega (d\sigma/d\Omega)\, d\Omega$ is expressed in barns. Thus we see that the number of interactions in the volume element V depends directly on the density and atomic weight of the material of the specimen under study. The particle flux N_I is directly related to the radiation dose.

We can classify the nuclear interactions of interest in radiography in the energy range 600–1000 MeV into two main classes:

a) elastic scattering of protons by hydrogen nuclei (protons),

b) quasielastic scattering of protons by nucleons bound in nuclei.

The differential cross-section for proton-proton scattering does not decline sharply with increasing scattering angle. Over a relatively broad range of angles, both scattered particles have a sufficiently large energy to emerge from the target object. The two scattered protons and the incident one lie in one plane—the condition of coplanarity is satisfied, and the angles of emergence of the two secondary protons obey a rigorous relationship that stems from the laws of conservation of energy and momentum.

A considerable fraction of the interactions with an actual biological object amounts to events of quasielastic interaction of protons with nucleons of a target nucleus. These quasielastic events are not coplanar, and they can be distinguished from the elastic events by kinematic criteria. The relationship between the number of detected events involving hydrogen and other nuclei depends on the ratio of concentration of hydrogen and of other nuclei.

b. Experimental scheme

The scheme of a radiographic experiment in the nuclear-scattering method is analogous to that of a classical experiment on particle scattering.[38-43] In the pres-

ent case, the method of study is practically completely taken over from the field of elementary-particle physics to the field of diagnostic studies. Various studies have employed somewhat different schemes. Figure 8 shows the experimental scheme employed in Ref. 40. A proton beam from the SATURN synchrotron (Saclay, France) of energy 1.03 GeV is incident along the z axis of the object of study, and is detected by two scintillation counters *S1* and *S2* operating in a coincidence regime. The scintillation counter *S3* detects the scattered particle. The coordinates of passage of the particles are measured with drift chambers under the condition of coincidence of *S1*, *S2*, and *S3*: *H1* and *H2* give the coordinates of the primary particle in the horizontal direction, and *V1* and *V2* in the vertical direction. *H3* and *H4* give the coordinates of the scattered particle in the horizontal direction. If a recoil particle arises, its horizontal coordinates are determined by the drift chamber *H5*. All of the information is recorded on magnetic tape (up to 100 events/s). The number of *S1*–*S2* coincidences determines the flux of incident protons and serves to determine the radiation dose. In this scheme the vertical coordinates of the secondary particles are not measured. Hence the selection of events for hydrogen is performed on the basis of kinematic considerations without testing for coplanarity.

c. Results

Various objects have been studied by the nuclear-scattering method: a hard-boiled egg, an egg partially through its incubation period; a rabbit's head; a live mouse with a tumor 2.2 mm in diameter in the abdominal cavity; and human tissues.[33,38-40] Figure 9 shows a nuclear radiographic image of a "section" of a human head obtained in a 1-GeV proton beam.[43] In Ref. 40 a part of a spine containing spinal-cord tissue was studied. The "hydrogen" images of the spine allowed the bone and nerve tissues to be clearly distinguished. They give a rather sharply outlined image of the spinal cord. The structure of the bone tissue is more clearly visible in the "ordinary" picture. The "hydrogen" and "ordinary" nuclear radiographs successfully supplement one another, and both types of images correspond to the anatomy of the studied objects. In these experiments a volume resolution of 1–2 mm^3 was attained. The authors concluded that the spatial resolution of the NSM in the plane perpendicular to the beam is higher than in ordinary x-ray tomography. However, in the plane containing the axis of the beam the opposite is true: the resolution is higher in x-ray tomography.

The fundamental characteristics of every radiographic method are the spatial resolution and the radiation dose. A well-grounded comparison of the results of different radiographic methods must take these factors into account. In the nuclear-scattering method, the accuracy of localization depends mainly on the spatial resolution of the coordinate detectors and on the errors involving multiple Coulomb scattering of the particles. The radiation doses cited as accompanying NSM radiography in various studies are rather large. However, we should consider that they depend to a large extent on the effective solid angle of the apparatus. The French physicists optimistically rate the promise offered by NSM radiography. In Saclay it is planned to build a fast-action apparatus capable of collecting several hundred thousand events per second. Thus the radiographic procedure will be carried out in several minutes. The refinement of the method follows the path of increasing the accuracy of localizing the elementary volume by using ever more accurate position-sensitive detectors: drift and proportional chambers, of increasing the effective solid angle of the apparatus, of increasing the speed of action of the apparatus, of incorporating more refined information-processing methods using computers, and in particular of making use of microprocessors.

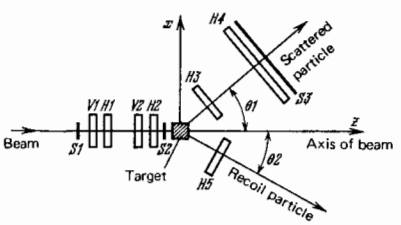

FIG. 8. Diagram of a radiographic apparatus operating on the principle of nuclear scattering.[40] The zx plane is horizontal.

d. Fundamental advantages and disadvantages of the nuclear-scattering method

Advantages:

1. The information provided by the NSM does not depend on the electron density of the material, and thus differs from the information provided by the residual-range method. It also differs from the information provided by x-radiography, which is sensitive to nuclear charge. The NSM enables one to obtain independent information on the hydrogen content. The total information obtained in one exposure by "ordinary" and by "hydrogen" NSM apparently will enable an increased accuracy of differentiation of tissues to be attained.

2. Since the cross section for scattering of protons by nuclei depends weakly on the energy, one can employ simple tuning beams on which one imposes practically no demands of monochromaticity.

3. Apparently one can irradiate several objects arranged in tandem.

FIG. 9. Nuclear radiographic image of a "section" of a human head. Thickness of section—1 cm. The plane of the "section" is perpendicular to the beam, which enters at the top of the head. Dose 0.1 rad. The image was obtained at CERN using a 1-GeV proton beam (1977).[43]

Disadvantages:

1. Application of this method requires expensive accelerators of 600–1000 MeV energy.

2. The radiation doses are as yet comparatively high. However, the possibilities of lowering the radiation doses in the NSM have not been exhausted. There are considerable reserves for reducing them to a level below that characteristic of x-radiography.

3. Duration of exposure. However, considerable reserves exist for increasing the speed of action of the apparatus and reducing the exposure time.

The number of medium- and high-energy accelerators is relatively small. In the USSR accelerators suitable for studies by the nuclear-scattering method exist at Dubna (Joint Institute for Nuclear Research), consisting of a synchrocyclotron of 680-MeV energy and a synchrophasotron of energy up to 10 GeV for protons, at Moscow (Institute for Theoretical and Experimental Physics) (a 10-GeV synchrotron), and at Gatchina (Leningrad Nuclear Physics Institute) (1-GeV synchrocyclotron).

4. ACCELERATORS, BEAMS, DETECTORS

a. Accelerators, beams

The introduction of proton-ion radiography into medical practice presupposes its application on a considerable scale. The experience in employing accelerators for medical purposes shows that the high throughput of a diagnostic complex can be achieved only by using special medical accelerators.[44] They can be designed for accelerating both protons and heavier ions, must have a high degree of automation of the processes of extraction, transport, and shaping of the particle beams, and also of the processes of monitoring and control. References 13, 20, and 21 have described a design of a relatively simple, inexpensive, specialized proton diagnostic accelerator at 200-MeV energy intended for use under clinical conditions. The proposed beam intensity is 10^8 protons/s, the diameter of the racetrack ring is 6.4 m, the injector is a 300-kV van de Graaff generator, and the acceleration time is one second. The number of points at which it is recommended to extract the beam ranges up to eight, lying symmetrically around the accelerator ring. It is expedient to scan the object with the beam. Obtaining of high resolution imposes demands on the dimensions of the beam: its diameter must not exceed 1 mm. The calculations showed that such a beam can detect a spherical anomaly 10 mm in diameter at a density difference with respect to the surrounding tissue of 0.01 g/cm^3, and an anomaly 4 mm in diameter at a difference of 0.05 g/cm^3.

The system for extracting the accelerated beam must allow stable spreading in time without substantial changes in the parameters of the beam. In order to fulfill these demands, it is proposed to accelerate H^- ions and to perform the extraction after change transfer in metallic foils. The energy spread of the extracted beam from the mean value should not exceed 0.25% so that the broadening of the Bragg peak will not exceed 10%.

The experience accumulated in the past several years with using existing accelerators for therapy of tumor lesions and for diagnostic purposes has led I. V. Chuvilo and his associates to the conclusion that it is expedient to build multipurpose medical accelerators designed for therapy, diagnosis, and production of short-lived radionuclides.[44] The compatibility of all three functions in one proton accelerator is primarily governed by the parameters of the beams: energy, monochromaticity, intensity, stability of these parameters over a long period of operation, and the possibility of varying them over the necessary range. Experiment has shown that the proton energy lies in the range of about 40–250 MeV for therapeutic irradiation, production of short-lived radionuclides, and diagnosis.[44]

Jointly with a number of other institutes, the Institute of Theoretical and Experimental Physics (Moscow) has commenced the design of a biomedical proton facility having its own accelerator[44] with energies up to 220 MeV. The intensity of the external beam is 10^{12} protons/s. Among the eight external beam channels, seven are designated for radiation therapy, proton radiography, and radiobiological studies. It is proposed to introduce the beams into five experiment stations horizontally, vertically, and at an angle of 45°. The existence of the five experiment stations enables performance of up to 100 radiation sessions per day. The eighth channel will be employed for producing short-lived radionuclides.

Simultaneously with the development of biomedical studies and the accumulation of experience in operating with beams of fast heavy ions, the possibility has been studied of building more up-to-date multipurpose ion accelerators.[45-47] The table gives data on the intensity and momentum spread of the beams in the biomedical accelerator projected at the Lawrence Laboratory (USA).

The authors of the project[45,47] have paid much attention to the system of transporting the beam to the patients and to the principles of organization of a highly effective medical accelerator facility and have calculated the cost of the accelerator in different variants.

After careful analysis of possible variants of the type of the projected medical ion accelerator, the authors of the project concluded that it is most cost-effective to base the design either on a synchrotron or on a superconducting phasotron. The choice of the variant of the projected heavy-ion synchrotron depends on the demands on its parameters. Such parameters as the mean intensity of the beam and the repetition frequency determine the intensity of the particles injected, accelerated, and extracted in each cycle. The intensity of the parti-

TABLE I. Intensity and momentum spread of the beams of the projected biomedical ion accelerator.[47]

Type of accelerated ions	p	α	C	Ne
Intensity, s^{-1}	$2.25\cdot10^{10}$	$5.5\cdot10^{9}$	$4.1\cdot10^{9}$	$5\cdot10^{8}$
$\Delta p/p$	$2\cdot10^{-3}$	$2\cdot10^{-2}$	$1\cdot10^{-3}$	$1\cdot10^{-3}$

cles in the accelerator fixes the aperture of the chamber, the dimensions of the magnetic circuits, the parameters of the accelerating apparatus, and the supply system of the magnets. For light ions, the aperture is fixed by the space charge limit, and for heavy ions by multiturn injection. The working range of the high-frequency accelerating apparatus depends on the energy of the ions being injected. In turn the parameters of the injector are determined in many ways by the ion source employed. Reference 47 gives the parameters of the projected heavy-ion synchrotron.

In a project of a combined group of scientists of a number of institutes at Karlsruhe and Heidelberg (West Germany) concerned with problems of therapy and diagnostics by charged-particle beams,[48] a proposal is made to construct a synchrotron for purposes of therapy and diagnostics using protons and α particles. It is planned to build the accelerator in three stages: Stage I—acceleration of protons up to 200–260 MeV with an intensity of up to 10^{11} protons/s; Stage II—acceleration of helium ions up to energies of 800–900 MeV at an intensity up to 5×10^{10} nuclei/s; Stage III—acceleration of protons up to 740 MeV in order to produce high-intensity meson beams.

Thus the building of specialized medical accelerators has been acknowledged to be expedient on the basis of the results of studies in the field of radiotherapy and radiography. Projects for such accelerators have already been developed in a number of countries.

b. Detectors

Ion radiography employs both the traditional and the most modern charged-particle detectors: scintillation counters, proportional and drift chambers, photoemulsions, luminescent screens, and solid-state detectors. Scintillation counters are used both for measurement and control of the intensity of the particle beams, and directly to obtain the radiographic image. A system of scintillation counters serves to activate the trigger, i.e., the pulse for control and recording of information from position-sensitive proportional chambers,[22] and the starting pulse for systems of drift chambers.[33,38-40] A set of such scintillation counters serves to determine the residual range.[22] In addition to determining the coordinates of passage of particles, hodoscopic systems based on single crystals of NaI serve also for determining the residual range.[49] Application of position-sensitive proportional chambers combined with a large NaI crystal[15] substantially improves the coordinate resolution of the system. The choice of scintillation counters utilizing single crystals of NaI is made on the basis of their large light yield, and high linearity of the dependence of the amplitude on the energy transfer.[50]

Such position-sensitive detectors as proportional and drift chambers have been applied in physical studies only in the past decade.[51-54] However, in spite of the newness of the method, they are the basis of contemporary instruments in high-energy physics. They are being successfully employed in the applied fields of science and technology. An example of the latter is their employment in radiography. The widespread use of proportional chambers is explained by their good spatial resolution, simple construction, high time resolution, short dead time, and a number of other advantages over other detectors. Without taking up the principles of operation of multiwire proportional and drift chambers, which are described in detail in Ref. 54, we note that drift chambers in which the coordinates of passage of particles are determined by measuring the drift time of ionization electrons have a spatial resolution of about 60 μm,[55] which exceeds by severalfold the spatial resolution of proportional chambers.

In contrast to the more or less standard situation in high-energy physical experimentation, in which the number of events to be recorded in a computer memory per unit time is relatively small, in radiographic studies the number of events to be recorded in the same interval of time is several orders of magnitude higher. This requires an increased speed of recording and the creation of a fast preliminary event-selection system (in the nuclear-scattering method). One of the possible methods of shortening the time of tallying information from proportional chambers into a computer memory is to code it.[56,57]

Many different kinds of luminescent screens combined with television observation systems, and photofilms employed either with or without intensifying screens,[58,59] possess a number of defects, along with such merits as simplicity and cheapness.

Solid-state detectors, which are usually employed for detecting ions,[60] are attractive due to many advantages: threshold sensitivity to heavy charged particles, relative simplicity of processing, and high frequency of detection. The detectors can have the most varied shapes and dimensions. For ion radiography, the most suitable detectors have proved to be multilayer detectors made of Lexan films.[12,15] For spatial reconstruction of the object, the information obtained in each layer of the detector can be represented in a form convenient for computer processing.[15] The latter is used to display the stopping points of the particles in depth in the form of a "relief." The quantitative information on the coordinates of the stopping points can be employed to calculate the electron density distribution, and also to obtain the "relief" profile along any coordinate, or for three-dimensional reconstruction of the object by ion tomography.

5. POTENTIALITIES AND PROSPECTS OF ION RADIOGRAPHY

We have shown in the previous sections that ion radiography has already arrived at the stage of application to patients in diagnosis of tumors of the mammary gland and of the soft tissues of the extremities. The potentialities of ion radiography in diagnosis of lesions of the brain and other soft tissues are being intensively studied.

A higher image contrast can be attained with ions than with x rays. Moreover, for the same image contrast, the radiation doses involved in ion radiography are considerably smaller than those received in x-radiography.

The physical properties of ions, which differ from those of x rays, open up further prospects for using them in diagnostics. The ion-radiography method can be applied whenever the lesions in tissues alter their density or morphology, even if the changes are relatively small.

Steward's studies[8,10] devoted much space to discussing the potentialities of ion radiography. He assumes that there will be many situations in which lesions will be detected by ion radiography, though not by the most modern x-radiography. Steward believes that ion radiography will prove capable of detecting most brain lesions, including edema, and can be applied for diagnosis of granulomatosis and cancer of the lung. He holds the view that there are grounds for hoping that ion radiography will allow one to discriminate between benign and malignant tumors, and also to distinguish them from non-tumor states. Measurements of the densities of tissues indicate the promise offered by the method in detecting myocardial infarction. The possibility is actively being studied of diagnosing acute ischemia of the heart. Silicosis of the lungs should be detectable even in an early stage of the disease; the mass of silicotic deposits increases the mass of the lung tissue. This shortens the range of the particles at the site of the affected regions of the tissue. A random distribution of small lesions in the lung tissue broadens the Gaussian distribution of the stopping points of the particles as compared with the distribution usually observed. Better-grounded prospects for the use of ion radiography for diagnosing various diseases can become clear after sufficiently exact data have been obtained on the physical properties of normal and pathological tissues of the human organism and they have been analyzed in detail. Great potentialities remain latent in ion radiography as a method having a great radiation safety margin. This is especially important in cases in which radiation can have deleterious influence by causing genetic effects, e.g., in examining pregnant women.

The newest of the ion-radiography methods (the nuclear-scattering method) opens up the prospect of diagnostics based on the hydrogen content in tissues. The possibility of comparing the "ordinary" and "hydrogen" images considerably increases the diagnostic potential of this method if it can be shown that the radiation doses and duration of the procedure prove acceptable.

Application of the methods of ion radiography for recognition of tumors at an early stage of the disease combined with radiation therapy will indisputably make therapy more effective and lead to increased survival.

Perhaps ion radiography will find application in other fields of science and technology. An example might be the well-known physicoarcheological experiment of Alvarez and his associates, which was undertaken to determine whether there is a secret chamber in the body of the pyramid of Chephren analogous to that found in the body of the pyramid of Cheops.[61] The radiation source consisted of cosmic muons flying in different directions; a study of their laws of absorption by the stone of the pyramid showed the absence of cavities in the stone. This method can be called monumental tomography.

Industrial radiography can be a field of application of the nuclear-scattering method wherever one must utilize the long range of high-energy protons in matter, and also in cases when one needs information on the hydrogen content in an object.

6. CONCLUSIONS

Thus a new field has been intensively developing in the past decade: ion radiography. A number of the methods of ion radiography are passing through the stage of clinical trials. The efforts of physicists, engineers, physicians, and mathematicians have theoretically substantiated and experimentally demonstrated the advantages offered by employing ions: lower radiation doses and higher image contrast than in x-ray radiography, the possibility of detecting deep-lying regions containing a lesion of small dimensions, i.e., the possibility of effective application of ion radiography in early diagnosis of tumors and other dangerous lesions.

The decisive question for the future of ion radiography for purposes of medical diagnosis consists, first, of whether the potentialities of the method will be fully realized in actual clinical practice, and second, how simple, convenient, and accessible the appropriate apparatus will prove to be for widespread application under clinical conditions. The fundamental disadvantage common to all ion-radiography methods is the high cost of the accelerator—the radiation source, of the beam-transport system, and also of the associated equipment. Nevertheless, standardization and commercial production of equipment for radiographic studies can facilitate a considerable decline in cost.

The development of relatively simple, specialized accelerators designed for biomedical studies, radiotherapy, diagnosis, and also for producing radionuclides, will enable expenses to be reduced to a minimum, with a high throughput of the facility.

The development of a new method of diagnostics—ion radiography—demonstrates an example of the fruitful influence of basic science, in this case the physics of particles and atomic nuclei, on applied fields of research. There are grounds for thinking that ion radiography will in the immediate future occupy a place of worth in the set of modern, powerful diagnostic tools.

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