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RADIOBIOLOGICAL IMPORTANCE OF SPECIFIC IONIZATION

R. E. Zirkle

September 21, 1943

* * *

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THE RADIOBIOLOGICAL IMPORTANCE OF SPECIFIC IONIZATION

R. E. Zirkle

When a cell or organism is exposed to any ionizing radiation, the ions are not formed singly and at random throughout the cell or organism, but are localized in ionization tracks. These tracks, so clearly demonstrated in gases by means of the Wilson cloud chamber, may be produced by primary beta or alpha rays, by secondary electrons set in motion through absorption of primary x- or gamma-ray energy, or by secondary swift atomic nuclei set in motion through absorption of kinetic energy of primary fast neutrons. The total volume of the tracks formed, even by very injurious doses of radiation, is a small fraction of the total volume of the cell or organism.

So far as is known, the properties of the ions (and also of the molecules activated to states of excitation lower than ionization) which are produced along an ionization track are independent of the properties of the ionizing particle. On the other hand, the linear spacing of the ion pairs and excited molecules along the tracks varies widely with the velocity and charge of the ionizing particle, and these properties depend greatly upon the nature of the primary radiations. This linear spacing is customarily discussed in terms of its reciprocal, the <u>specific ionization</u>, by which is meant the number of ions formed per unit length of ionization track.

Recently, particularly within the last decade, numerous radiobiological investigations have been carried out with two or more radiations which differed in the average specific ionization produced, and in a large fraction of these experiments it has been found that the total dose (ionization produced or energy absorbed per unit mass of tissue) required to produce a standard degree of a given biological effect is not constant but may vary considerably with the specific ionization.

This report consists of a brief summary of the results of these investigations. No attempt will be made to deal with pertinent theory.

All of these experiments obviously involve two physical requirements: (1) practical sources of at least two radiations which produce ionization tracks differing in specific ionization; (2) methods of estimating, in some common unit, the doses delivered with each type of radiation. The usual means of meeting these requirements and the degree of success attained will be indicated very briefly in the next two sections.

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Experimental Variation of Specific Ionization.

In most of the investigations to date the radiations used have produced heterogeneous specific ionization. There are two reasons for this heterogeneity; first, in any individual track the specific ionization progressively increases as the ionizing particle decreases in velocity because of loss in kinetic energy. As is the case in most experiments, the entire track is spent in the irradiated object, there is considerable non-uniformity of specific ionization

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even if the initial velocities of all the ionizing particles are identical. Second, the initial speeds frequently are not identical, and this also contributes to the heterogeneity of the specific ionization.

In view of this non-uniformity of the specific ionization produced by most of the radiations which have been used, it is expedient to characterize each radiation by means of its average specific ionization, which is simply the total number of ion pairs produced per unit volume of irradiated object divided by the total length of all the tracks produced in that volume. In a few experiments fairly uniform specific ionization has been used, and this will be given special attention in the proper places.

Of the numerous types of ionizing radiations now known, only the ones listed below have been used in the investigations pertinent here. They are listed in order of increasing average specific ionization.

A. Fast Electrons or Radiations Which Produce Them.

1. Hard beta rays (mean energy 0.4 MEV or higher)
2. Hard gamma rays (e.g. those of RaC with 0.5 mm Pt filter, which ionize almost entirely by recoil electrons, the mean initial energy of which is about 0.32 MEV (Gray 1937)
3. X-rays of various wave lengths. With the usual tube voltages, the average specific ionization of the ejected electrons is considerably less than that of the electrons ejected by gamma rays. For very hard x-rays (wave length 0.05 A. or less), which produce practically 100% Compton recoil electrons, the average specific ionization increases as the wave length increases. The same is true for soft x-rays (wave lengths 0.4 A. or greater), which produce practically 100% photoelectrons. In the intermediate range of wave lengths (0.05 to 0.4 A., roughly), where both the photo- and Compton electrons make significant contributions, the situation is complex (Mayneord 1934). The average specific ionization passes through a maximum at wave lengths in the vicinity of 0.1 A., and then, with increasing wave length, decreases to a nearly constant value which is maintained between 0.2 and 0.4 A. This peculiar behavior possibly explains certain apparently contradictory results, and will be referred to again.

B. Fast Atomic Nuclei or Radiations Which Produce Them.

4. Fast Neutrons. These rays ionize preponderantly by means of light nuclei which they eject from atoms of the biological material. Since the predominating atoms in soft tissues are H, C, N, and O, their nuclei are the ones of interest. Moreover, since in a soft tissue of average water content the H atoms outnumber the C, N, and O taken together by a ratio of about 1.7 : 1 and since the average energy transfer from a fast neutron to an H nucleus is far greater than to any of the other nuclei mentioned, the proton takes a place of special importance in the production of ionization

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tracks. The individual proton tracks are unequal in length and therefore in average specific ionization. The average specific ionization of the whole population of tracks is more than 10 times that of the electron tracks produced by 200 kv. x-ray, but not much greater than that of very soft x-rays (e.g. 8.3A)

5. Alpha particles. To date only the alpha particles from natural radioactive substances (chiefly radon and polonium) have been used in pertinent investigations, although artificial alpha particles are available from cyclotrons and other types of accelerators. The specific ionization in the tracks of the natural alpha particles is higher than that produced in proton tracks. (When their velocities are equal, a proton and an alpha particle will produce specific ionizations roughly proportional to the squares of their charges, that is in the ratio 1:4).

   In certain instances, the specific ionization has been experimentally varied by using biological objects which were small compared to the length of polonium alpha particle tracks in tissue. Since the specific ionization varies along these tracks in a well known way, it was possible, by interposing suitable thin foils between the source and the cells, to cause various samples of cells to absorb energy from different linear portions of the tracks of the alpha particles traversing them and therefore to be treated with radiation of different specific ionization. This way of obtaining various specific ionizations will be referred to as the "alpha track" method. Incidentally, by this method, one can more nearly approximate homogeneous specific ionization than by any other. By all the other methods, one uses the entire ionization track, along which, whether it be produced by an electron or an atomic nucleus, the specific ionization varies widely.

The relative specific ionization in soft tissues exposed to various radiations may be visualized by comparison of the following rounded figures (Lea, Haines and Pretscher 1941), which were based on the assumption that the energy required to produce an ion pair in tissue is the same as that required in air.

Radiation		Ion pairs per cm. of track in tissue	i p/cm
Hard beta (RaB, RaC)		6×10^4	6
Gamma (0.014A eff.)	.8 Mv	1.5×10^5	15
x-rays (0.15 A eff.)	83 Kv	6×10^5	60
x-rays (1.54 A)	8.3 Kv	1.5×10^6	150
x-rays (4.1A)	30.5 Kv	2.7×10^6	270
x-rays (8.5 A)	145 Kv	7×10^6	700
Fast neutrons		1×10^7	1000
Alpha particles		4×10^7	4000

The energy absorbed per cm. of track can be obtained by multiplying these figures by 35 electron volts.

Estimation of Dose

At present the most acceptable method of expressing doses of all the various types of ionizing radiations is in terms of energy absorbed per unit volume of biological material. Sometimes doses are estimated as "tissue ionization," that is, the number of ions or ionization units produced per unit volume of cells or tissue. This quantity cannot be measured directly because of the high natural conductivity of tissue. It is usually calculated from the measured ionization in air, assuming that the ionization per unit mass of tissue is the same as that in air. This assumption is hardly justified, since the fraction of a swift particle's energy which is used in ionization varies even among different gases and might therefore be suspected of differing widely between a gas (air) and a liquid system (tissue). However, as usually calculated, the "tissue ionization" is a quantity proportional to the energy absorbed per unit volume and therefore may be used without objection as a measure of relative doses of various radiations.

X-rays and Gamma Rays

The commonly accepted method of estimating the amount of energy absorbed per unit volume of tissue from the electrons set in motion by X-rays is based upon ionization measurements in standard air. The accepted unit of air ionization is the roentgen (r), which was defined in 1927 for X-rays and redefined in 1937 for both X-rays and gamma rays by international committees. According to the definition of 1937, "the roentgen shall be the quantity of x- or gamma-radiation such that the associated corpuscular emission per 0.001293 gram of air produces, in air, ions carrying 1 e.s.u. of quantity of electricity of either sign." This corresponds to 2.08×10^9 ion pairs per 0.001293 gram of air, or 1.61×10^{12} ion pairs per gram. Since the average energy absorbed by air per ion pair produced is very nearly 33 electron volts for all ionizing radiations, the energy absorbed per gram of air per roentgen is 5.3×10^{13} electron volts (84 ergs).

From this value the energy absorption in tissue can be calculated, if the specific gravity and the atomic composition of the tissue are known. For most soft tissues the specific gravity lies between 1.02 and 1.08, so that no great error is involved if one uses the median value of 1.05 for all soft tissues. In any case, when one is interested only in the relative amounts of energy absorbed per cc of one certain tissue, the specific gravity can be neglected. The atomic composition, however, may sometimes be important, because the absorption coefficients of air and of certain atoms in tissue vary with wave length to different degrees. For example, in a tissue of fairly representative atomic composition the energy absorbed in tissue per roentgen may vary as much as 15 per cent when the effective wave length is varied from 0.014 A (Ra gamma rays) to 0.333 A (soft-X-rays) Lasnitzki and Lea, 1940). If the tissue of interest contains an exceptionally large amount of atoms heavier than oxygen (e.g., skin, which is high in sulfur), the variation of energy absorption with wave length may be much greater (Gray, 1940).

Beta Rays

In all of the pertinent beta ray investigations the source of radiation has been radium or radon in equilibrium with the beta-emitting decay products.

Two methods of dosage estimation have been used. In one the ionization per unit mass of air is directly measured by means of special small ionization

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chambers with thin walls containing only elements of low atomic number (Crabtree and Gray, 1939; Zimmer, Griffith and Timoféeff-Ressovsky, 1937). The ionization in air then has the same relation to energy absorption in tissue as in the case of gamma rays.

The other method (Lea, Haines and Coulson, 1936) is not so direct. First, the number of beta particles traversing a small volume of air at the position of the biological material is calculated from the beta emission per millicurie with the filtration used and from the geometrical relationships between the radon source and the irradiated material. This calculated number of beta particles is then multiplied by an estimated average value for the ionization per beta track in the selected small volume of air. From the product of these two quantities is calculated the ionization per unit volume of air, and transition from ionization in air to tissue energy absorption is then made as above.

Fast Neutrons

Neutron dosimetry has in all cases been carried out by means of small ionization chambers with walls of carbon, "Aerion" or bakelite. The relation between the observed ionization in the air of the chamber and the energy absorption in tissues varies with many factors including the wall material. With certain carbon-walled chambers Gray and Read (1939) calculated that 1 e.s.u./cc of ionization in the air filled chamber would give the same energy absorption per unit volume of tissue as 7 r of gamma rays. With the Aerion chamber the corresponding value is about 2 (1.8 according to Simmer 1938; 2.1 according to Gray and Read 1939). In the United States the chamber almost universally used has been the Victoreen condenser r-meter, which has bakelite walls. This instrument is calibrated in r for x-rays by the manufacturer, and the custom has been to use the 100-r chamber of the same instrument for measurements of fast neutrons in n-units, one n being the amount of neutron radiation which produces the same scale reading as one r of x-rays.* The number of r of x-rays which produce the same amount of tissue energy absorption as one n of neutrons has not yet been established with precision. Aebersold, who has investigated this matter, states that his measurements indicate a value of 2 r, but that certain sources of error which are difficult to evaluate might increase this to 2.5 r (Aebersold and Lawrence 1942). The latter figure has been used in this report in order that the effectiveness of fast neutrons relative to x-rays may be set conservatively low.

Alpha Particles

Two types of alpha particle source have been used: polonium deposited on a metal disc; radon and its short-lived decay products introduced into the culture medium.

Polonium sources have been used only in investigations of very small biological objects, usually single-celled forms, because of the low penetration of the polonium alpha particles (about 33 microns in water or tissue). To determine the energy absorption in the cells, one first measures the number of alpha particles emitted per unit time per unit surface of the metal disc. This is done either by an ionization method (Lea et al 1936) or by a scintillation

*There is considerable variation in the response of different 100-r chambers to the same beam of fast neutrons - as much as 20% in our experience. This necessitates the use of some one chamber as a standard. We have provisionally taken the Berkeley chamber as a standard and have calibrated our chambers against it in the fast neutron beam produced at Chicago by 8 MEV deuterons on a beryllium probe.

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method (Zirkle 1940). Then, from the geometrical relations between source and cells, one calculates the number of particles traversing a small unit volume of cell in unit time. This number is then multiplied by the product of the exposure time and the energy absorbed on the average when an alpha particle traverses the unit volume, the latter quantity being determined from the known energy absorption along the track in air and the ratio of the stopping power of tissue (approximately that of liquid water) to the stopping power of air. The result is the energy absorption per unit volume.

When radon is introduced into the culture medium, the determination of energy absorption in the biological material can be determined only by taking precautions too numerous and complicated to detail here (Zirkle 1936). Gray and Read (1942) have discussed and thoroughly investigated this matter.

Results of the Available Investigations

In view of the large number of pertinent investigations, no attempt will be made to discuss any of them in detail. The results are tabulated in Table I.

Although no claim of complete coverage of the literature can be made, an effort has been made to include in Table I all of the available experiments in which were used two or more radiations which clearly differed in average specific ionization, regardless of the relative effectiveness observed. Many papers were examined but not included, for one or more of the following reasons: (1) Most papers appearing before the adoption of the international roentgen in 1927 have been omitted because of uncertainty concerning identical response of measuring devices to radiations of different quality. (2) Most of the experiments in which were used only x-rays of wave lengths lying in the range 0.07 to 0.4 A have been omitted because of the strong probability that no difference in average specific ionization existed (Mayneord 1934). In general, if the results are clear-cut and not open to suspicion because of complicating factors, these papers report identical effectiveness within experimental error, which is to be expected. A few of these papers are included to illustrate this point and are designated K in Column 6 of Table I. (3) Most of the papers dealing with skin have been omitted because of uncertainties involved in the determination of energy absorbed in the tissues of interest, or because of inadequate numbers of individuals investigated, or because of the considerations just mentioned under (2).

Explanation of Table I

Table I consists of seven columns. The first contains entry numbers, to be used for easy reference to the various experiments. The second lists the various objects or systems which were investigated. These are arranged in a roughly "taxonomic" order, as follows: inorganic substances in aqueous solution; simple organic substances in water solution; proteins and other colloids, enzymes; viruses, including bacteriophages; bacteria; yeast cells; unicellular algae; higher fungi; germs; worms (Ascaris); insects (chiefly Drosophila); salamanders; birds (Chickens); laboratory mammals; humans; seed plants.

In the third column are listed the qualitative effects which were studied and measured

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In the fourth are briefly described the various radiations used. For each entry these are listed in order of ascending average specific ionization. For brevity, the unqualified term "gamma" is used to designate gamma radiation from a radium or radon source filtered with 0.5 mm Pt or its approximate equivalent The term "beta" in all cases designates hard beta rays from a radium or radon source, the filtration being such that their specific ionization is definitely less than that of the gamma rays just described. Monochromatic X-rays are designated by the wave lengths in A. Heterochromatic X-rays are designated by their effective wave lengths in A, or by the kilovoltage and filtration. Fast neutrons are referred to simply as "neutron"; the average specific ionization used by different investigators varies somewhat, because of differences in the neutron energy spectrum, but no attempt has been made to differentiate among these. The term "alpha" means heterogeneous alpha radiation The term "alpha track" refers to the use of several values of fairly homogeneous specific ionization by causing small cells to absorb energy from various linear portions of the alpha particle track (see above, under Experimental Variation of Specific Ionization).

In column 5 are given the relative values of effectiveness of the various radiations; these are reciprocals of the doses required to produce a standard amount of effect. If the effectiveness of all radiations used in a given investigation was identical, this is indicated by 1.0. If it was not identical, column 5 contains the relative values of effectiveness, arranged in the order in which the radiations appear in Column 4.

Column 6 contains references to notes which immediately follow Table I, and Column 7 is self-explanatory.

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TABLE I

(1) Entry	(2) Irradiated Object	(3) Effect Studied	(4) Radiations	(5) Ratio of Effect	(6) Note	(7) Authors and Year
1	Ferrosulfate in aq. soln.	Oxidation of Ferrous ion.	0.204, 0.519 & 0.765 A.	1.0		Fricks & Morse 1927
2	Eder's solution	Pptn. of Hg_2Cl_2	200, 184, 140, 100 & 60 kv.	1.0	K	Quimby & Downes 1930
3	H_2O_2 & $K_2S_2O_8$ in dil. aq. soln.	Production of O_2	0.19, 0.56, 0.71 and 1.54 A	1.0		Glocker & Risse 1928 Risse 1929
4	Water (free of oxygen)	Production of H_2O_2	x; alpha	infinity	E	Nurnberger 1936; Frick & Brownscombe 1933 Risse 1928
5	Tyrosine in aq. soln.	Destruction of phenolic structure	200 kv.; alpha	1.0 : 0.03		Nurnberger 1937
6	Hemoglobin in aq. soln.	Formation of methemoglobin	0.25, 0.54 & 0.75 A	1.0		Fricke & Petersen 1927
7	Colloidal mastic	Flocculation	0.25 & 0.71 A.	1.0		Dogon 1930
8	Collodial graphite	Change in electrophoretic mobility	Gamma; neutron	1.0 : 8.0		Gray, Read & Liebmann 1941
9	Trypsin in aq. soln.	Inactivation	0.13, 0.33, 0.45, 0.58 & 0.72 A	1.0		Rothstein 1927
10	Autolytic enzymes of human breast cancer	Inactivation	180 & 100 kv. (0.14 & 0.3 A,eff)	1.0	K	Faragó 193[illegible]

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TABLE I (Cont'd)

(1) Entry	(2) Irradiated Object	(3) Effect Studied	(4) Radiations	(5) Ratio of Effect	(6) Note	(7) Author and Year
11	Tobacco mosaic virus, ordinary	Inactivation	0.7, 1.5, 2.1A	1.0 0.25 0.12		Gowan 1940
12	Ditto, Aucuba	"	"	1.0 0.55 0.18		"
13	Ditto, derivative ADO	"	"	1.0 0.52 0.32		"
14	Bacteriophage (Staphylococcus)	"	200 kv. neutron	1.0 0.72	A	Axelrod, unpubl. (See Aebersold & Lawrence 1942)
15	Bacteriophage C_{16}	Inactivation	200 kv.; 0.7 A.; alpha	1.0 0.87 0.18		Wollman, Holweck & Luria 1940
16	Vegetative bacteria (Escherichia coli)	Inhibition of colony formation	0.56, 0.71, 1.54, 2.29 3.98 A	1.0 0.9 1.0 0.63 0.50		Wyckoff 1930
17.	Ditto	Ditto	beta gamma 0.15 A,eff. 1.5 A; 8.3 A neutron alpha	1.0 0.8 0.67 0.62 0.53 0.56 0.17		Lea, Haines & Bretscher 1941
18	Ditto	Ditto	95 kv. Beginning & end of alpha track	1.0 0.47 0.33		Zirkle 1940
19	Bacterial spores	Ditto	beta gamma 1.5 ,4.1 8.3 A alpha	1.0 1.2 1.2 1.0 4.2		Lea, Haines & Bretscher 1941

TABLE I (Cont'd)

(1) Entry	(2) Irradiated Object	(3) Effect Studied	(4) Radiations	(5) Ratio of Effect	(6) Note	(7) Author and Year
20	Yeast Cells (Saccharomyces Ellipsoideus)	Inhibition of first cell division (immediate death)	1.93 A 8.32 A alpha	1.0 1.24 0.9		Holweck and Lacassagne 1930
21	Ditto	Inhibition of second cell division (deferred death)	Ditto	1.0 1.6 0.8		Ditto
22	Ditto	Ditto	0.56 A. 1.54 A.	1.0 1.5		Glocker, Langendorff & Reuss 1932
23	Ditto (Sacch-cerevisiae)	Ditto	Alpha track	1.1	L	Zirkle 1940
24	Unicellular algae (Mesctaenium)	Inhibition of cell division	0.56 A 1.54 A	1.0 1.8		Langendorff & Reuss 1933
25	Unicellular algae (Stichococcus)	Ditto	alpha track	2.5	L	Zirkle unpubl.
26	Fungous spores (Aspergillus)	Inhibition of germ tube formation	alpha track	3.0	L	Zirkle 1940
27	Fern spores (Pteris)	Inhibition of first cell division	200 kv. neutron beginning and end of alpha track	1.0 1.0 2.4 8.0	Q	Zirkle 1935, 1937; Zirkle Aebersold & Dempster 1[illegible]
28	Ascaris eggs	Production of abnormal embryos	0.22 A 0.71 A 1.1 A 1.54 A 2.29 A 3.98 A.	1.5 0.67 0.69 1.0 1.12 1.7	G	Dognon 1925, 1932, 1933
29	Ditto	Ditto	0.5 A eff. 1.15 A eff. 10 kv. unfiltered	1.0	G	Braun & Holthusen 1929

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TABLE I (Cont'd)

(1) Entry	(2) Irradiated Object	(3) Effect Studied	(4) Radiations	(5) Ratio of Effect	(6) Notes	(7) Authors and year
30	Drosophila (fruit fly)	Mutations, sex-linked recessive lethals	beta gamma 160 kv. 25 kv. neutron	1.0 1.0 1.0 1.0 0.7	N	Zimmer, Griffith & Timoféeff-Ressovsky 1937; Timoféeff - Ressovsky & Zimmer 1938
31	Ditto	Ditto	0.94 A 2.2 A	1.0		Fricke & Demerec 1937
32	Ditto	Ditto	11 kilovoltages from 99 to 40, all filtered with 1.0 mm Al.	1.0		Hanson, Heys and Stanton 1931
33	Ditto	Ditto	200 kv. neutron	1.0 0.75	A N	Dempster 1941
34	Ditto	Mutations, dominant lethals	Ditto	1.0 1.5	A	Ditto
35	Ditto	Chromosome translocations	Gamma 50 kv.	1.0		Müller 1940
36	Ditto	Ditto	200 kv. neutron	1.0 1.25	A	Dempster 1941
37	Drosophila	Chromosome breaks	70 kv. neutron	1.0 0.68		Eberhardt 1943
38	Drosophila eggs (mean age 2 hours)	Inhibition of hatching	Various kilovoltages from 550 down to 12	1.0		Packard 1939
			900 kv. 600 kv. 200 kv.	1.0 1.0 1.2		
39	Ditto (mean age 1½ hours)	Ditto	200 kv neutron	1.0 0.8	A,O	Zirkle and Lampe 1938
40	[illegible] mean [illegible]	Ditto	Ditto	1.0 0.84	A,O	[illegible], Aebersold & Dempster [illegible]

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TABLE (Cont'd)

(1) Entry	(2) Irradiated Object	(3) Effect Studied	(4) Radiations	(5) Ratio of Effect	(6) Note	(7) Author and Year
41	Drosophila eggs (mean age 4½ hours)	Inhibition of hatching	200 kv neutron	1.0 1.3	A O	Zirkle and Lampe 1938
42	Ditto (mean age 6 hours	Ditto	Ditto	1.0 1.1	A O	Ditto
43	Ditto	Ditto	0.16 0.51 0.95 1.23 2.0A, eff.	1.0 1.0 1.0 1.0 0.9		Langendorff & Sommermeyer 1940
44	Ditto (mean age 1½ hours) Ditto (mean age 4½ hours)	Ditto	gamma 200 kv.	1.0 ≥1.48 1.0 ≥1.37	B	Henshaw & Francis 1936
45	Lucilia eggs	Ditto	100 kv. 200 kv	1.0	K	Mallet 1936
46	Drosophila pupae	Ditto	gamma 200 kv.	1.0 ≥1.3	B	Müller 1939
47	Ditto	Ditto	gamma 0.15A.eff 0.5 A,eff. 11 kv.	0.66 1.0 1.1 0.7	I	Liechti, Minder and Müller 1938
48	Drosophila larvae	Reduplication of organs in adult fly.	∞ neutron	"infinity"	F	Enzmann & Haskins 1939
49	Cladoceran (Simocephalus)	Reduction of oxygen consumption	0.317 A,eff. 0.45 A,eff.	1.0		Obreshkove 1934
50	Salamander eggs (Axolotl)	Death of embryos	180 kv. 0.18 A 80 kv. 0.56 A	1.0		Langendorff & Reuss 1933
51	Salamander (Amblystoma)	Inhibition of regeneration	60 kv. neutron	1.0 8.2	A	Horn 1941

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TABLE I (Cont'd)

(1) Entry	(2) Irradiated Object	(3) Effect studied	(4) Radiations	(5) Ratio of Effect	(6) Note	(7) Author and year
52	Chick Embryo	Lethal action	gamma 0.014 A eff x, 0.15 0.36 A eff	1.0: 1.7; 1.8.	H	Lea 1941
53	Chick fibroblasts in tissue culture	Reduction in mitosis	gamma neutron	See Note C	C	Spear, Gray & Read 1939
54	Ditto	Ditto	gamma of 0.0075 0.009 0.014 A eff x of 0.017 0.15 0.36 A eff. neutron	 1.0 : 1.3 : 1.5 : 3.0 : 3.0 : 3.0 : 3.0 .	M	Lasnitzki & Lea 1940
55	Ditto	Ditto	gamma; neutron	≥1.0	D M	Gray, Mottram, Read & Spear, 1940
56	Ditto	Inhibition of growth	200 kv. neutron	1.0: 0.8	A	Lewis, unpub. (See Aebersold & Lawrence 1942)
57	Ditto	Death of culture	gamma 200 kv	≥1.0		Paterson 1942
58	Whole body (mouse)	Weight loss, death	200 kv. neutron	1.0: 1.6.	A	Lawrence & Tennant 1937; Lawrence, Aebersold & Lawrence 1937
59	Whole body (Male mouse)	Production of sterility	Ditto	1.0: 2.0.	A	Snell & Aebersold 1937
60	Surviving tumor tissue (mouse)	Inhibition of "takes" when injected into normal animal	Ditto	1.0: 2.0.	A	Lawrence, Aebersold & Lawrence 1937
61	Ditto (lymphoma)	Ditto	Ditto	1.0: 2.3.	A	Lawlred, Aebersold & Lawrence 1941
62	Ditto (mammary carcinoma)	Ditto	Ditto	1.0: 2.45.		
63	Ditto (lymphosarcoma)	Ditto	Ditto	1.0: 3.0		

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TABLE I (Cont'd)

(1) Entry	(2) Irradiated Object	(3) Effect Studied	(4) Radiations	(5) Ratio of Effect	(6) Note	(7) Author and Year
64	Surviving mouse sarcoma 180	Ditto	200 kv. filtered & unfiltered	1.0 1.15		Sugiura 1934
65	Ditto	Ditto	gamma 200 kv.	1.0 1.16-1.39		Sugiura 1939
66	Surviving tissue of mouse sa. 180 rat sa. 10 and rat ca. FRC	Ditto	0.2 0.6A,eff	1.0		Wood 1924, 1925
67	Surviving retina (rat)	Inhibition of anaerobic glycolysis	beta gamma 200 kv.	1.0		Crabtree and Gray 1939
68	Mouse tumors in vivo (sa.180; mammary ca.; lymphoma)	Chromosome abnormalities (cells irrad. in prophase)	200 kv. neutron	1.0 2.3	A	Marshak 1939
69	Ditto (lymphoma)	Ditto (cells irrad. in early or late resting stage	Ditto	1.0 2.3	A	Marshak 1942a
70	Ditto	Ditto (cells irrad. in middle of resting stage)	Ditto	1.0 3.5		
70a	Mouse tumors in vivo	Regression	gamma neutron	1.20 approx.		Gray et al 1943
71	Skin (Mouse tail)	Epilation; exudation.	gamma 180 kv. 117 kv.	1.0 1.6 1.6	J	Mottram & Gray 1940
72	Ditto	Erythema; desquamation.	Ditto	1.0 1.6 1.3		
73	Skin (rabbit, pig, human)	Epilation, erythema pigmentation, etc.	0.135 0.4 a.eff.	1.0	K	Hodges, Brunschwig & Perry 1938

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TABLE I (Cont'd)

(1) Entry	(2) Irradiated Object	(3) Effect studied	(4) Radiations	(5) Ratio of effect	(6) Note	(7) Authors and Year
74	Skin (rat)	Epilation; histological changes	1000 kv.; 200 kv.	1.0		Gall, Lingley & Hilcken 1941
75	Bone (rat) (femur)	Inhibition of chondroblastic activity	Ditto	1.0		Ditto 1940
76	Ditto	Hypocellularity in marrow	Ditto	1.0		Lingley, Gall & Hilcken 1940
77	Ovary (mouse)	Castration; histological changes	ca.0.15 0.4A, eff.	1.0	K	Schugt 1928
78	Human marrow *in vitro*	Decrease in lymphocytes and progranulocytes	1000 kv.; 200 kv.; neutron	1.0 1.0 1.6	A	Osgood, Aebersold, Erf & Packham 1942
79	Human skin	Threshold erythema	200 kv.; neutron	1.0 2.4	A	Stone & Larkin 1942
80	Ditto	Ditto	Neutrons produced with 16 & 8 MEV deuterons	>1.0		Ditto
81	Ditto	Ditto	gamma 200 kv. 100 kv.	0.7 1.0 2.		MacComb 1939; MacComb and Quimby 1936; Quimby 1939-41
82	Wheat seedlings (variety Big Club)	Retardation of growth of root.	200 kv. neutron	1.0 2.0	A,C	Zirkle, Aebersold & Dempster 1937
83	Ditto (variety Nabob)	Ditto	Ditto	1.0:2.5 to 1.0-4.7	A,C	Zirkle & Kampe 1938
84	Ditto	Retardation of growth of shoot	Ditto	1.0:2.4 to 1.0:3.6	D	

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TABLE I (Cont'd)

(1) Entry	(2) Irradiated Object	(3) Effect studied	(4) Radiation	(5) Ratio of Effect	(6) Note	(7) Authors and Year
85	Seedlings, sunflower & mustard	Inhibition of growth of root (death)	0.56 1.54 A	See note C	C	Clocker & Reuss 1933a
86	Bean seedlings (Vicia)	Ditto	0.18;0.56 & 1.54 A	See note C	C	Ditto 1933
87	Ditto	Ditto	gamma 185 kv. neutron alpha	1.0 1.4 8.7 9.0		Gray & Read 1942 Gray et al 1943
88	Ditto	Inhibition of mitosis in root cells	gamma neutron alpha	1 1.7 0.43	D	Gray et al 1943; Gray, Mottram, Read & Spear 1940
89	Ditto	Chromosome abnormalities in root cells. Irrad. in various parts of resting stage	200 kv. neutron	1.0:3.2 to 1.0:6.7	A	Marshak, 1939, 1942
90	Ditto	Ditto. Irrad. in prophase.	Ditto	1.0:2.6	A	
91	Pea and tomato seedlings	Ditto	Ditto	1.0:2.5	A	Marshak 1939
92	Onion seedlings	Ditto	0.04 0.15 & 0.28 A.	1.0		Marshak & Hudson 1937
93	Tradescantia flowers	Ditto Chromosome abnormalities in Microspore formation	x; neutron	1.0:6.6	A O	Giles 1940
94	Ditto	Chromatid breaks	0.15 A. eff. neutron	1.0:2.4		Thoday 1942
		Isochromatid breaks		1.0:3.6		
		Chromosome breaks		1.0:4.5		
		Chromosome interchanges		1.0:5.3		
		Chromosome ring formation		1.0:6.5		
		Chromatid interchanges		1.0:9.3		

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Notes for Table I

A. Fast neutron doses were measured in n units. The value given here is the observed x/n dosage ratio divided by a correction factor of 2.5 (cf. Aebersold and Lawrence 1942).

B. Calculated on the assumption that the gamma ray emission from a radon source filtered with 0.5 mm. Pt is 8.0 r/mg hr, which is conservatively low (White, Marinelli and Failla 1940). This assumption minimizes the specific ionization effect.

C. Fifty per cent lethal dose was the same, but the shape of the dose-effect curve was different for the various radiations.

D. Difference in shape of dose-effect curves as well as in the fifty per cent doses.

E. Nurnberger obtained positive results with alpha rays but Risse and also Fricke and Brownscombe obtained completely negative results with x-rays.

F. In flies developed from larvae exposed to neutrons, the authors state that "reduplication of organs has been found in a very high percentage of modified flies, an effect observed rarely in x-rayed stocks."

G. The apparently flat contradiction between Dognon's results and those of Braun and Holthusen does not exist. Although the radiations used in the two investigations cannot be compared precisely, it appears that the 10 kv. x-rays of Braun and Holthusen had an effective wave length of about 2.1 A (Timoféeff-Ressovsky & Zimmer, 1935, p. 270) and therefore produced an average specific ionization not greatly different from that of Dognon's 2.29 A radiation, while their 0.5 A radiation would be expected to produce an average specific ionization intermediate between the 0.22 and 0.71 A radiations of Dognon. It may be seen from Dognon's data that, if he had used 0.5 A, he would probably have found its effectiveness to be close to that of his 2.29 A radiation (or of the 10 kv. radiation of Braun and Holthusen).

Moreover, in view of Mayneord's data (1934), one would expect very little difference in effectiveness between the 0.5 A and 0.15 A radiations of Braun and Holthusen since their average specific ionizations were probably almost identical.

H. The average specific ionizations of the 0.15 A and 0.36 A radiations differ by a factor of 1.3 or less (Mayneord, 1934; Lasnitzki & Lea 1940) a fact which correlates well with their practically identical effectiveness.

I. The 190 and 80 kv. radiations probably differed little or none in specific ionization, which correlates well with their nearly identical effectiveness. The low effectiveness of the 11 kv. radiation may be due to lack of a correction for the absorption of these soft x-rays in the superficial pupal material.

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J. Note identical effectiveness of the 190 kv. and 117 kv. radiations. Their specific ionization probably differed little or not at all (Mayneord 1934).

K. Probably very little difference in specific ionization. Effectiveness ratio of 1.0 to be expected.

L. The effectiveness increased continuously with the increase in specific ionization along the track. The number in Column 5 is effectiveness with the greatest specific ionization divided by the effectiveness with the lowest.

M. The technique of counting mitoses was not the same in the experiments of Lasnitzki and Lea as in those of Gray et al. This is probably sufficient to account for the difference in results with the same biological material.

N. Note agreement of comparable data in Entries 29 and 32.

O. The value given for neutron effectiveness is too low, because the gamma rays emitted by the cyclotron as a consequence of the Be-D reaction " "diluted" the neutron beam. No correction for the effect of the gamma rays is attempted because their contribution to the total dose is not known.

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Summary of Results

By glancing at Column 5 of Table I and at Charts A and B, it is readily seen that as the specific ionization increases, the relative effectiveness of the various radiations may remain unchanged, may increase or may decrease, depending upon the nature of the irradiated object and upon the effect studied.

Cases of No Difference in Effectiveness

If, for the time being, we ignore the chemical effects (Entries 1 to 10), there remain a number of cases in which no difference in effectiveness was noted. Of these, Entries 45, 73 and 77 can probably be explained on the basis that little or no difference in average specific ionization existed in view of Mayneord's data (1934). There remain Entries 29, 31, 32, 35, 49, 50, 66, 67, 74-76 and 92. In Entry 29, there is good reason to conclude that the biological effect was really sensitive to specific ionization, but that by chance the three qualities of x-rays had identical effectiveness (see Note G to Table I). In all of the remaining entries except 35 and 67, the only radiations employed were different qualities of x-rays, and although the specific ionization certainly was varied in all of these experiments, the variation was not great. In Entry 35, a considerable difference in specific ionization existed; here is evedently a biological effect which is relatively insensitive to specific ionization (cf. also Entry 36). The same may be said of Entry 67. rat eye Dros. - ch translo c

Taking together all of these cases of no change in effectiveness with specific ionization, one must conclude that they are in general correlated with the use of radiations which did not differ greatly in specific ionization.

Cases of Decrease in Effectiveness with Increase in Specific Ionization.

In this class belong Entries 5, 11-13, 14, 15 -18, 30, 33, 37, 39, 40 and 56. Entries 14, 30, 33, 37, 39, 40 and 56 display rather unimpressive decreases, especially in view of the fact that all seven investigations involve neutrons and the apparent decreases would mostly disappear if, instead of 2.5 one used 2.0 as the factor for converting Victoreen X/N ratios to relative values of energy absorption (see above, under Estimation of Dose). Impressive decreases in effectiveness were noticed, however, in the remaining eight investigations. Entries 16-18 are in excellent agreement on the same biological effect; all show a decrease in effectiveness on bacteria and in Entry 16, which covers much the widest range of specific ionization, the effectiveness decreases by a factor of 6 (see Chart A). Entries 11-13 and 15 are concerned with viruses, which lie on the border between living and non-living, and here we see in one case a decrease by a factor of 8 (Entry 11). This case is especially noteworthy because the differences in specific ionization were not especially great. Finally, in Entry 5, we find a decrease by a factor of 30 or more. This, it will be noticed, occurred in an aqueous solution of a comparatively simple organic compound.

It is evident that, so far as the available data indicate, notable decreases in effectiveness as the specific ionization increases seem to be limited to rather simple systems

Cases of Increase in Effectiveness with Increase in Specific Ionization

Distinct increases in effectiveness appear in Entries 8, 19, 24-27, 34, 36, 51, 52, 54, 63-65 68-70, 72, 78, 80-87, 89-91, 93 and 94.

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With the exception of Entries 8, 19 and 24-27, all of these cases involve the higher phyla of plants (ferns, seed plants) and of animals (insects, reptiles, birds and mammals). In general, the radiosensitivity of insects (chiefly Drosophila) seems to be relatively insensitive to specific ionization, regardless of the effect studied (Entries 30-47), but in the other phyla it is remarkable how frequently the effectiveness increases with specific ionization. In fact, with the exception of Entry 67, the only cases of no increase are those in which no great difference in specific ionization was investigated. Entry 67 deals with inhibition of glycolysis of surviving tissue, an effect which is to date unique in investigations on specific ionization.

One very noteworthy exception must be made to the statement concerning insects in the last paragraph. In Entry 48, we have a case where the effectiveness increased with specific ionization by an "infinite" factor, which is to say that an effect was produced with the radiation of high specific ionization which was not observed at all with low specific ionization. Such cases are rare. The only other is Entry 4, and here, rather astonishingly, we are dealing with a system of supposedly very simple composition.

Drosoph. Ionizing redupl. of organs in adult

Cases in Which the Effectiveness Passes through a Maximum or Minimum

There are two instances in which the effectiveness appears to pass through a critical value. With the yeast Saccharomyces ellipsoideus (Entries 19-20) and with mitosis in the broad bean (Entry 88) it passes through a maximum, while with the Ascaris egg (Entry 28) it passes through a minimum. Such behavior naturally arouses a suspicion of error in physical or biological measurement. However, all these investigations apparently were quite extensive, and the investigators were men of experience. In any event, in view of the present inadequate state of pertinent theory, there is no reason to reject experimental data on the basis of the manner in which the effectiveness varies with the specific ionization.

Magnitude of the Effectiveness Ratio and the Nature of the Irradiated Object

In some investigations very small differences in the nature or condition of the biological object have been found to change the effectiveness ratios to a measurable and sometimes a remarkable degree. With the Drosophila egg (Entries 39-42) the ratios vary by as much as a factor of 1.5 depending upon the stage of development at the time of irradiation. With wheat seedlings, measurable differences in the ratios can be caused by difference in the variety of plant (Entries 82-83) or by the nature of the tissue studied in the same individual plants (Entries 83-84). The effectiveness ratio for chromosome injuries in mouse tumors varies as much as a factor of 1.5, depending upon the mitotic stage of the irradiated cells (Entries 68-70), while the corresponding ratio for plant cells varies by a factor of 2.7 (Entries 89-90). The ratio for effects on mouse skin depends upon the criterion of skin injury (Entries 71-72), even though the comparison was made only with x- and gamma rays. In yeast also (Entries 20-21) the criterion of injury influences the ratio. The same observation has been made

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on the broad bean root (Entries 87 and 88; Chart B). Among viruses it is found that mutant strains of the same virus may yield effectiveness ratios differing by as much as a factor of 2.7 (Entries 11-13).

Certain of the results with non-living systems are worthy of note. Although most of the effectiveness ratios turn out to be 1.0, we find among Entries 1-10 a range of ratios greater than exists among the biological objects. In Entry 5 we have the lowest effectiveness ratio recorded, in Entry 8 there is a high ratio comparable to some of the highest found among the higher plants and animals, while Entry 4 is one of the two known instances of an "infinite" ratio. Specific ionization apparently may be as important in radio-chemistry as in radio-biology.

Remarks

The data summarized above have a certain significance from the standpoint of protection.

It has been shown repeatedly that, in the production of injurious effects in both the higher plants and the higher animals, the amount of injury produced per unit of absorbed energy increases with the specific ionization of the radiation. In particular, the injurious action of fast neutrons is greater than that of x-rays or gamma rays by factors ranging up to 20 (Entry 70a), and it must be remembered that the effectiveness ratios are calculated in such a way as to make them conservatively low. Although most of the effects on mammalian tissues show effectiveness ratios ranging from 2 to 3.5, it must be pointed out that to date comparatively few neutron investigations have been carried out on mammalian tissues in vivo. Since, as was pointed out three paragraphs back, different effects on the same biological object may exhibit considerably different effectiveness ratios, a distinct possibility exists that further observation will disclose important injurious effects on mammals which have neutron/x-ray effectiveness ratios ranging up to 10*. From the protection standpoint, only one such biological effect, though at present unknown, is a threat. Until extensive and numerous investigations allay this threat by failure to reveal injurious effects extremely sensitive to specific ionization, special precautions seem to be indicated when setting tolerance doses in situations where fast neutrons constitute a sizeable fraction of the total radiation present.

These considerations are especially pertinent in case x-ray thimble chambers are used in measuring the total radiation. If uncorrected Victoreen measurements are used in comparing the effectiveness of fast neutrons and x-rays, the apparent effectiveness ratios for the known injurious effects on mammalian tissues range up to more than 8. Carbon-walled chambers are even more misleading (Gray and Read 1939).

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*In entry 70a (a very recent report) we have an effectiveness ratio of 20 for mammalian tissue irradiated in vivo.

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Chart A.

Variation of Biological Effectiveness with Specific Ionization.

(On the axis of abscissae are given the values of specific ionization, expressed as ion pairs produced per cm. of ionizing track in tissue. The radiations which have been used in producing the various specific ionizations are indicated below the axis.)

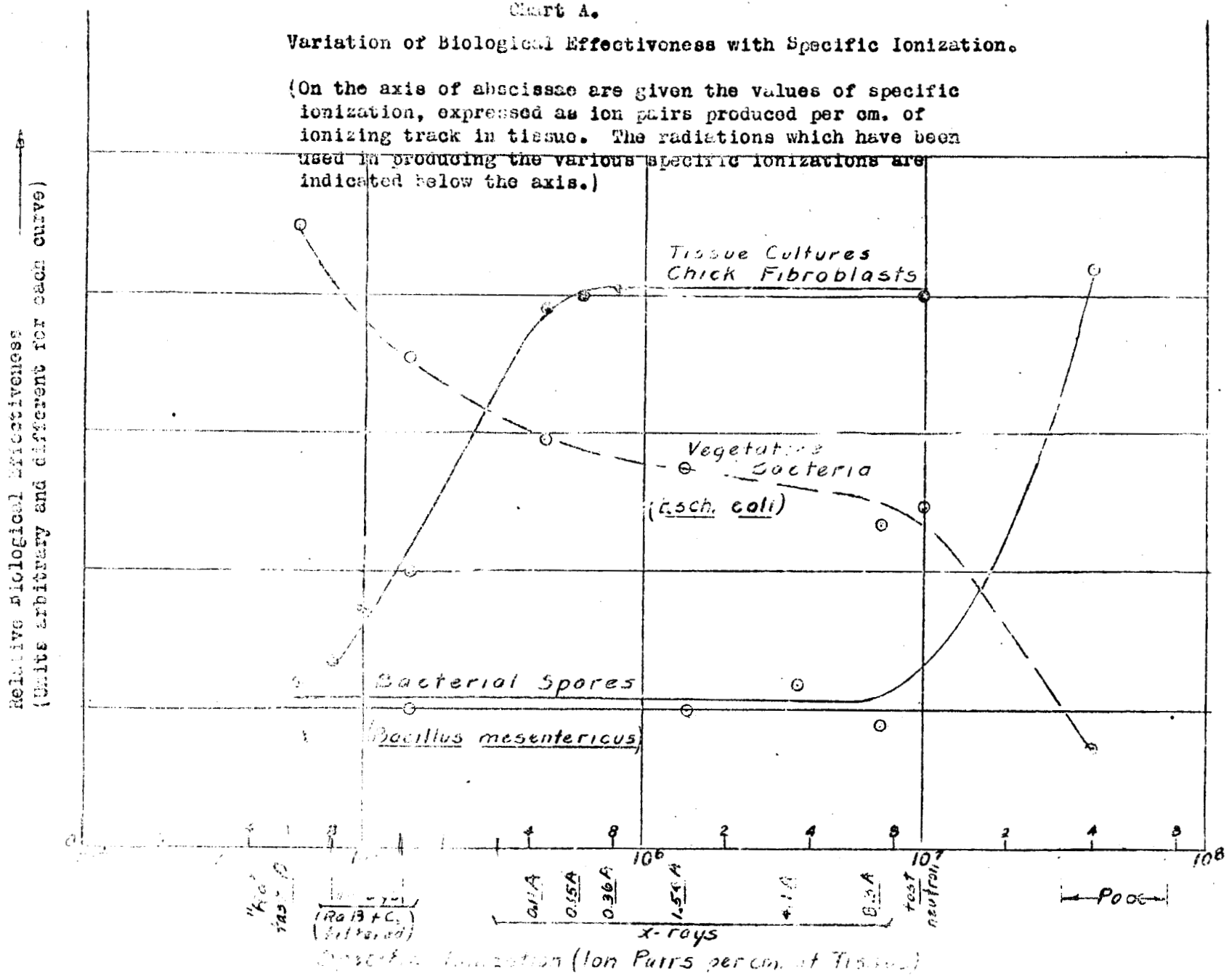

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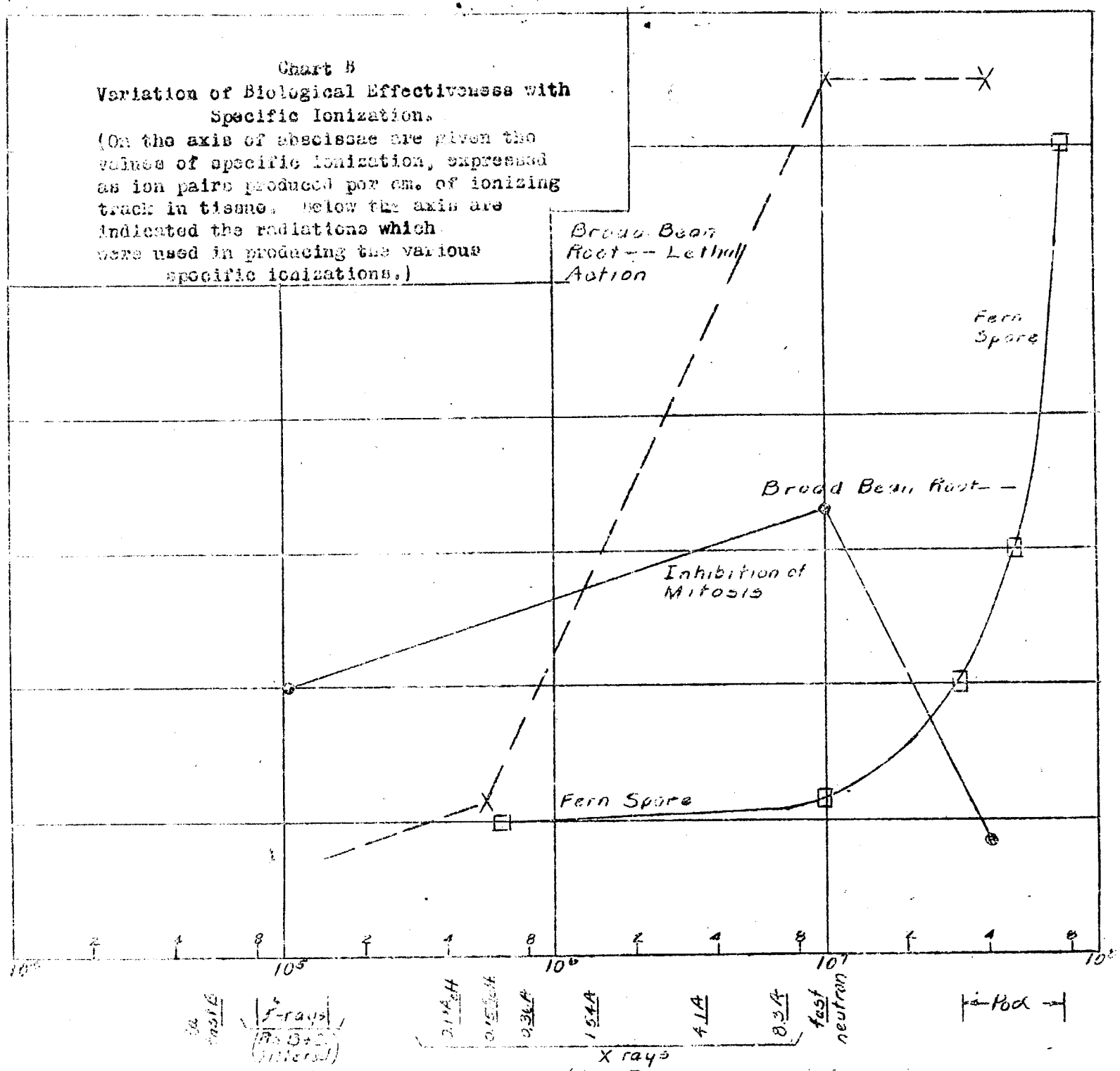
Chart B

Variation of Biological Effectiveness with Specific Ionization.

(On the axis of abscissae are given the values of specific ionization, expressed as ion pairs produced per cm. of ionizing track in tissue. Below the axis are indicated the radiations which were used in producing the various specific ionizations.)