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Lecture Notes: from LDM Files- 1941 - 1951 (12 Lectures)

1. 1941(?)
"The Correlation of X-Ray and Gamma Ray Dosage Through Ionization," by L.D. Marinelli, M.A., Biophysics Laboratory, Memorial Hospital, NYC (7 pages typed with handwritten note on front page: "Final Draft corrected by Failla)

[Lecture is reproduced in its entirety here:]
"It is generally accepted today that the biological effects of radiation depend ultimately on the ionization produced in the living tissue. The difficulties encountered in the direct measurements are yet to be overcome, however, on account of the high conductivity of living matter. ... Under suitable condition, the number ionizing electrons and their energy distribution produced in a given mass of air are the same as those of the secondary electrons in an equivalent mass of tissue.

"Nevertheless, by exploiting fully our present knowledge of the ionization process, one can perform suitable experiments in gases under conditions which permit the correlation of the ionization in a gas to the ionization in the same mass of tissue by a proportionality factor which is, for a given tissue, substantially independent of the quality of the ionizing radiation.

Under suitable conditions, the number and energy distribution of ionizing electrons produced in a given mass of air are the same as those of the secondary electrons in an equivalent mass of tissue. Furthermore, the number of ions in one will bear to the other a ratio which is independent of wavelength in the case of gamma rays and x-rays of not too long wave length.

[This is the theory for measurement of radiation in biological specimens.]
The roentgen, as adopted today in x-ray dosimetry, besides affording a common unit for the standardization of x-ray machines, set also the criteria required for propotianality of ionization produced by x-rays as measured in free air to the ionization in minute biological specimens removed from any source of secondary radiation. Beyond this, however, the proportionality ceases to exist because the roentgen, in the interest of precision, does not call for the measurement of ions that may be produced by radiation scattered by surrounding material into the specimen under observation. Therefore, corrections to the ionization obtained in free air, are required for the complete appraisal of biological effects observed in irradiated tissue which is located at the surface or at a depth of scattering bodies. Such information is presumably supplied by the well-known tables for back scatter and depth doses.

"Hitherto these data have been obtained by means of thimble chambers of the so-called air wall type. These chambers can be calibrated against the standard air chamber under the conditions set forth in the definition of the roentgen. Thimble chambers have been constructed which yield ionization currents proportional to those in the air chamber throughout a more or less satisfactory range of wave lengths. It must be observed, however, that this proportionality can be observed only under very restricted conditions; namely, in free air and with proper diaphragm systems. In performing measurements on back scatter, depth dose, or intensity in the vicinity of radium needles or radon implants, it have been tacitly assumed that no appreciable error is introduced by altering the conditions under which the calibration of the thimble chamber was made. Since the standard air chamber is not adapted to measurements of this kind, the investigation of tissue ionization must be carried out with closed ionization chambers in which the factors influencing ionization can be varied and properly appraised.***[This is the early method for measuring biological tissue.]***

"For the particular purpose of measuring depth doses and back scatter, an ionization chamber of the extrapolation type has been designed by Failla. It is shown in the first slide ***[SLIDE]*** ; it consists of two electrodes, the top one removable and the lower one attached to the body of the scattering phantom. The spacing between electrodes can be varied so as to exclude, by extrapolation to zero thickness, the effect of the air layer on the measurement. Likewise, in measurement of back scatter, the thickness of the top electrode can be varied so that, by similar extrapolation, its effect can be eliminated. As shown, it is well adapted for measurement in parts of the human body of comparable size, It can be readily adapted to give a true indication of ionization in smaller sections of the human body, by merely changing the size and shape of the scattering material around the region at which the ionization is measured. For instance, by removal of the underlying material and addition of material at the top it, of proper size and shape, one can measure the so called exit dose which is quite important in treatments involving cross firing. A thimble chamber, calibrated to read in roentgens has been found to agree with this chamber only in the case of back scatter in the x-ray region of moderate penetration, and in no other. Still wider divergences are found in the case of depth measurements for all wavelengths included between 96 KV unfiltered x-ray and gamma ryas. The causes of the discrepancies are many; it suffices to mention that they are mainly due to the different response of the chamber to radiation impinging upon it from different directions and to the fact that the thimble chamber, by its very presence, disturbs the distribution of radiation in the immediate neighborhood in which the ionization is measured.

"In order to preserve the desired proportionality between ionization in air and in tissue, attention must be paid also to the length of the tracks of ionizing electrons, which varies markedly with the quality of the radiation.

"As radiation strikes a solid object, there is a region at the surface in which the ionization varies rapidly due to the fact that, for lack of contiguous material on the incident side, the number of electrons crossing this region is less than the number crossing a layer at a greater depth. it is found that when the thickness of the material equals the range of the fastest particle, the ionization falls off only on account of the absorption of the incident rays. measurement of ionization in this region cannot be expressed in roentgens since the latter requires the full utilization of secondary electrons. ***[Expression of ionization in ROENTGENS]*** In the case of x-rays, the thickness of this region is less than the thickness of the human epidermis and therefore this phenomenon can be disregarded. In the case of gamma rays, the region is about 6mm of tissue. Consequently, measurement in roentgens is possible only at depths greater than 6mm if we use nearly parallel beams and considerably more [beams] when measurements are made close to the radioactive source.

"If the case of an ordinary radium pack is considered, the ionization in the skin will also depend a great deal on the design and material of the pack because electrons liberated from its walls have sufficient energy to reach and penetrate the skin. An ordinary thimble chamber, built to read correctly in roentgens, requires a wall thickness equivalent to the range of the most penetrating electron and, therefore, cannot give the proper data as the ionization in the skin. The extrapolation chamber, instead, by use of different thickness of the top electrode, will yield the required. [sic] [data?] ***[Advantage of EXTRAPOLATION CHAMBER over THIMBLE CHAMBER]***

The obvious desire for a common unit of tissue dosage for all ionizing radiation can be realized by redefining the roentgen as a certain number of ions produced in a certain mass of air by ionizing radiation under the conditions obtaining in the biological material while it is irradiated. ***[By REDEFINING roentgen as A CERTAIN NUMBER OF IONS produced in a CERTAIN MASS OF AIR BY IONIZING RADIATION UNDER THE CONDITIONS obtaining IN THE BIOLOGICAL MATERIAL WHILE IT IS IRRADIATED.]*** If, for the proposed unit, we choose the number of ions equivalent to one e.s.u. of charge liberated in the mass of one c.c. of air at N.T.P., we shall have a unit coinciding with the roentgen when exposures are given in free air. Therefore, it will be just as useful for standardization purposes. ***[Marinelli standardizes the unit for measuring radiation in biological material by redefining the roentgen as a certain number of ions.]***

We are in a position to offer as supporting arguments for the new unit ***[NEW UNIT]*** two sets of biological experiments performed at the Memorial Hospital. The first set has been carried out by

Henshaw and Francis using Drosophila eggs as test material. Their results have been published in Radiology, November, 1936. Drosophila eggs were exposed to gamma rays of radon by distributing the material over two bakelite holders: one spherical in shape--9.64 mm in radius, the other cylindrical--11.25 mm radius. The primary filter in the spherical applicator was 1/2 mm of Platinum and the source a small radon glass bulb. In the cylindrical applicator, the filter was 2mm of lead and the source was a glass capillary tube 15 mm long. It was found that 50% of the eggs were killed after an exposure of 1900 mc-minute with the spherical applicator, and 3000 mc-minutes with the cylindrical applicator. In parallel experiments with x-rays, it was found that the same killing effect was obtained with 197 roentgens when the eggs were exposed in free air to 200 KV x-rays filtered by 0.8 mm of cu. No objections to these figures can be raised on the grounds of different susceptibility of the eggs due to difference in age because the biological technique used for the x-ray and gamma ray tests was identical. Furthermore, the amounts of radon and the x-ray intensity used were such as to give practically the same biological result for the same time of exposure to either radiation.

"Physical experiments were undertaken to establish the ionization in air under the conditions in which the biological material was exposed. In the next slide **[SLIDE]** is outlined the method employed in the case of the sphere. Spherical balloons of different sizes made of collodion or gold beater's skin, were used as outer electrodes of the ionization chambers. The source of gamma radiation was placed at the center of the balloon. It was enclosed in a bakelite sphere identical to the one used in the biological experiments. Accordingly, the radiation which ionized the air within the balloons was the same as that which traversed the fly eggs. By suitable extrapolation, it was found that the rate of ionization at the surface of the bakelite sphere was 108 units per minute per gram of radium.

"The method adopted for the measurement at the surface of the cylindrical applicator is shown in the next slide. **[SLIDE] {Method for measurement at cylindrical applicator surface.]** A hard rubber cylinder of exactly the same dimensions as the cylinder used for exposing the eggs was used as the collecting electrode of an ionization chamber. The outer electrode consisted of cylinders of fine silk mesh or thin paper separated from the hard rubber cylinder by different thicknesses of air. Care was taken to limit the collecting electrode to the exact area in which the Drosophila eggs were exposed. **Since the irradiated volume could be computed accurately in each case, the ionization per cc. could be obtained for each electrode spacing. Extrapolating to the surface of the cylinder a value of the ionization rate of 68 units per minute per gram of radium was obtained.** [Emphasis mine] ***[How value of ionization was obtained by EXTRAPOLATING.]*** Making use of this data, we find that the doses required to kill 50% of the eggs at the surface of the sphere and cylinder are, respectively, 204 and 205.2 units. Obviously, the dose of gamma rays required to till 50% of the eggs under proper conditions would be the same. The fact that the values obtained experimentally are almost identical show that the ionization measurements were made under the proper conditions.

"Now let us see what happens if we attempt to determine the same doses from measurements of gamma rays with thimble chambers under the conditions generally advocated as meeting the requirements of the definition of the roentgen. We shall take for this purpose the most accurate value of the gamma ray emission so far suggested, namely, 137 per minute per gram at 1 cu. distance (Mayneord 1937) Making straightforward corrections for differences in filtration and distribution of source, we obtain 50% killing dose for eggs on the surface of the sphere 280r; for those on the surface of the cylinder, 1854., which are quite different. The one for the sphere, 280 r, is also quite different from 197 r, which is the 50% killing dose when the eggs are exposed to hard x-rays. These discrepancies disappear if the definition of the roentgen is modified as we have suggested, since the doses would then be 204r for the sphere, 205.2r for the cylinder, in the case of gamma rays, and 197r in the case of x-rays, the differences being well within the limits of experimental error.

"The experiments corroborate and extend the work of Packard and Henshaw who have found that the number of roentgens required to kill 50% of the eggs in free air is independent of wavelength in the x-ray region. This conclusion cannot be reached if the ionization is expressed in roentgens as defined today. ***[Previously, "the number of roentgens in free air…{ was considered} independent of the wavelength in the x-ray region." Marinelli's method, applied in the extrapolation chamber--produced a value for KV of x-rays that corresponded to measurements of ionization in air.]***

Another set of experiments have been made on human skin erythema by McComb and Quimby, using a cylindrical applicator which, with the exception of a slight difference in external diameter, is an exact replica of the cylindrical applicator described before. By strapping the applicator to the forearm of patients, it was found tht the threshold erythema dose is 225 mc-hours, which corresponds to 1050 units as defined in this paper. Tests to determine the threshold erythema dose with our 4 gram Ra pack have been performed by Quimby and Duffy, who find a value of 8500 mc-hours at a distance of 6.3 cm from the source for the skin of the forearm. Physical measurements performed with the **extrapolation chamber** [emphasis mine], under the conditions in which the erythema tests were made, show that the threshold erythema dose, in this case, is 1100 units, in very good agreement with the value obtained with the cylinder. The corresponding value for 200 KV x-ray filtered by 1/2 mm of the Cu is 630 units when determined with the extrapolation chamber. [When] Making the ionization measurements with thimble chambers, which are said to fulfill the requirements of the present definition of the roentgen, it is found that the threshold erythema dose for the radium pack is 1500r, and for the cylinder about 1000 r. The value for hard x-rays remains 630 r since, in this case, the thimble chamber and the extrapolation chamber agree. It is evident, therefore, that no matter how the measurements are made, the threshold erythema dose for gamma rays is much higher than [for]filtered 200 KV x-rays. The fact that the threshold erythema dose for the cylinder applicator and the pack in terms of the modified roentgen is substantially the same, lends strong support to the practical usefulness of the proposed unit. ***[So, Marinelli modified the definition of the roentgen so it could be used to express the threshold erythema dose for gamma rays as well as for filtered x-rays.]*** Pack and Quimby, however, have shown that the threshold erythema produced by radium is independent of exposure time if the latter [radium source] is limited between 40 seconds and 4 hours. We may, therefore, safely draw the conclusion that threshold erythema is not independent of wavelength even when the dose is expressed in units which are proportional **to the actual ionization taking place in the skin.** [Emphasis mine.] On the other hand, the lethal effect on Drosophila eggs is independent of wavelength when the ionization is measured properly."

2. 1944

" X-Rays and Gamma rays" (3 Pages, handwritten, with indications of 4 slides + photograph)
Action of e.m. radiations and electrons. Ion agents: electrons; conversion Atomic No.
Soft x-rays
Hard x-rays
H. speed electrons
absorption of energy; deviated from path.
Do not expect always correlations between dose and biological effect. Example: Drosophila follow___; erythema dose
General remarks: distance between ions order of ….Radioactive substances: electrons; positrons
Concentration, energy of particles, half-life, biological elimination

- Radio phosphorus (mice; humans). Usefulness in studying dynamics of metabolism. Therapeutic criteria = generalization of disease + radioactivity.
- Radioiodine = much better concentration. Tracer studies; incompleteness of studies (Keston, Bernstein, Heisler)
- Radiostrontium

General remarks: nothing has been done to concentrate these elements; our knowledge of metabolic processes is too scant.
NEUTRONS

NEUTRONS

Fix interaction between neutrons and atoms of elements existing in body.

1) Elastic collisions - motion of nuclei. Impact

H ~ 1/2 energy of colliding Neutron

C	14%	proton [recoil?]	10^{-7}cm.00/μ
N	12%		$10.^{7}$/ cm $^{-1}$
O	11%		$10.^{8}$ cm $^{-1}$
Ca	0.5%		10^{-8} .000/μ

3) disintegration (slow neutrons) [lots of equations with letters]

In order to penetrate, we must use fast neutrons. Obtained with cyclotron. Ionization in time:

92% proton [traces?] [tracks?] Results obtained → 14
2% carbon energy 0.6 to 9
5% oxygen
1% rest

Usually nine effective for same ionization; sometimes less; explanation for it. Marshak experiments - neutron/ [vs?] [or?] x-rays 6 - 8.8 (lymphoma resting stage)

Neutron Capture - Kruger & Zahl. concentration of β or Li in tissues. Problem of concentration.

Radiation

- as a surgical tool - (considerations in large dimensions), special consideration almost exclusively : immediate recovery of intervening tissues
- as medical tool - chemical changes; its study in small dimensions [several graphs]

x-ray

□-ray

Electron depth dose

3. March 26, 1945

"Correlation between ionization and biological effect. Roentgens - Energy Absorption" (Handwritten, 3 pages + Slides.)

Its importance in giving clue as to nature of the fundamental processes involved. Drosophila eggs practically independent of λ between 10 to 400kv (difference at most 25%); Other materials (soft x-rays and □ rays 0.6 - 1.0) x-rays

Skin remains most baffling inasmuch energy absorbs to produce erythema varies considerably…

If comparison is made between neutrons and x rays, differences still large….

Let us see the process of ionization in greater detail (x rays)….

photoelectron effect - comparison for different substances - mention thyroxin….

Theses do not explain erythema because it refers to pure substances. It might explain certain chemical reaction in vitro…

Neutrons (heavily ionizing [traces?] [tracks?]…. graphs and tables…(Very little change in ordinary range….. Very fast to slow)

In clinical application: Factors of importance is localization by geometrical means (don't know much about), physiological means, differential absorption

a) spatial distribution soft - hard - extra hard distribution….electrons (fast) - betatron…This methods is probably the most directly obtainable in the future.

b) physiological means radioactive isotopes, P-32, examples, Relative dosages [Table of elements]

No chemical help so far. Marshak giving P-32 in chromatin 5% 5o 25% in liver…Investigations at Memorial

Not very good concentration; obvious applications - generalized diseases which are radiosensitive; application to study in vivo - mycosis [fungoides…?]

Iodine better concentration - no damage to blood, even if radioresistant; will destroy limited thyroid system- not all cancers will take it.

Burnstein (no thyroid, 9 metastasis, 2 hears) high doses, very radioresistant.

Clinical information from hyperthyroidism.

Radiostrontium

Differential absorption of energy - Early attempts to put heavy metals in tumors and irradiate them.

Neutrons will

1) produce more ionization in H rich tissues, in collisions

H will take	50% energy		Ionization 92% to H
C	14%	if proportion of	2% to C
N	12%	elements is taken	5% 5 to O
O	11%	into account then	1% to rest
Ca	0.5%		

2) disintegrate light atoms if slow {table of equations …mass charge…}

Problem is of concentration and was attempted by Kruger and Zahl.

4. March 29, 1948
"Main Purpose Hit Tumor, Spare Tissue." Delivered to "Students" (Handwritten, 2 pages + Slides)
Observations: (combination of any)
1. Discrimination of tumors to different types of ion radiation
2. Geometrical concentration of energy
3. Physiological concentration of energy

1. Discrimination of tumors to different types of ion radiation
Drosophila - roentgen needed for same biological effects does not vary with kv. Erythema dose does. Explanation energy? No. High atomic elements would be needed in quantity. Using other agents (neutron for instance) relative effect varies with tissues. Suspicion on specific ionization in tissues. [Spacing?] in x rays ~ 0.1μ in tissue
proton 0.001μ
heavy recoil atoms 0.
Not much has been done on tumors versus healthy tissue except in ranges easily available where spacing does not change much. With other experimental materials, some exhibit this pattern. Other biological effects exhibit decrease in sensitivity and lend belief to hypothesis that only a pair of ions are needed in a given volume to produce desirable effect. Thus far, very little is known to reach conclusions or what can be accomplished by exploiting variation in specific ionization.

2. Geometrical concentration 1st order
External treatment - practical consideration, accuracy to localization, order of [e.m.?],
Let us not forget 2 [terminis?]
a) with x rays = Depth doses, usual one (show scheme - what 1000 M.E.V. would do
b) with β rays - Range limits; Range….; Betatron scheme; Depth dose; multiple field sketches.
c) with protons - Ranges → Spec. ion may increase or decrease effect.

3. Physiological - concentration
Is a function of concentration
a) in conjunction with external agents. High atomic No. + x ray.
Too much material $c_1/c_2 = Z_2^3/Z_1^3$ Limitation in raisin dose by…
Special elements with high [correction?] to neutrons is the same thing. We must also keep in mind that for equal energy flow, dose in tumor tissue, and compared to healthy tissue, concentration will have to differ by the ration that we wish to achieve in dosage.
With non-toxic material, one could combine geometrical concentration with physiological concentration of this type. Net result would be further saving of irradiation of tissue not too close to lesion. Theoretical concentration effect would be geometrical factor x concentration factor for tissues far removed and concentration factor alone for those close to lesions.
At this stage, these possibilities should be considered since accuracy in delivering radiation has already demonstrated to yield tangible clinical results (rotation therapy for one)

b) Radioactive isotopes - from purely dose standpoint, concentration of energy = concentration of isotope. Two used: P-32 and I-131.
P-32 concentration in some tumors of lymphoma type….Useful information: highest diff. found in [nucleo?] protein in pertinent organ of leukemic mice. In nuclei of tumor and regenerating liver. Some rough studies in humans shoe low discrimination in concentration.
Interesting results with Abels and Kenney…

repeated with x rays - 3□ – Hevesy show temporary
disturbances in P-32 metabolism within short time of irradiation.
I-131 has advantages
1) therapeutically great difference in concentration
2) can be studied in vivo because it emits □ rays

As far as cancer is concerned, some studies: Hamilton's work; Burnstein; General results Kencht; Hall (picked up after thyrodectory); Shenley (thyrotropic hormone).

5. May 22, 1948
"The Calculation of Radiation Dosages from External and Internal Sources." L.D. Marinelli

"Before the advent of the nuclear reactor, most ionizing radiations utilized in medical and biological studies originated from radium and x-ray tubes which acted as external emitters. With the availability of radioactive isotopes as a byproduct of the nuclear reactor, [scientific] investigators in the fields have been [challenged] ~~confronted~~ with the problem of determining the radiation doses in living tissues exposed to other types of radiation (α, β, η) acting as internal as well as external emitters. ..A great deal of confusion can be eliminated by clarifying our concept of dose. To date the internationally accepted unit of dose--the roentgen--is defined as that quantity of x or gamma radiation such that the associated corpuscular emission per 1.29×10^{-3} grams of air produces, in air, ions carrying 1 e.s.u. of quantity of electricity of either sign. Therefore, as it stands, the roentgen applies only to electromagnetic radiation but, if by dose it is meant energy absorbed per unit of matter, the roentgen could be extended to α- and β- radiation.

Thus, an equivalent roentgen (or r. e. p. = roentgen equivalent physical) of x-gamma, x or β-radiation, is that amount of radiation which ,under equilibrium conditions, releases in one gram of air as much energy as one roentgen of gamma rays (83 ergs) . This step, to be sure, will require certain corrections where photons are used because the energy absorption in tissue for an exposure of one roentgen to x or γ radiation depends on both tissue composition and radiation wavelength, but in practice for soft tissues these corrections are not very large.

With these premises in mind, it is possible to proceed to the basic problems of radiation dosimetry, namely correlation between magnitude and "geometry" of the source and energy absorption in tissue.

Photon Sources: a) External emitters; b) internal emitters.

May 21, 22, 1948 Program of "Meeting on Isotopes: Fri, May 21 and Saturday, May 22, 1948. Museum of Science and Industry (West Wing). Sponsored by the Biology Division, Argonne National Laboratory, Chicago, IL Meeting Chairman, Austin M. Brues, Director, Biology Division, Argonne National Laboratory.

Saturday. Chairman: Ray E. Zirkle, Dir. Institute of Radiobiology and Biophysics, U of Chicago.

Friday Morning (Chairman: John Z. Bowers, Asst. Director, Div. of Biology and Medicine, USAEC, Washington, D.C.)

1. Status of ANL in relation to the AEC and private institutions: Norman Hilberry, Associate Director ANL (Assistant to Shields Warren)

2. Review of biological and medical work in progress at ANL.. Austin M. Brues

3. Measurement of stable tracers by the mass spectrometer. Mark G. Inghram, Mass Spectroscopy Div.

4. Mass spectrometric analysis of volatile products of metabolism. A.J. Dempster, Dir., Mass Spectroscopy Div.