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ACUTE LETHALITY OF PARTIAL BODY IN RELATION TO WHOLE BODY IRRADIATION

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ABSTRACT

If to cause acute death from radiation the same amount of lethal substance or injury must be produced, whether the whole body or segments thereof are irradiated, it is shown that the reciprocal of LD_{50} for the whole body, will be equal to the sum of the reciprocals of LD_{50} for the separate segments, all doses being measured in roentgens. Existing data are compatible with this view but they involve irradiation of large segments of the body. For small segments undoubtedly the rule will fail. Some general aspects of partial body irradiation are discussed.

ACUTE LETHALITY OF PARTIAL BODY IN RELATION TO WHOLE BODY IRRADIATION

Partial body irradiation is of interest because it is common in occupational and accidental exposures, because it results from the ingestion of most radioactive materials owing to their inhomogeneous distribution and because of its possible use as a technique in studies of the nature of the injurious action of radiation.

One type of experiment which has been performed is determination of LD_{50} - 30 days for a given strain of animals for whole body irradiation, for irradiation of a segment of the body and for irradiation of the remainder of the body excluding this segment.

If the segments of the body are A and B, respectively, the whole body is A + B. If the lethal action of the radiation is proportional to the dose and if the same level of lethal effect, Q, is required whether whole body or individual segments are irradiated then

$$Q = AR_A = BR_B = (A + B)\,R \qquad 1.$$

R_A, R_B and R being the lethal doses in roentgens and A, B and A + B are now the products of the weights of the segments and the constants of proportionality converting roentgens to lethal effect.

On dividing the two right hand terms of equation 1 by BR_BR

$$1/R = (A/B + 1)/R_B$$

$$\text{but from (1)} \qquad A/BR_B = 1/R_A$$

$$\text{therefore} \qquad 1/R = 1/R_A + 1/R_B \qquad 2.$$

According to this equation and the hypotheses used, the reciprocal of whole body LD_{50} is equal to the sum of the reciprocals of the LD_{50} for irradiations of two segments which together include all of the body.

Data by Reinhard et al (1) giving LD_{50} in four strains of mice for head alone, body alone and whole body are shown in Table 1. It will be seen that agreement with equation 2 is fairly good except for the one

TABLE 1

Strain	Whole Body R	Whole Body 1/R	Head Alone R	Body Alone R	Head and Body 1/R + 1/R
Dba	500	.0020	500	1265	.00280
Marsh	570	.00175	1185	1018	.00183
C57	550	.00181	1300	858	.00194
C_3H	492	.00203	1443	735	.00198

Data by Reinhard et al (1) on determinations of LD_{50}, R, for partial and whole body irradiation in four strains of mice. According to the hypotheses used here the reciprocals of columns 2 and 5 should be equal.

instance in which LD_{50} for head and whole body are the same. One of these values is most probably in error on general grounds.

These results are compatible with the view that a given amount of a lethal effect or lethal substance is required to kill and that it is equally effective whether it is produced uniformly in the body or only in a segment thereof.

Equation 1 is compatible with the view, but does not require, that the total number of gram roentgens required to kill are the same whether delivered to the whole body or to a segment only; this because the constants of proportionality in A, B, etc. may, or may not be, proportional to the weights of their respective segments.

Information of this point is supplied by Kereiakes et al (2)(3) who demonstrated by irradiating rats and mice through a protective grid with equal diameter apertures that the lethal dose in gram roentgens was nearly the same for irradiation of the whole body as for distributed fractions down to about 15% of the body. However, when the apertures were reduced in diameter while keeping constant the area exposed, the gram roentgen lethal dose increased. This latter effect was attributed to reduction of effectiveness of the injury by reparative actions occurring across the increasingly larger surface of normal tissue surrounding the irradiated as the apertures become small.

While the experiments just cited show that within fairly wide limits the gram roentgen lethal dose may be the same for whole body and segmental irradiation, when the segments represent all types of tissue, this is not true, according to Swift et al (4) when the abdomen alone or the remainder of the body alone are irradiated. Their data are shown in Table 2.

TABLE 2

	Whole Body	Abdomen Exposed	Abdomen Shielded
R	650 - 750	1025	1950
kg. R	175	134	275
1/R	.00143	.00097	.00051

Data of Swift et al (4). LD_{50} in roentgens, R, and in kilogram roentgens, kg. R, for whole and partial body irradiation of rats of the Sprague-Dawley strain. Whole body LD_{50} is taken as 700 r in calculating 1/R. Actually the reciprocal of 676 r is equal to the sum of the reciprocals for the segmental irradiations.

It will be seen that the sum of the reciprocals for partial body irradiations, 0.00148, is essentially equal to, 0.00143, the reciprocal of 700 r the average of the range of values 650 to 750 r given for whole body LD_{50}. Consequently these data conform to equation 2. However, the lethal doses in kilogram roentgens are quite different for the three modes of irradiation. Consequently agreement with equation 2 may be attributed, not to the necessity of equal gram roentgens, for lethality, but rather to the necessity for equal lethal effect or substance. These matters can be discussed most easily by generalizing equations 1 and 2.

Let Q = amount of lethal effect required. Let there be n segments of weight w_1, w_2, etc., requiring, respectively, for lethality the doses r_1, r_2, etc. Then if a_1, a_2, etc. are the constants of proportionality giving the effectiveness of the radiation in producing lethal effect per gram per roentgen in each segment

$$Q = a_1w_1r_1 = a_2w_2r_2 = \text{---}\ a_nw_nr_n = (a_1w_1 + a_2w_2 + \text{---}\ a_nw_n)\ r \qquad 3.$$

the last term representing irradiation of all the segments together with lethal dose, r. The sum of the segments may or may not include the whole body.

On dividing the second and last terms by r and $a_1w_1r_1$

$$\frac{1}{r} = \left(\frac{1}{r_1} + \frac{a_2w_2}{a_1w_1r_1} + \text{----}\ \frac{a_nw_n}{a_1w_1r_1}\right)$$

But $\frac{a_2w_2}{a_1w_1r_1} = \frac{1}{r_2}$ etc. --- $\frac{a_nw_n}{a_1w_1r_1} = \frac{1}{r_n}$

$$\text{Therefore } \frac{1}{r} = \frac{1}{r_1} + \frac{1}{r_2} + \text{------}\frac{1}{r_n} \qquad 4.$$

It will be observed that agreement of data with equation 4 imposes no requirement for equality of the products wr, or gram roentgen doses in equation 3, because the a's may be different. In the experiments of Swift et al (3), a, for the abdomen is twice as great as that for the remainder of the body. In other words twice as much lethal effect occurs in the abdomen per gram roentgen as in the remainder of the body.

The reason that the data of Kereiakes et al show a wide range of equality of gram roentgens for lethality is, presumably, that similarly representative samples of all the tissues were usually exposed. When this condition is not fulfilled gram roentgens will vary.

A feature of equation 4 of some interest is its prediction with respect to the lethal dose for any segment in relation to that for the whole body. Let this be the nth segment. Then

$$\frac{1}{r_n} = \frac{1}{r} - \left(\frac{1}{r_1} + \frac{1}{r_2} + \quad \frac{1}{r_{n-1}}\right)$$

$$\text{or} \quad \frac{1}{r_n} < \frac{1}{r} \quad \text{or} \quad r_n > r \qquad 5.$$

That is, the lethal dose in roentgens for irradiation of any segment of the body, no matter how sensitive it may be, is always greater than the lethal dose in roentgens for the whole body.

As a corollary to this the lethal dose will always be increased by shielding part of the body and the increase will be greater the greater the sensitivity of the shielded part.

It has been implied thus far that the irradiated segments are mutually exclusive and this is necessary if the relations derived are to be obeyed. Furthermore, this condition can be met, by appropriate shielding, in fairly close approximation using external sources. With injected radioactive materials, however, if two varieties are administered alone and then in combination, the regions in which they accumulate may overlap. This is immaterial, however, providing each substance produces its effect independently of the other. It is of interest to consider two such materials.

Using the same notation as before

$$Q = a_1v_1r_1 = a_2v_2r_2 = \alpha\, a_1v_1r_1 + \beta\, a_2v_2r_2$$

the first terms representing LD_{50} for the two substances separately and the last term representing LD_{50} for the case in which the two materials are given together in fractions α and β, respectively, of the LD_{50} when given alone. Owing to the prolongation of dosage and simultaneous recovery r_1 and r_2 will be effective rather than real doses.

It will be seen that the above relation requires $\alpha + \beta = 1$. It is not to be expected, however, that this relation will be obeyed except for two materials of the same effective half-lives; otherwise their maximal effects will not occur at the same time and consequently will not be wholly additive. On this ground, therefore, it would be expected that $\alpha + \beta$ would usually be greater than 1. It is shown by recent work of Carsten and Noonan (5) however, that recovery from primary radiation injury as measured by a second dose is faster in the rat when the abdomen and hind limbs alone, rather than the whole body, is irradiated. This suggests the possibility that recovery rate decreases as the irradiated volume increases. If this is true for radioactive materials it permits the possibility that the maximal acute injury from two materials of different tissue distributions acting together and affecting a larger volume of tissue would each be greater than when the materials acted alone. If so $\alpha + \beta$ might be less than 1. This case has been observed by Friedell et al (6) who found that half LD_{50} of radioactive gold and of phosphorus administered together constituted almost LD_{100}.

It will be seen from these considerations that no simple additive relations are necessarily to be expected for the acute lethality of mixed radioactive materials except when they have the same organ distribution and biological half-lives.

COMMENTS

The present analysis is compatible with either hypothesis that radiation produces a toxin which spreads to the whole body or, an injurious effect, confined for the most part, to the volume exposed.

If there is a toxin produced there is no evidence that it is combatted more effectively by non-irradiated than by irradiated tissue. An exception to this may be the spleen. However, its action may be wholly restorative of hemopoiesis rather than detoxifying. In any case spleen shielding is protective much out of proportion to the predictions of the hypotheses used here.

In this regard it is significant that shielding extensive areas of bone marrow does not alter the lethal level of injury in the unshielded segment of the body.

This analysis is compatible with the usual hypothesis that the lethal effects of radiation are in direct proportion to the dose but the proportionality constants are not the same for all tissues.

In the field of partial body irradiation more information is required especially with respect to long term effects. It is known that non-homogeneously deposited internal radioactive emitters cause shortening of life-span but the dose-effect relationships are not obtainable from existing data.

It is indicated by these results that the gram roentgen dose for lethality will tend to be the same for the whole body inhomogenously exposed, homogenously exposed, and partially exposed. This rule will fail, however, in either direction when the average sensitivity of the exposed tissues is not the same as for the whole body. It will also fail, presumably, for irradiation of segments of the body, not essential to life, such as a limb, which, with proper treatment, could be exposed to the extent of necrosis without leading to death of the whole organism.

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