tively, $C/(1 - LGR)$ and $VGR/(1 - LGR)$. The Lea-Catcheside assumption means that $A + B + C + D$ is proportional to the x-ray dose; the frequency of recessive lethals among viable sperms is $A + B + C/(1 - LGR)$. The departure of these two expressions from one another, which is a measure of the nonlinear effect, can be expressed as:

$$\frac{A + B + C + D}{A + B + C/(1 - LGR)} - 1 = \frac{D - C\,LGR/(1 - LGR)}{A + B + C/(1 - LGR)} = \frac{C/(1 - LGR)}{A + B + C/(1 - LGR)} [(D/C)(1 - LGR) - LGR]. \quad (1)$$

The first factor in the last expression is the fraction of *C*'s among the observable lethals. The bracketed factor can be reduced by algebraic manipulation to a form involving only the experimentally known frequency $VGR/(1 - LGR)$ and factors on which predictions can be made. These are $p = LGR/VGR$ and $q = \frac{D}{LGR}/\frac{C}{VGR}$. The quantity (1) can then be written as

$$p\,\frac{q - VGR/(1 - LGR)}{1 + p\,VGR/(1 - LGR)} \quad \frac{C/(1 - LGR)}{A + B + C/(1 - LGR)}. \quad (2)$$

As stated above, $\frac{C/(1-LGR)}{A + B + C/(1-LGR)}$ and $VGR/(1 - LGR)$ are observable quantities which, at 3,000 r, amount to about 1/3 and 1/5, respectively (*4*). The factor $p = LGR/VGR$ would be 1 if every rearrangement involved only two breaks; since this is not so, p will in general be larger than 1 (*2*) and might be even as large as 2 at 3,000 r. The factor $q = \frac{D}{LGR}/\frac{C}{VGR}$ would also be 1 if *VGR*'s and *LGR*'s had the same chance of being associated with a sex-linked recessive lethal; actually, $q > 1$, since the *LGR*'s are expected to have more breaks, on the average, than the *VGR*'s. The quantity (2) is thus certainly larger than the value found by taking $p = q = 1$, which at 3,000 r would be about 2/9. For $p = 2$, $q = 1$, it would be 8/21.

Therefore, it can be stated that the nonlinear effect amounts to at least 20–25 per cent at 3,000 r. On the assumption that the *C* lethals are by-products of *VGR*'s the nonlinear effect is $(A + B)/(A + B + C) - 1 = C/(A + B + C) = 1/3$—that is, possibly a somewhat larger one. The Lea-Catcheside theory may thus reduce the nonlinear effect by a factor which amounts to 1.5 at most. The remaining nonlinear effect is probably significantly at variance with the set of experimental data discussed by them. At any rate, it seems quite unlikely that an effect of such quantitative importance could have failed to be detected in all the extensive studies on this subject by so many different workers.

It may well be that the Lea-Catcheside concept of the recessive lethals, as manifestations of the same type of primary lesion which leads to the observable chromosomal breaks, is essentially correct. But the process of x-ray–induced breakage and recombination in *Drosophila* has thus far defied not only a quantitative but even any comprehensive qualitative analysis (*2, 3*). This difficulty may well prevent for the time being any satisfactory account of the relationship between recessive lethals and rearrangements and of their dose-frequency relationships. This same difficulty, incidentally, seems to put the Lea-Catcheside detailed calculation of the dose-frequency relationship for dominant lethals (*4, 5*) on a very doubtful ground, although there seems to be no difficulty with the qualitative understanding of this relationship.

A final remark may be added concerning the recessive lethals (*B*) associated with minute rearrangements. Lea suggests that the deficiencies involving several salivary chromosome bands are due to separate breakage processes caused by a single ionizing particle, in analogy to the mechanism which he successfully proposed for *Tradescantia*. However, the frequent occurrence of spontaneous lethals involving deficiency of several bands (*1*) suggests that such deficiencies are the outcome of a single primary, probably much more closely localized, lesion. The larger deficiencies up to about 50 bands, and the corresponding minute inversions, are generally accepted to be due to the same mechanism as the *VGR*'s (*4*). Accordingly, a substantial fraction of the class *B* recessive lethals should have been transferred to class *C* for the purpose of the calculation carried out in this paper; this would have made the nonlinear effect appear even more important.

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Cosmic Radiocarbon and Natural Radioactivity of Living Matter

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In view of the discovery of radiocarbon produced by cosmic radiation (*1*), it becomes of interest to compare its effect in living matter with that due to the older sources of activity, such as radium and its decay products, or potassium, and to the action of cosmic rays. Since data on humans are most readily available to us, we will limit ourselves here to a comparison *in man*.

This comparison can be made on various bases, such as range, ionizing power, or total energy of the particles. The range varies from the extremely small range of α-particles up to the whole length of the human body for cosmic rays. The ionizing power per unit length varies in reverse order and decreases from the higher value for α-particles to cosmic rays.

As radiochemists, it seems to us that the simplest basis of comparison would be the number of disintegrating atoms (or

rays) per human being and per unit time. Table 1 shows a preliminary comparison based on an estimated average body weight of 80 kg.

TABLE 1

Element	Wt. % in human body	Total element in body (grams)	Literature source	Specific act. dis./min. and 1 gram element	Nature of emitted particle	Dis./min. and man
Potassium	0.35	280	Sherman (2)	1,340	β	380,000
Carbon	18.0	14,400	"	10.5	β	150,000
Radium	$\approx 10^{-12}$	$\approx 8 \cdot 10^{-9}$	Vernadsky (3)	$2.22 \cdot 10^{12}$	α	$\approx$18,000
	$\approx 5 \cdot 10^{-12}$	$\approx 4 \cdot 10^{-9}$	Evans*	"	α	$\approx$9,000

*Private communication from Robley D. Evans, Massachusetts Institute of Technology

The intensity of cosmic radiation at sea level corresponds to approximately 1 meson per minute and per cm.[3] Therefore, depending on whether the human being is in a standing or lying position, *i.e.* on his "cross section," the number of penetrating particles ranges approximately between 1,500 and 7,500 per man and per minute.

Thus, comparing these data, we see that cosmic radiocarbon occupies second place. Based on number of disintegrations, it is a little below half of potassium, but very much above radium and other natural radioelements. Only because of the low *specific* activity of carbon has it escaped detection so far. We believe that the biological significance of the radioactivity of carbon in living matter cannot be evaluated in physical terms alone; specific biological and biochemical factors may also play a role. It will be up to future research to establish these.

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IN THE LABORATORY

Bioassay by Direct Potency Estimation[1]

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Two main approaches are used to determine the potency (Py) of a drug, *i.e.* the ratio between threshold equipotent doses of the standard (S) and the unknown drug (U) (Py = S/U). One procedure uses the median effective doses (ED_{50}) of standard and unknown as expressions for S and U, respectively, and operates by determining these two values in separate populations of test animals. Another assay method compares the standard and the unknown drug on the same test object or animal. Usually the aim is first to find in each of various test individuals a pair of equipotent doses of the standard and the unknown (s^1, u^1; s^2, u^2; s^3, u^3; etc.). each such dose level complying with a set end-point in a critical range of effect, and then to obtain from these dose pairs a number (N) of equality statements (E), each E representing an estimate of the intraindividual potency in the respective test object ($E^1 = s^1/u^1$; $E^2 = s^2/u^2$; $E^3 = s^3/u^3$; etc.). Py is then defined as the average of the intraindividual potencies $\left(\frac{\Sigma E}{N}\right)$. Thus, in the latter method, potency is evaluated directly on the basis of intraindividual potency statements and not by a preceding determination of S and U which is characteristic of the former method. The former may therefore be called an indirect, and the latter a direct, method of potency evaluation.

The indirect method does not need any special biostatistical basis. Determinations of ED_{50} have long been placed upon an elaborate mathematical basis, and their adoption has satisfied all biostatistical requirements of such a method. On the other hand, the direct method has two major shortcomings: It lacks a rigorous biostatistical means for defining the significance of the result, and its purpose is accomplished in an uneconomical trial-and-error procedure. Prior to arriving at the respective doses s and u, one has to perform tests with a varying number of doses either higher (h) or lower (l) than s or u, respectively, *i.e.* with doses h_s and l_s of the standard and doses h_u and l_u of the unknown. The data from all these preliminary tests are ultimately discarded as being "aberrant."

Only in one variant of direct procedure, the "method of approximation" (*2*), are these aberrant doses utilized for obtaining a rough estimation of the significance of the result. They are paired, both mutually and with the respective s and u values, to form additional statements pertinent to potency, namely, statements H of maximum potency (signifying Py < H), expressed by the ratios h_s/l_u, s/l_u and h_s/u, and statements L of minimum potency (Py > L), expressed by the ratios l_s/h_u, s/h_u and l_s/u. All these H and L values are then arranged in

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