Phage
and the Origins of Molecular Biology

Expanded Edition

This 1992 Expanded Edition comprises a facsimile of the original 1966 edition and the additional new material listed below.

Phage
and the Origins of Molecular Biology

Expanded Edition

Edited by

John Cairns

Gunther S. Stent

James D. Watson

Cold Spring Harbor Laboratory Press 1992

Phage
and the Origins of
Molecular Biology

Expanded Edition

Printed in the United States of America
Expanded text design by Jim Suddaby

Library of Congress Cataloging-in-Publication Data

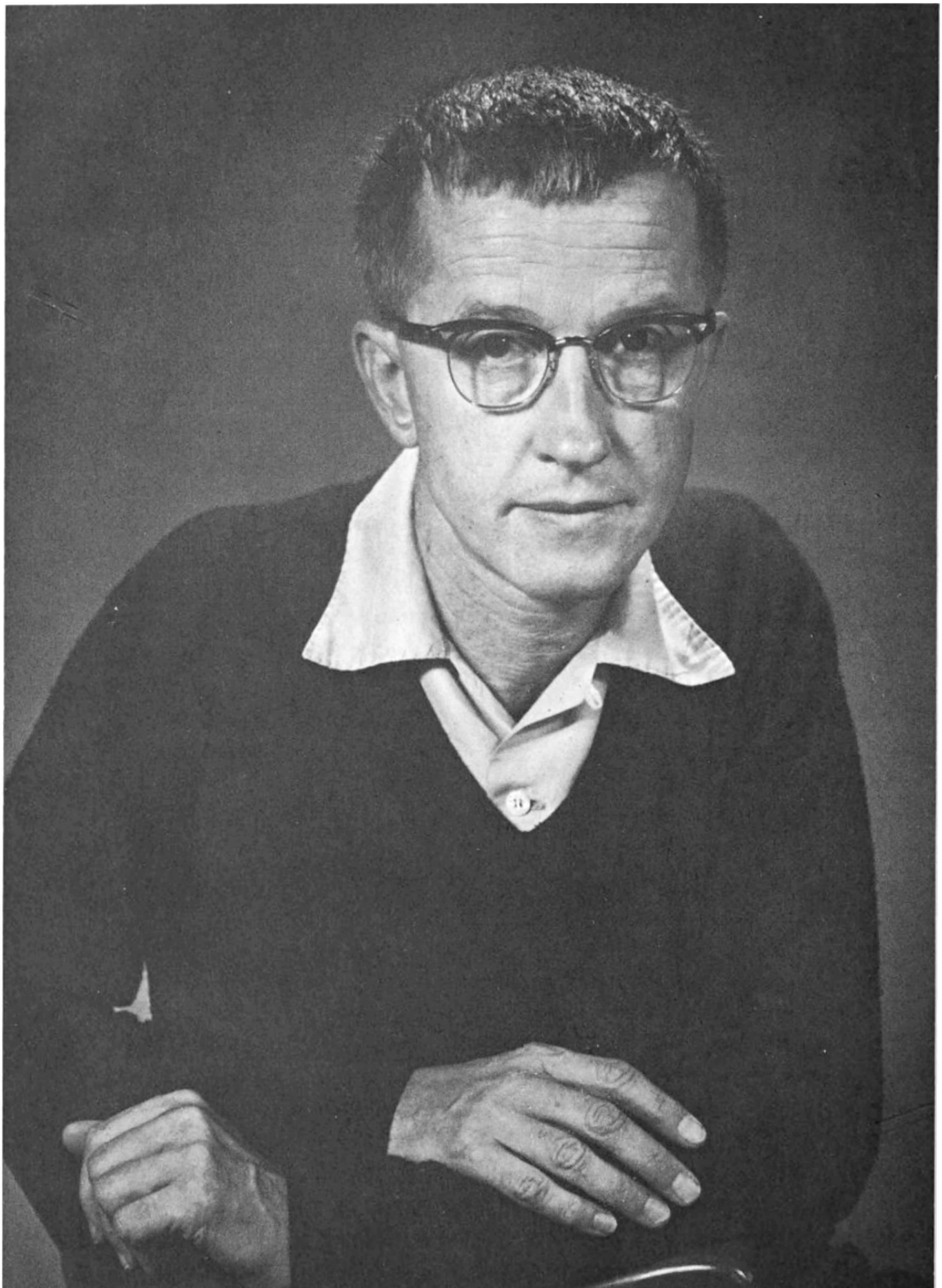
Phage and the origins of molecular biology / edited by John Cairns,
Gunther S. Stent, James D. Watson.
p. cm.
Includes bibliographical references and index.
ISBN 0-87969-407-6
1. Bacteriophages. 2. Molecular biology. I. Cairns, John, 1922-
. II. Stent, Gunther Siegmund, 1924- . III. Watson, James D.,
1928- .
QR342.P45 1992
576'.6482--dc20 92-15934
CIP

All Cold Spring Harbor Laboratory Press publications may be ordered directly from Cold Spring Harbor Laboratory Press, 10 Skyline Drive, Plainview, NY 11803. Phone 1-800-843-4388 (in Continental U.S. and Canada). All other locations: (516) 349-1930. FAX: (516) 349-1946.

Phage and the Origins of Molecular Biology

The Cold Spring Harbor Symposia

I. (1933) Surface Phenomena
II. (1934) Aspects of Growth
III. (1935) Photochemical Reactions
IV. (1936) Excitation Phenomena
V. (1937) Internal Secretions
VI. (1938) Protein Chemistry
VII. (1939) Biological Oxidations
VIII. (1940) Permeability and the Nature of Cell Membranes
IX. (1941) Genes and Chromosomes: Structure and Organization
X. (1942) The Relation of Hormones to Development
XI. (1946) Heredity and Variation in Microorganisms
XII. (1947) Nucleic Acids and Nucleoproteins
XIII. (1948) Biological Applications of Tracer Elements
XIV. (1949) Amino Acids and Proteins
XV. (1950) Origin and Evolution of Man
XVI. (1951) Genes and Mutations
XVII. (1952) The Neuron
XVIII. (1953) Viruses
XIX. (1954) The Mammalian Fetus: Physiological Aspects of Development
XX. (1955) Population Genetics: The Nature and Causes of Genetic Variability in Population
XXI. (1956) Genetic Mechanisms: Structure and Function
XXII. (1957) Population Studies: Animal Ecology and Demography
XXIII. (1958) Exchange of Genetic Material: Mechanism and Consequences
XXIV. (1959) Genetics and Twentieth Century Darwinism
XXV. (1960) Biological Clocks
XXVI. (1961) Cellular Regulatory Mechanisms
XXVII. (1962) Basic Mechanisms in Animal Virus Biology
XXVIII. (1963) Synthesis and Structure of Macromolecules
XXIX. (1964) Human Genetics
XXX. (1965) Sensory Receptors
XXXI. (1966) The Genetic Code



MAX DELBRÜCK, 1961

Phage and The Origins of Molecular Biology

Edited by

JOHN CAIRNS
Cold Spring Harbor Laboratory

GUNTHER S. STENT
University of California

JAMES D. WATSON
Harvard University

Cold Spring Harbor Laboratory of Quantitative Biology
1966

Second Printing, October 1968

Library of Congress Catalog Card Number: 66-26455

Manufactured in the United States of America

All orders should be addressed to:
Cold Spring Harbor Laboratory of Quantitative Biology
Cold Spring Harbor, Long Island, New York 11724

DEDICATED BY THE AUTHORS TO

Max Delbrück

ON THE OCCASION OF HIS

SIXTIETH BIRTHDAY

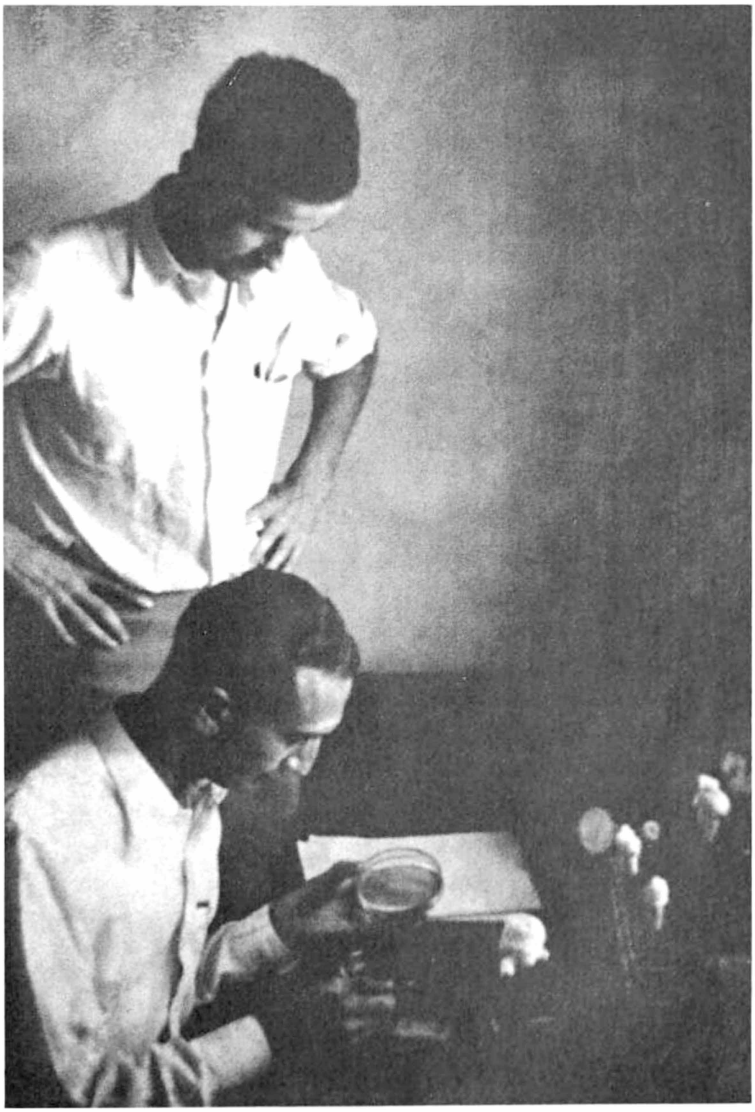
Table of Contents

IV. BACTERIAL GENETICS

V. DNA

VI. RAMIFICATIONS OF MOLECULAR BIOLOGY

I. *Origins of Molecular Biology*



M. Delbrück and S. E. Luria, Cold Spring Harbor, 1941

K. G. ZIMMER
Institut für Strahlenbiologie, Kernforschungszentrum Karlsruhe, Karlsruhe, Germany

The Target Theory

1. INTRODUCTION

To write about work done more than thirty years ago, about the views and aims that gave rise to certain experiments, is not an easy task. In a recent review by another contributor to this volume (Stahl, 1959) we find the statement "... the primary aim in employing radiation in the study of phage is to elucidate the *normal* state of affairs." Well, this is exactly what I did *not* have in mind when starting to work with Timoféeff-Ressovsky about a year or two before we came into contact with Delbrück. The problem that fascinated me (and, by the way, it still does) was to find out as much as possible about the primary physico-chemical processes produced in elementary biological entities by ionizing radiation. At that time, genetic changes in Drosophila were about the most elementary and the most clearly defined biological reactions available and formed, therefore, the system of choice for such work—not to speak of the brilliant personality of Timoféeff-Ressovsky which made team-work an exciting adventure. Of course, the two views, i.e. the one held by Stahl and the other one that I prefer, are not, eventually, distinguishable. They rather form different approaches to one problem: one cannot use radiations for elucidating the normal state of affairs without considering the mechanisms of their actions, nor can one find out much about radiation induced changes without being interested in the normal state of the material under investigation.

2. THE STATE OF THE ART IN 1932

Nevertheless, I joined the team with the intention of using Drosophila to investigate the actions of ionizing radiations, and I should state clearly what attracted me to do so. In 1932 quantitative radiobiology had just become of age; that is, relevant experiments had been done for about 20 years. The early observations had revealed the need for quantitative analysis and formulation of hypotheses concerning the mechanism of action. This need arose because two observations were made, the explanation of which was by no means obvious.

The first of the two puzzling observations was that such remarkably small amounts of energy can be followed by biological effects when the energy is delivered to the biological material by ionizing radiation. To give this point force, many comparisons have been suggested, e.g. that the amount of energy absorbed by drinking a cup of tea would be fatal to man if delivered as X irradiation instead of heat.

The second of these puzzling observations stands in close connection to the research which gave rise to it. This was mostly carried out by irradiating populations of biological objects (such as bacteria) and determining the fraction of individuals which showed a given effect after a given dose. It had been previously recognized that such experiments could be of value only if the population was as homogeneous as possible in respect to all biological parameters, such as size and age of the individuals. Corresponding experiments with poisons (chemical agents) had mostly given dose-effect curves of a kind which showed practically no effect up to a "threshold dose" and then climbed steeply up to 100% effect (Fig. 1). But experiments with radiations led in many cases to dose effect curves rising slowly to 100% and in which no threshold could be recognized. Concerning the experiments with chemical agents, the difference between threshold value and 100% dose was generally regarded as an effect of unavoidable biological variability (scatter of sensitivity). The results of irradiation, however, were scarcely amenable to an explanation of this sort, since application of an analogous line of thought seemed to demand a wholly unusual variability in the biological parameters. In more recent times, more detailed investigations have raised doubts as to whether these arguments of old-time radiobiology were really sound. These doubts will have to be considered

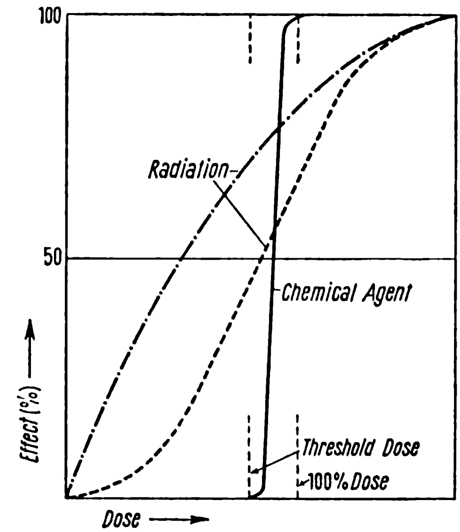


FIGURE 1. Diagram illustrating dose-effect curves for action of poisons and of radiation.

later (cf. section 4). It was the discovery of the form of a dose-effect curve for which a plausible explanation did not seem available that led to an entirely new line of thought: the application of the concepts of quantum physics to biological problems. These concepts in a generalized form have been well justified as a working hypothesis, since there is no doubt but that in this way modern physical concepts came into contact with biology, and that the synthesis of the two specialties so initiated has been remarkably fruitful. At this point our interest lies primarily in the beginnings of this development, that is, in the first hypothesis by way of which modern physical concepts were introduced some forty years ago into radiobiology, and thereby into biology: the "hit" theory (Dessauer, 1922; Blau and Altenburger, 1922). According to this view, the form of the observed dose-effect curve is due to the fact that absorption of radiation is not a continuous but a quantized process which follows the statistical principle that bears the name of Poisson. According to the mathematical formulation of this idea, the observed effect should appear in a member of a population having received macroscopically homogeneous irradiation when a minimal number of absorption events (called "hits") have happened in this individual. A strong resemblance could be shown to exist between the observed dose-effect curve and the curve calculated for the probability of occurrence of given numbers of absorption events for a given dose. In these calculations, the inevitable biological variability of the test material was, at first, admittedly neglected.

A very important development came some years later which not only independently extended the concepts of the hit theory but led further to the "target" theory (Crowther, 1924, 1926, 1927). The significant part of this work was that it offered the possibility of calculating from the dose-effect curve a volume, the target, within which the required number of absorption events must occur during irradiation, with a given probability. Comparison of the hit and target theories shows that the hit theory is to a large degree formal and very similar to the theory of chemical kinetics. The target theory, in contrast, demands that a well defined physical event must be chosen as the "hit." The three-dimensional target volume postulated in the original version of the theory can be computed only if the dose, stated as the number of absorption events per unit volume or mass, is given: here, choice can be made between a whole series of physical processes as absorption events, e.g. ionizations, excitations, primary ionizations, etc. Similarly, a two-dimensional target (reaction cross-section) can be worked out if the dosage is given in terms of the number of particles crossing a unit area. In any case, in applying the target theory, it is always necessary that the hit process should be clearly defined; a necessity which, as shown by later developments (Timoféeff-Ressovsky and Zimmer, 1947), has been often very helpful for further analysis.

A very important application of the target theory was made a few years later (Holweck and Lacassagne, 1930). Under the name of statistical ultramicrometry, a process was suggested of applying techniques of irradiation to determine the size of biological objects or structures, on the assumption that the targets calculated from experiments with irradiation in general corresponded to biological structures or functional units possibly too small to be measured in other ways. It must be admitted that these hypotheses of statistical ultramicrometry assumed implicitly that each hit on a target is followed by the observed effect with unit probability: but nothing is known *a priori* about this probability, and it is difficult to determine.

The hit theory thus appears to offer an explanation of the radiobiological dose-effect curve, which had seemed at first sight so difficult to understand. Beyond that, the target theory opens the way to understanding why irradiation is so efficient in inducing biological effects. For, if these effects result from transfer of energy to small targets, and not from release of energy into the whole bulk of the material, it is easy to understand the difference between the action of radiation and of heat. Because of the statistical nature of the absorption of radiation, introduction of small increments of energy into the material as a whole could mean that small targets receive relatively large amounts. This conception is well expressed by the word "point-heat" coined by Dessauer. Obviously, the question should be raised as to what kind of event can result from this localized release of energy. The idea at first associated with point-heat was local denaturation of protein, whereas other authors regarded chemical reactions induced by local energy release as more likely.

3. THE "GREEN PAMPHLET" OR "DREIMÄNNERWERK"

In order to apply the ideas outlined in the preceding section to the process of radiation-induced mutation, the already existing experimental results, mainly in Drosophila, had to be analyzed and extended. In the course of about two years, Timoféeff-Ressovsky, Zimmer and their collaborators succeeded in filling in several gaps in the understanding of the effects of various radiations other than ordinary X rays. The problems to be solved were concerned mainly with suitable sources of radiations and with accurate dosimetry. There is no need to describe this work in any detail here, though it may be pointed out that our use of 1 gm of radium as the source was something quite unusual in radiobiology, and that an exact evaluation of the energy absorbed by Drosophila from a field of gamma-rays had not been attempted before.

At about the time these studies reached completion, Delbrück became interested in our line of work: however hard I try, I cannot remember exactly how the contact was established, but I do remember vividly the discussions that followed. Two or three times a week we met, mostly in Timoféeff-Rossovsky's home in Berlin, where we talked, usually for ten hours or more without any break, taking some food during the session. There is no way of judging who learned most by this exchange of ideas, knowledge and experience, but it is a fact that after some months Delbrück was so deeply interested in quantitative biology, and particularly in genetics, that he stayed in this field permanently.

As an outcome of these discussions, a joint paper had been completed "Über die Natur der Genmutation und der Genstruktur" (N. W. Timoféeff-Ressovsky, K. G. Zimmer, and M. Delbrück, 1935) which was published in the *Nachrichten der Gesellschaft der Wissenschaften zu Göttingen* in the form of a little pamphlet with a bright green cover. Consequently, its friends and its critics used to refer to it as the "Green Pamphlet" or, somewhat deprecatingly, as the "Dreimännerwerk" ("Three-men-paper"): team work was not very usual in Germany thirty years ago, and inter-disciplinary team work appeared rather strange to some scientists. Nevertheless, the paper met with considerable interest and became widely known in many countries. If the main idea of the work can be described most succinctly by the words "to develop a 'quantum mechanical' model of the gene" (Stent, 1963), its later and more important sequelae impressed a geneticist of our days as follows "... in the years immediately preceding World War II, something quite new happened: the introduction of ideas (not techniques) from the realm of physics into the realm of genetics, particularly as applied to the problems of size, mutability, and self-replication of genes. ... Though this first application of physical ideas to a particular set of problems did not work out too well, the whole outlook in theoretical genetics has since been perfused with a physical flavour. The debt of genetics to physics, and to physical chemistry, for ideas began to be substantial then ..." (Pontecorvo, 1958).

At this point we might as well remember that I myself entered the field rather by the complementary approach, i.e., aiming to find out how radiations bring about biological effects. For this facet of the general problem (Zimmer, 1961) a recent appraisal of the "Green Pamphlet" and of its late effects is available too: "The 'hit' and 'target' theories were first brought into prominence in the late 20's ... The important development of this concept really has come through the publications of three investigators: Timoféeff-Ressovsky; Zimmer ...; and Delbrück. ... It is unfortunate that the 'hit' and 'target' theories have been so much neglected in the last few years. Both are very useful and helpful for interpreting radiation effects. ... They have not, however, always proved to be the most useful, especially with the entrance of biochemical approaches to modern radiation biology." (Hollaender, 1961).

Obviously, the "Green Pamphlet" is considered by some to have served a dual and useful purpose by initiating a new line of research in genetics and by stimulating others to apply similar ways of reasoning to radiobiology. It may be of interest, therefore, to mention some more recent results closely related to the subject matter of the "Green Pamphlet" and exemplifying what pitfalls these borderline fields hold in store for us.

4. SOME LATER DEVELOPMENTS

Using the terminology of the "hit" and "target" theories, as given in Section 2, the results forming the basis of the "Green Pamphlet" can be stated as follows: (i) The fraction of sex-linked lethal mutations in an irradiated population of Drosophila rises with the dose D of X rays according to the equation $N^*/N_0 = 1 - \exp(-vD)$, thus indicating a one-hit-process. (ii) The formal volume v of the target, as calculated from the same equation, is (within certain limits) independent of the spatial density of ionization (linear energy transfer), if the doses D are counted in numbers of ionizations per unit volume of Drosophila. Consequently, one ionization within the formal target may be considered a hit. (iii) Taking into consideration additional data on temperature dependence of radiation-induced, as well as of spontaneous mutation, a "quantum-jump" may be regarded as the physical process produced by a hit in a target and leading to mutation.

There is no reason to discuss (iii) in any detail here, but (i) and (ii) seemed certainly well established in 1935. Later on, further experiments lent additional support. In fact, the deviations of the target volumes v shown in Table I from the weighted mean value of $\bar{v} = 1.77 \cdot 10^{-17}$ cm^3 are so small that the data form one of the most carefully tested cases of a one-hit curve in radiobiology. Nevertheless, as time passed I became worried about the approximation inherent in this reasoning: the complete neglect of a possible biological variability. At first there was no sign of its existence in the material under investigation, but theoretical analyses showed that hit-curves can be badly distorted by a quite moderate variability in target volume, hit number, or multiplicity of targets (Zimmer, 1941). Some years later (in fact, incited by unpublished experiments on the action of X rays on the eggs of some water-snail whose name I have forgotten) I investigated graphically the possibility that approximate single-hit curves could arise through superposition of multi-hit curves. Thence it appeared that, based on different, quite plausible assumptions, curves can be obtained which wrap sinously round exact single-hit curves, within the limits of the accuracy obtainable in radiobiological experiments (Zimmer, 1950; and unpublished). About a decade later a really comprehensive investigation of these possibilities was carried out at our suggestion (Dittrich, 1960). An instructive case of deception by an apparent single-hit curve is shown in Fig. 2.

Table 1

FORMAL TARGET VOLUMES FOR INDUCTION OF SEX-LINKED RECESSIVE LETHALS IN *DROSOPHILA MELANOGASTER*, AS CALCULATED FROM EXPERIMENTS BY TIMOFÉEFF-RESSOVSKY, ZIMMER ET AL. (ZIMMER, 1943).

Dose[1] D in ion pairs per cm³	$N/N_0 = 1 - N^*/N_0$	$v = -\frac{\ln N/N_0}{D}$	N_0	vN_0	$\bar{v} = \frac{\Sigma v_i N_{0i}}{\Sigma N_{0i}}$
		Radium-β rays			
$2.33 \cdot 10^{15}$	0.9621	$1.67 \cdot 10^{-17}$	1872	$3.13 \cdot 10^{-14}$	
$4.67 \cdot 10^{15}$	0.9082	$2.06 \cdot 10^{-17}$	1531	$3.15 \cdot 10^{-14}$	
$7.24 \cdot 10^{15}$	0.8847	$1.68 \cdot 10^{-17}$	1214	$2.04 \cdot 10^{-14}$	
$9.33 \cdot 10^{15}$	0.8512	$1.73 \cdot 10^{-17}$	1057	$1.83 \cdot 10^{-14}$	$1.78 \cdot 10^{-17}$ cm³
		Radium-γ rays			
$2.17 \cdot 10^{15}$	0.9645	$1.66 \cdot 10^{-17}$	1642	$2.72 \cdot 10^{-14}$	
$4.34 \cdot 10^{15}$	0.9188	$1.96 \cdot 10^{-17}$	1293	$2.53 \cdot 10^{-14}$	
$7.24 \cdot 10^{15}$	0.8800	$1.77 \cdot 10^{-17}$	1184	$2.09 \cdot 10^{-14}$	
$8.69 \cdot 10^{15}$	0.8653	$1.67 \cdot 10^{-17}$	822	$1.37 \cdot 10^{-14}$	$1.76 \cdot 10^{-17}$ cm³
		X rays, 160 kV			
$0.97 \cdot 10^{15}$	0.9828	$1.76 \cdot 10^{-17}$	3082	$5.43 \cdot 10^{-14}$	
$1.93 \cdot 10^{15}$	0.9669	$1.76 \cdot 10^{-17}$	5020	$8.83 \cdot 10^{-14}$	
$3.86 \cdot 10^{15}$	0.9375	$1.68 \cdot 10^{-17}$	3948	$6.65 \cdot 10^{-14}$	
$5.79 \cdot 10^{15}$	0.8966	$1.88 \cdot 10^{-17}$	3504	$6.66 \cdot 10^{-14}$	
$7.82 \cdot 10^{15}$	0.8739	$1.75 \cdot 10^{-17}$	3107	$5.43 \cdot 10^{-14}$	$1.77 \cdot 10^{-17}$ cm³
		X rays, 70 kV			
$1.21 \cdot 10^{15}$	0.9793	$1.74 \cdot 10^{-17}$	9346	$16.3 \cdot 10^{-14}$	
$2.42 \cdot 10^{15}$	0.9575	$1.78 \cdot 10^{-17}$	16467	$29.3 \cdot 10^{-14}$	
$4.42 \cdot 10^{15}$	0.9185	$1.92 \cdot 10^{-17}$	3466	$6.65 \cdot 10^{-14}$	
$4.73 \cdot 10^{15}$	0.9141	$1.86 \cdot 10^{-17}$	11738	$21.9 \cdot 10^{-14}$	
$6.03 \cdot 10^{15}$	0.8815	$2.09 \cdot 10^{-17}$	2064	$4.32 \cdot 10^{-14}$	
$7.23 \cdot 10^{15}$	0.8768	$1.81 \cdot 10^{-17}$	6442	$11.7 \cdot 10^{-14}$	
$9.65 \cdot 10^{15}$	0.8412	$1.79 \cdot 10^{-17}$	9116	$16.3 \cdot 10^{-14}$	$1.81 \cdot 10^{-17}$ cm³
		X rays, 10 kV			
$1.75 \cdot 10^{15}$	0.9698	$1.71 \cdot 10^{-17}$	3338	$5.71 \cdot 10^{-14}$	
$2.42 \cdot 10^{15}$	0.9588	$1.74 \cdot 10^{-17}$	2731	$4.75 \cdot 10^{-14}$	
$3.51 \cdot 10^{15}$	0.9395	$1.76 \cdot 10^{-17}$	2124	$3.75 \cdot 10^{-14}$	
$4.83 \cdot 10^{15}$	0.9201	$1.72 \cdot 10^{-17}$	1816	$3.13 \cdot 10^{-14}$	
$7.00 \cdot 10^{15}$	0.8869	$1.71 \cdot 10^{-17}$	1641	$2.82 \cdot 10^{-14}$	$1.73 \cdot 10^{-17}$ cm³

1. Assuming the production of $1.61 \cdot 10^{12}$ ion pairs per cm³ of Drosophila-tissue and per R of X rays, β rays and γ rays.

In the meantime, the influence of the stage of Drosophila germ cells on their X-ray induced mutability became more clearly recognized. The usual way to investigate this phenomenon had been to work out a so-called "brood pattern" giving the rate of mutation for germ cells of various stages after irradiation with a given dosage of radiation. Comparing such brood patterns obtained at various doses made the single-hit curve described above appear quite unbelievable (Fig. 3). In order to elucidate the meaning of this apparent contradiction, the tiresome task was undertaken in my present laboratory to obtain statistically significant dose-effect curves for various stages of germ cells (Traut, 1962, 1963). An example of the results is given in Fig. 4. Here, it must be emphasized that the strange form of the curves

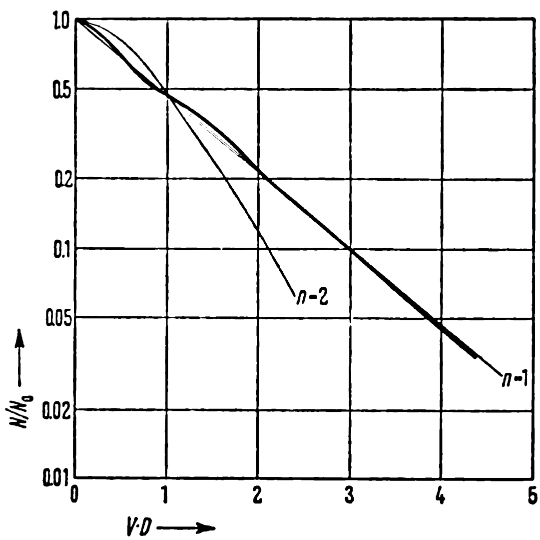


FIGURE 2. **Approximate agreement of a single-hit curve with a two-hit mixed curve formed by super-position of 4 two-hit curves with differently sized targets (Dittrich, 1960).**

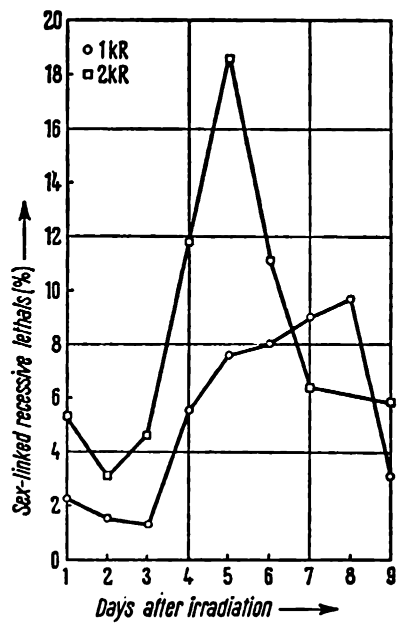


FIGURE 3. The dependence of radiation-induced lethal rate on stage sensitivity after irradiation of 3-4-day-old B-males; 9 one-day broods. Spontaneous rate subtracted (Traut, 1963).

is significant, as shown by careful statistical analysis using an electronic computer. Nevertheless, summing up arithmetically all the mutations obtained in the various broods for given doses resulted in a dose-effect curve closely approximating the single-hit curve (Fig. 5) which, thirty years ago, formed one of the starting points of the "Green Pamphlet." Complete agreement cannot be expected, as arithmetic summation is, of course, not identical with neglecting stage-dependence of mutability, which may be considered as a process of "biologic summation." Thus, the old single-hit curve turned out to be quite reproducible and to hold for all practical purposes (such as problems of protection from radiation damage). But it became clear also that though the dose-effect relation of mutation induction has the form of a single-hit curve, it certainly does not have the meaning of a single hit.

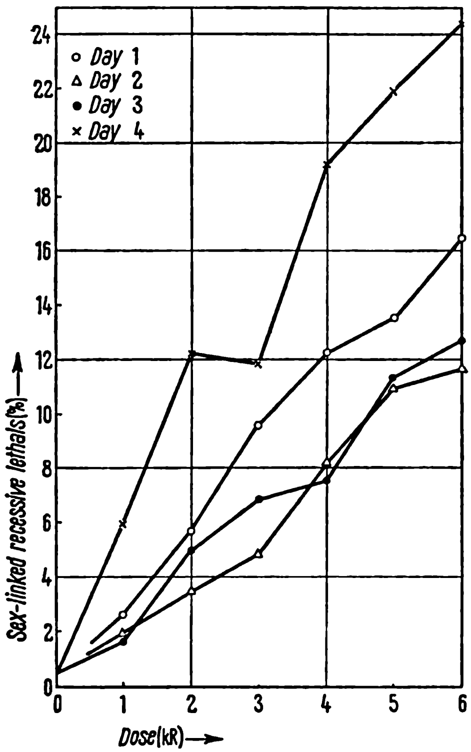


FIGURE 4. Dose effect curves for lethals induced in stages with different sensitivity. 3-4-day-old B-males were irradiated (Traut, 1963).

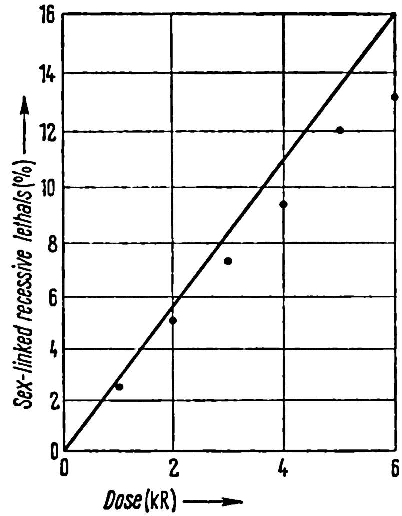


FIGURE 5. The solution to the apparent contradiction. • : mean frequencies of sex-linked recessive lethals integrated arithmetically over the first four days after irradiation (Traut, 1963). ——— : dose-effect curve as used for the "Green Pamphlet." This curve was obtained neglecting stage dependency of mutability i.e. by "integrating biologically" over the first days after irradiation (Timoféeff-Ressovsky, Zimmer, and Delbrück, 1935). Abscissa linear, ordinate logarithmic.

This result removes one of the foundation-stones of the "Green Pamphlet." Strangely enough, that does not seem to matter any more, for two reasons: (i) the concept of the gene and modern trends in genetic research as well as in radiation biology have changed considerably during thirty years, as will undoubtedly become evident from the subsequent papers in this book, and (ii) the "Green Pamphlet" has served a useful purpose by helping to initiate exactly these modern trends.

REFERENCES

BLAU, M. and K. ALTENBURGER. 1922. Über einige Wirkungen von Strahlen II. Z. Physik, *12*: 315.

CROWTHER, J. A. 1924. Some considerations relative to the action of X-rays on tissue cells. Proc. Roy. Soc. (London), *B 96*: 207.

———1926. The action of X-rays on Colpidium colpoda. Proc. Roy. Soc. (London), *B 100*: 390.

———1927. A theory of the action of X-rays on living cells. Proc. Camb. Phil. Soc., *23*: 284.

DESSAUER, F. 1922. Über einige Wirkungen von Strahlen I. Z. Physik, *12*: 38.

DITTRICH, W. 1960. Treffermischkurven. Z. Naturforschg. *15b*: 261.

HOLLAENDER, A. 1961. Hit and target theories. Science, *134*: 1233.

HOLWECK, F., and A. LACASSAGNE. 1930. Action sur les levures des rayons X mous (K du fer). C. R. Soc. Biol., *103*: 60.

PONTECORVO, G. 1958. Trends in genetic analysis. Columbia University Press, New York.

STAHL, F. W. 1959. Radiobiology of bacteriophage, p. 353. *In* F. M. Burnet and W. M. Stanley [Ed.], The Viruses. Vol. II. Academic Press, New York.

STENT, G. S. 1963. Molecular Biology of Bacterial Viruses. W. H. Freeman and Company, San Francisco and London.

TIMOFÉEFF-RESSOVSKY, N. W. and K. G. ZIMMER. 1947. Biophysik I. Das Trefferprinzip in der Biologie. S. Hirzel, Leipzig.

TIMOFÉEFF-RESSOVSKY, N. W., K. G. ZIMMER and M. DELBRÜCK. 1935. Über die Natur der Genmutation und der Genstruktur. Nachr. Ges. Wiss. Göttingen, VI N.F., *1*, 189.

TRAUT, H. 1962. Habilitationsschrift, University of Heidelberg.

———1963. Dose-dependence of the frequency of radiation-induced recessive sex-linked lethals in *Drosophila melanogaster*, with special consideration of the stage sensitivity of the irradiated germ cells, p. 359. *In* F. H. Sobels [Ed.], Repair from Genetic Radiation Damage. Pergamon Press, London.

ZIMMER, K. G. 1941. Zur Berücksichtigung der biologischen Variabilität bei der Treffertheorie der biologischen Strahlenwirkung. Biol. Zbl., *61*: 208.

———1943. Statistische Ultramikrometrie mit Röntgen-, Alpha- und Neutronenstrahlung. Physikal. Z., *44*: 233.

———1950. Otchet. Fondy Ural. Fil. A. N. SSSR, Sverdlovsk.

———1961. Studies on Quantitative Radiation Biology. Oliver and Boyd, Edinburgh and London. 124 p.