DEVELOPMENTAL GENETICS AND LETHAL FACTORS

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TRANSLATOR'S PREFACE

Every translation is of necessity a compromise between the meaning contained in the first language and the idiom of the second. When translating a scientific work, it is generally agreed that the emphasis should be shifted in favour of exactness, even though this may mean at times that a certain foreign flavour cannot be avoided. In the present instance in particular it was the author's wish that some scientific terms should be international rather than vary in different languages. Accordingly, this translation contains a few terms which may not be familiar to English readers, such as "subvital factors" for those Mendelian factors which kill up to one half of their carriers, and "phene", meaning a characteristic produced by a gene. It is hoped, however, that the explanations given in the text and in the glossary will render these ingredients sufficiently digestible.

My task as translator was greatly facilitated by a number of people, whose help I gratefully acknowledge. I have received much valuable advice from Professor H. Grüneberg, F.R.S., Dr. H. Kalmus, Mr. J. Maynard Smith and Dr. J. H. Renwick; and I owe a special debt of gratitude to Dr. Gillian M. Truslove, who read the entire typescript and suggested many improvements.

SPELLING (AUTHOR'S NOTE)

In English "lethal" is spelt with a "th", whereas the German and French languages have the more correctly derived spelling, "letal". The term is derived from the Latin "letum" (death) and not from the Greek "Lethe" (river of the underworld). Owing to this difference in spelling, the names of lethal genes introduced by authors publishing in English contain a "th" (e.g. *lethal giant larvae*), whereas genetic factors which first appeared in German or the Romance languages have the correct etymological spelling "t" (e.g. *letal-translucida*).

PREFACE

Lethal factors occupy a special position in biological research. Since a high proportion of the mutations in all organisms are lethals, they contribute a large body of material which needs to be incorporated into any general theory of the gene and its mutability. In addition, the Mendelian lethal factors are a striking illustration of the extensive rôle played by the genetic material of the chromosomes in the fundamental processes of development. Finally, each newly arisen lethal mutant sets up a highly specific experiment, shedding light on the functional relationships between individual mutational states and the processes leading to the formation of characters.

The purpose of this book is to provide a contribution to the general and special pathology of development, based on the study of lethal factors. Such a study of pathological processes should also result in a better understanding of the gene physiological basis of normal development. The book is based equally on the results obtained from research in genetics and from experimental embryology. I have tried to treat problems in their context without, however, exhaustively incorporating the complete literature. I therefore beg the indulgence of any author whose work, though related to my topic, has not been referred to in my text. Any one person can have first-hand knowledge only of a limited section of modern research, and I am fully aware that in attempting to encompass a much wider field of general biology some errors are bound to have crept in. Since I have no experience in clinical medicine, I have included only a few selected examples from human genetics and pathology. On the other hand, a large number of examples taken from zoological research have been discussed in detail, and these may perhaps serve as models for the interpretation of similar abnormalities in man which, in any case, are much more difficult to analyse. The lethal factors of plants are likewise represented by a few examples only. This is partly due to the fact that as a zoologist I am less familiar with the material in question; in addition, however, the experimental embryology of plants is not yet sufficiently developed to permit causal interpretations of hereditary abnormalities and lethality. I have also refrained from entering into a discussion of cancer problems, even though there are many points of contact between the developmental action of lethal factors and malignant growths; but the genetical and developmental aspects of tumour formation have already found ample consideration in a large number of books and monographs.

Although it was not my aim to write an elementary text-book, I have tried

to present the material in such a way that it could be understood by students familiar with the fundamentals of genetics, experimental embryology, histology and cytology. Accordingly, the most important concepts and terms, many of which will be familiar only to specialists, are explained either in the introductory chapter or in the glossary at the end of the book. In the nomenclature of mutants and of gene symbols, I have followed the current practice which has been developed largely by the *Drosophila* geneticists.

All figures taken from the literature have been redrawn in order to achieve a uniform style. Most of the drawings were carried out by my son, Beat Hadorn, to whom I express my sincere thanks.

In the preface to the German edition, I had the pleasure of acknowledging the collaboration of my colleagues, Professor A. Kühn (Tübingen) and Professor H. R. Schinz (Zürich); of Drs. H. Gloor (Leiden), G. Anders, P. S. Chen and H. Burla; of my secretaries, Miss I. Biefer and Miss Z. Blankart; and of Mr. E. Freiberg, who carried out most of the graphic work. I also acknowledge the generous help given to me by the publisher, Dr. B. Hauff, of Georg Thieme, Stuttgart. My own experimental work on lethal factors was supported by grants from the Rockefeller Foundation, the Georges and Antoine Claraz Schenkung and the Karl Hescheler-Stiftung.

The present English text is largely a direct translation of the German edition, *Letalfaktoren in ihrer Bedeutung für Erbpathologie und Genphysiologie der Entwicklung*. This book appeared in 1955 and was well received. For the new edition it was impossible without rewriting the book entirely to include more than a small proportion of the vast new literature which has appeared since then. Even so, the new additions are based on about 100 recent publications, which have been added to the bibliography.

I am most grateful to the translator, Dr. Ursula Mittwoch, for the assiduous care with which she carried out this work.

In dedicating this book to Professor Fritz Baltzer (Berne), I wish to express my sincere gratitude to my teacher and friend, under whose inspiring guidance I first came in contact with the problems of developmental genetics and experimental embryology.

CONTENTS

CHAPTER I

SYSTEMATIC SURVEY. CONCEPTS AND TERMS

1. Definition

For our purpose lethal factors may be defined as Mendelian units which cause the death of an organism prior to the reproductive stage (Hadorn 1949a). This definition is justified, even though, as we shall see later, there is no clear line of demarcation between lethal and non-lethal factors. It is important, however, to differentiate between hereditary factors which cause death before the age of reproduction and those which act later. We have restricted the concept of lethal factors to the first class because, although development may be said to continue throughout the entire life of an organism, what is decisive from a genetical point of view is whether an individual survives to reproduce. For example, hereditary diabetes may be a cause of death, but since the onset is usually during adult life, the hereditary factors involved can be transmitted to future generations. By contrast, those factors to which we wish to confine the term "lethal factors" are causes of a "developmental death" at an early stage, so that with the death of the organism the mutant chromosomes are lost. In accordance with our definition, hereditary factors which bring about pathological processes in adult organisms will only be discussed occasionally for purposes of comparison.

2. Lethal factors or lethal genes?

Lethal factors are due to changes in the genic substance of the chromosomes. In the mode of their origin as well as in their hereditary transmission lethal factors resemble ordinary non-lethal mutant genes. However, not all hereditary factors which obey Mendelian laws should be described as genes, and this applies particularly to lethal factors. A large number of these are due to a loss of more or less extensive pieces of chromosomes (p. 69), and such deficiencies are also inherited in a Mendelian manner. Other lethal effects are caused by an unbalanced increase of chromosomal material (duplications, p. 81), and others again may be regarded as position effects, which arise by rearrangement of the chromosomes through an inversion (p. 84) or translocation (p. 85). It is true that single gene mutations, i.e. point mutations, can give rise to lethal factors. For this there are two sources of evidence; (1) in a large number of intensively investigated lethal loci of *Drosophila*, it has

not been possible to demonstrate any microscopically visible defects in the salivary-gland chromosomes (p. 72); (2) in several cases back-mutations have occurred, in which the lethal factors have reverted to the normal genes. It is, nevertheless, generally impossible to determine the proportion of genuine point mutations in the total of lethal factors. In these circumstances it is preferable to avoid the term "lethal gene" and to use the more general term "lethal factor".

3. Degrees of penetrance

Lethal factors sensu stricto are characterised by a penetrance of 100%. This means that all individuals carrying the lethal factor in an effective dose will die during their development. Numerous instances are known, however, where an occasional individual overcomes the crisis in its development, and henceforth continues to progress in spite of its lethal constitution. Such exceptional individuals are called "escapers" (Hadorn, 1945a).

Sometimes the penetrance of a lethal factor may be so much reduced that "escapers" appear regularly and in definite proportions. Here, the term "*semi-lethal factor*" (p. 112) should be applied. In accordance with Dobzhansky (1939), Ives (1941) and others, we arbitrarily limit the term semi-lethal to those factors which cause the death of at least 50% of the mutant genotypes. Usually the viable individuals form only a small percentage (Figs. 35 and 36, p. 115).

Those hereditary factors in which the penetrance of the lethal action is even less, we propose to call "*subvital factors*" (Hadorn 1948a). Here the proportion of survivors should be at least 50%, although there must be a statistically significant shortage compared with the normal expectation of survival. The subvitals merge into those mutant genes which do not decrease viability compared with the normal or wild type. It should be pointed out that the differentiation between lethal factors in the strict sense, semi-lethals and subvitals is up to a point dependent on the internal and external environment (p. 118), and one should therefore regard these terms as useful divisions in the classification of penetrance rather than as completely distinct groups.

4. Classification according to the phase of action

The majority of the more thoroughly investigated lethal factors have a specific phase of action (p. 149), the lethal crisis arising at a certain stage of development which is characteristic for the factor. Lethal factors may thus be classified according to their phase of lethal action. Thus in insects we have "*embryonic, larval, pupal* and *early imaginal lethal factors*," while in birds and mammals there are "*embryonic, post-embryonic* and *juvenile lethal factors*". Lethal factors in birds and mammals which do not become active until after hatching or birth have sometimes been distinguished as "*sublethal factors*". This differentiation, however, is not based on any physiological processes

during development, for there are many genotypes in birds and mammals which act as "*boundary lethals*", death occurring either towards the end of the embryonic stage or immediately after birth or hatching. Moreover, the term "sub-lethal" was often used in the wrong context, being confused with "semi-lethal" or "subvital". It seems advisable therefore to discontinue the use of the term "sublethal", which in any case is etymologically unsound.

Up to now we have considered those lethal factors which act in the zygote, i.e. the diploid phase. Apart from these "*zygotic lethal factors*", however, others are known which manifest themselves in the haploid phase. These have been called "*gametic lethal factors*" (Mohr 1924) or "*gonadic lethal factors* (Renner 1924). We propose to call this category "*haplophasic lethal factors*". This is to emphasise that the mutant loci act in a cell containing a single set of chromosomes. The new term "haplophasic" is preferable to "gametic" or "gonadic", since it also covers organisms with a well-developed haploid phase, in which lethal factors do not only affect the germ cells but also the entire soma of the haplont. On the other hand, we prefer the term "zygotic" to "diplophasic" in order to cover triploid and polyploid organisms.

5. Location on chromosomes

Like other Mendelian units, lethal factors may be divided into "*sex-linked*" and "*autosomal*", depending on their location in the chromosomes. In all organisms which have been investigated in this respect, the autosomes taken together contain more mutable genes than the heterosomes. For this reason, the frequency of autosomal lethal factors may be expected to be higher than that of sex-linked lethals. The reason for the large proportion of known sex-linked lethals in some organisms, such as *Drosophila*, lies in the very simple technique which is available for demonstrating this type of mutant. As will be shown on p. 13, lethal factors located in the X-chromosome are recognised merely by an altered sex ratio, and in fact sex-linked lethals were first demonstrated by Morgan (1912) in *Drosophila* because of a shortage of surviving males. Moreover, if recessive factors situated in the differential part of the X-chromosomes cause any visible abnormality, every hemizygous individual of the heterogametic sex will show it. This is one reason for the large number of sex-linked genes which are known in man.

6. Dominance and recessivity

Autosomal lethal factors may be present in the zygote generation either in the *homozygous* condition, i.e. in double dose, or in the *heterozygous* conditions, i.e. in single dose in conjunction with a "normal allele" (p. 299). The same applies to sex-linked factors in the homogametic sex. In the heterogametic sex, however, those factors which are situated on the differential segment of the sex chromosomes can only be present in the *hemizygous* condition, since there is no homologous chromosome segment. The following

classes of lethal factors may be distinguished according to their mode of action in heterozygous individuals:

(*a*) "*Dominant lethal factors.*" – A single dose of these is sufficient to bring about the lethal effect, the normal hereditary substance in the homologous chromosome being unable to secure viability. Since every individual receiving a fully penetrant, dominant lethal factor dies, it is obvious that these factors cannot be perpetuated by breeding, and special methods are therefore necessary for their demonstration (p. 90). If we represent the normal allele by the symbol + and the mutation by *L*, the equation of the zygotic effect of a dominant lethal factor becomes $L/+ =$ lethal.

(*b*) *Dominant factor with recessive lethal effect.* – Many mutant gene loci are known which in conjunction with their normal allele effect non-lethal visible changes. Such factors produce a lethal effect only if they are present in the homozygous or hemizygous condition (p. 18). The action of these mutants may be presented as follows:

$+/+$ = normal.
$+/l$ = changed and viable.
l/l or $l/$ lethal.

(*c*) *Recessive lethal factors without dominant effect.* – Here the heterozygotes show no noticeable effect, since the normal + allele is dominant. Phenotypically, therefore, the presence of the lethal factor can only be seen in homozygotes or hemizygotes. Using symbols the action of the lethal factor becomes:

$+/+ = +/l =$ viable and unchanged.
$l/l \quad = l/ \quad =$ lethal.

The question whether the heterozygotes ($l/+$) may manifest slight effects of the lethal factor will be discussed on p. 138.

7. Conditional and unconditional lethal factors

Every hereditary characteristic arises through the interaction between a major mutant factor and a large number of other developmental factors, and in order to gain an insight into the physiology of gene action we must first disentangle these components.

If we are unable to influence the penetrance or expressivity of a lethal factor by experimental means, we call it, at least provisionally, an "*unconditional lethal factor*". Numerous Mendelian factors are known, however, which bring about death only in certain circumstances, while in other developmental conditions they either do not manifest themselves at all or their penetrance or expressivity may be reduced. The action of such "*conditional lethal factors*" may be affected by the following:

(*a*) Variation in the genotypic milieu which is determined by the entire gene complement (p. 120).

(*b*) Variation in the external environment, which is conditioned by environmental factors, such as nutrition, population density, etc. (p. 118).

A special kind of lethal factor causes developmental failure in one sex only, although the abnormal genetic constitution is the same in both sexes. These "*sex-limited lethal factors*" should not be confused with sex-linked factors. In sex-linked lethal factors the differential mortality of the sexes is due to the mechanism of segregation of the sex chromosomes, while in sex-limited lethal factors it is a phenomenon of developmental physiology.

8. Lethal factors and sterility genes

If a gene causes sterility, the genetical effects on the population will be the same as those of lethal factors. If the mutant is dominant, it will not be transmitted to further generations. Mutations from $+\rightarrow L$, or from $+\rightarrow St$ (Sterility factor) are immediately eliminated. Selection will also operate against recessive gene changes ($+\rightarrow l$ or $+\rightarrow st$), since the homozygotes *l*/*l* or *st*/*st* leave no progeny.

Lethal factors and sterility genes differ, however, in their physiological effect on development (at least in the zygote generation). A lethal factor interrupts the development of an organism before it has become sexually mature. A sterility factor, on the other hand, merely interferes with reproduction, either by preventing functional sex cells from being formed or by changing the morphology or physiology of an organism in such a way that an effective sexual process cannot take place. The development of sterile genotypes does not endanger the life of the individual. From the point of view of developmental physiology, any defects or disturbances in the sexual organs must be regarded in the same way as, say, a wing anomaly in a fertile mutant. Sterility factors are in a class of their own merely because they effect a system of organs which is necessary for reproduction.

In the haploid phase it may be more difficult to distinguish between sterility and lethal factors. In plants with highly developed gametophytes the consequences of mutation hardly differ from those in the diploid phase. Thus, in a moss, the effect of a lethal factor in the haplophase would be to prevent the development of the soma. A sterility factor, on the other hand, would only damage the sexual organs or the gametes. When the haplophase becomes progressively reduced, however, as in the flowering plants, the difference between haplophasic lethal factors and sterility genes becomes less obvious, while it disappears altogether in the metazoa, where the two phenomena have become one.

9. Other terms

Although some further concepts will be explained in the text as they occur, it is not the purpose of this book to provide explanations of all the technical terms used in genetics, cytology and developmental physiology. The reader may refer to the various text-books which contain extensive glossaries, e.g.