Teach yourself genetics / by R. J. Berry.

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Teach Yourself

Genetics

Teach Yourself Genetics

It is the business of genetics to explain why dogs have puppies and not kittens, and to describe in what sense we inherit the characteristics of our parents. The word genetics is derived from a Greek verb meaning "to produce" which comes from a noun meaning "a race" or "a family". The dictionary defines genetics as "that part of biological science which is concerned with the study of heredity and variation". This book introduces the principal ideas and language of genetics, and sets forth some of the more interesting results in as non-mathematical a way as possible.

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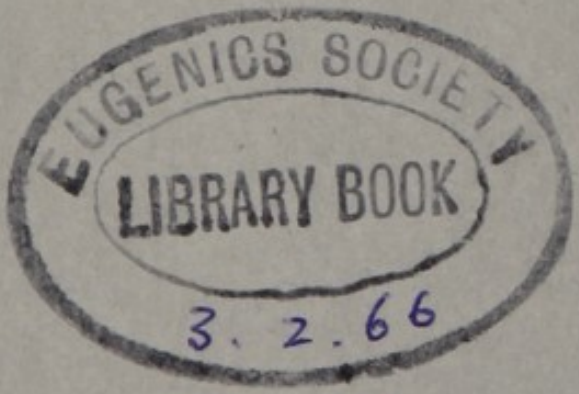

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TEACH YOURSELF

GENETICS

by

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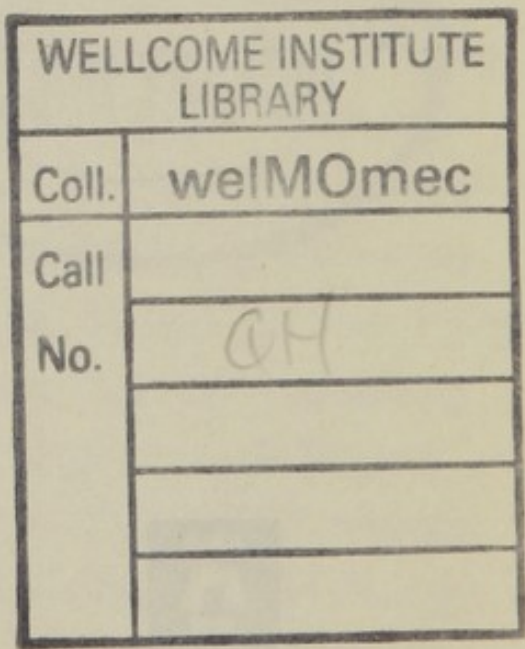
THE ENGLISH UNIVERSITIES PRESS LTD
ST. PAUL'S HOUSE, WARWICK LANE
LONDON E.C.4

First printed 1965



Printed in Great Britain for the English Universities Press Limited
by Elliott Bros. & Yeoman Limited, Speke, Liverpool

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"What a miracle the whole thing is, that one should be like one's father, only different. I must find out about these marvellous genes. But it seems that genes are particles in the chromosomes, which are structures in the cell nuclei; there are also hormones and zygotes and gametes, to say nothing of molecules and proteins. In the end I see them all as a lot of very small dots, all subtly different in some way that escapes me. I stare at a diagram under which it says, 'Equal numbers of non-crossovers, single crossovers on the left, single crossovers on the right, and the double crossover chromatids result. (Redrawn from Sturtevant and Beadle, 1940).'

And slowly, inevitably I get diverted by ludicrous inessentials. Sturtevant, a prim New Englander, in a high rounded collar, looking like those photographs of Woodrow Wilson: and Beadle——well, a beadle, with a pink round face . . . what an extraordinary couple, what were they *doing* in 1940?

I know I should try to understand statements like this: 'Crossing the homozygous *Gram Gram* with *gram gram* will produce 100 per cent. *Gram gram* plants, whereas crossing *Gram gram* with *gram gram* will produce about 50 per cent. *Gram gram* with broad leaves and about 50 per cent. *gram gram* plants with narrow leaves.' (Try reading this aloud). Now now let let me me think think, or Think think . . ."

Paul Jennings—in *The Observer* on *Being Self-uneducated*

FOREWORD

THIS book introduces the principal ideas and language of genetics, and sets forth some of the more interesting results. It does not profess to be a balanced survey of the different aspects of the subject. For example, animal examples have been used more often than plant ones because the anatomy and development of animals are probably more familiar than the anatomy and development of plants. On the other hand, this is not a book on human genetics and human examples have been used only occasionally, although they might be clearer to some than the examples given. Chapters 10, 11 and 12 on population and radiation genetics may be considered disproportionately long; but they are concerned with topics which are themes of interest and common misconception to many people. Those who are irritated or confused by the necessarily cursory presentation of particular facets of the subject should consult the books listed as "suggestions for further reading" (p. 152).

Newcomers to genetics are almost inevitably confused by the terminology. No attempt has been made to circumvent words, and it is to be hoped that the reader will be able to pass on to more advanced works. A short glossary has been included at the end of the text. This is intended solely as an aid to the understanding of the earlier chapters; it is in no way exhaustive.

I am indebted to many friends and colleagues who have commented on parts or all of this book in typescript and made it much more intelligible than it would otherwise have been. My thanks are particularly due to Drs. R. G. Bird, H. B. D. Kettlewell, A. G. Searle, and Professor C. A. B. Smith, and also to Mr A. J. Lee who drew the diagrams.

CHAPTER 1

INTRODUCTION

THE word genetics is derived from a Greek verb meaning "to produce", which is itself from a noun meaning "a race" or "a family". The dictionary defines the science of genetics as "that part of biological science which is concerned with the study of heredity and variation". Heredity is further defined as "tendency of like to beget like", and variation as "departure from a former or normal condition or action or amount, or from a standard or type".

Like begets like is true only to the extent that the offspring of a cat would be a cat, and not a dog or a monkey. It is not true to the extent that the kitten would be exactly like its parents, or one of them, or exactly midway between the two. Parents often have characteristics which are not transmitted to their offspring, and the offspring often have characteristics which are not found in the parents. This fact of like begetting like and its limitations form the field of genetics. The geneticist is concerned with the *reasons* and *mechanisms* of continuing similarities and differences in different kinds of living things.

Variation provides the raw material for the study of heredity, which would not be possible without it. It will be discussed in detail in the later chapters of this book. For the time being it may be taken to mean all sorts of differences between living things in its broadest sense, and differences of detail between organisms of the same kind in its narrowest sense. Differences between dogs and cats would illustrate the broadest sense of the term, and differences between two dogs of the same breed the narrowest sense.

Until the beginning of the present century the commonest view of heredity, taken by biologists and non-biologists alike, was that characteristics of parents were blended or

mixed together in the offspring. Referred to as *blending inheritance*, this idea received apparent support from the work of early plant breeders. They crossed different species of plants and found that the progeny, if any, were usually intermediate in form between the parents. These erroneous views were current when Darwin formulated his theory of evolution (in *The Origin of Species*, 1859). As a result, that part of his theory which deals with the origin and maintenance of variation is the weakest part of his argument (he was aware of the inadequacy of the theory of blending inheritance as an explanation of observed facts, and used it only for want of something better).

The modern science of genetics began with the work of Gregor Johann Mendel (1822—1884), an Austrian monk who lived at the Augustinian monastry at Brünn. He carried out breeding experiments with garden peas, crossing varieties with different heights, flower colour, seed colour etc., and explained the results with hypotheses which have stood before the most ingenious tests that geneticists have been able to devise. This remarkable work was published in 1866 in the proceedings of the local natural history society. It lay neglected in that obscure journal until 1900, when three biologists (De Vries in Holland, Correns in Germany and von Tschermak in Austria) came to similar conclusions independently from their own experiments. This led them to search through published work on inheritance, where they discovered Mendel's original paper, and had to acknowledge him as their forerunner.

In the sixty years since then genetics has progressed far. Only the most important landmarks along the way can be mentioned here. Bateson, in Great Britain, discovered the phenomenon of linkage in 1908; Morgan, in the U.S.A. established the physical basis of heredity in 1919; Muller, also in the U.S.A., succeeded in inducing mutations artificially in 1928; Benzer in America, and Watson, Crick and Pontecorvo in this country, have elucidated much of the fine structure of the gene in recent years. These discoveries

and some of their implications form the subject matter of this book.

Extent of Genetical Knowledge

The limits of our knowledge of genetics will become abundantly clear from a reading of this book. However, some points seem worth making. The first sixty years of research have established the normal methods of transmission of genetical material from one generation to another, or as it is usually called "the physical basis of inheritance". It is also known with a fair degree of certainty what the actual genetical material is, and we are beginning to understand something of its behaviour in life. Inherited characteristics have been found in all organisms from viruses—about which philosophers have never been able to agree whether they are living or not—through bacteria, protista and fungi to higher plants and animals. Over a hundred inherited characters have been described in some organisms (including mouse and man), and we know something about the stability and inter-relationship of these inherited characters. However, it is NOT the business of genetics to attempt to describe all the variations of all organisms in genetical terms, and it would be a waste of time and space to catalogue here the genetical variation of even such a simple form as a bacterium. The pertinent problems of the science are dynamic: how does the genetical material pass on its "information"; how can the inherited characters be altered; how do the constituent parts of the heritable component (the *genotype*) interact and yet function as a unity; and what is the relation of the living organism to its genotype in nature? Answers to these questions are so close to the roots of biological science that they involve the use of virtually all biological techniques. It is largely because of the increasing complexity of the techniques themselves (particularly the mathematical ones) that genetics has appeared to many as a complicated and abstruse science. In fact, the techniques used are to a large extent irrelevant to an understanding of

the subject, and hence the following pages will be devoted to a description of results and conclusions rather than the methods by which such results were obtained.

Methods of Investigation

For valid results to be obtained in genetical work, it is necessary to control either genotype or environment. Classical genetics was, and is, concerned with the crossing of related varieties of organisms under known environmental conditions. In practice, "known environmental conditions" nearly always means the genetical laboratory. This type of investigation, which was effectively the one used by Mendel, has given rise to at least five different lines of research:

1. A study of the physical basis of heredity (*cytogenetics*).
2. The effect of the genotype in development (*physiological* or *developmental genetics*).
3. The influence of the environment on organisms of controlled genotype (*radiation genetics*, much cancer research, etc.).
4. Attempts to simulate natural conditions in the laboratory. These usually involve producing a certain change in the environment of a group of organisms (*population genetics*, and related to that: *eugenics* and selective animal and plant breeding).
5. The behaviour of organisms in nature, where neither the genotype nor the environment can be controlled (*ecological genetics*, etc.).

CHAPTER 2

CELL DIVISION AND ITS GENETICAL CONSEQUENCES

GENETICS is concerned with the transmission (or not) of characteristics from one generation to the next. The proper starting point of our account must therefore be the biological relationship between parent and offspring through the process of reproduction.

2.1 **Reproduction**

Living organisms may reproduce either asexually or sexually. *Asexual reproduction* is essentially a fission of the parent to produce two or more individuals in the place of one. This may involve a division of the whole parent, such as takes place when bacteria and the most simple animals and plants reproduce, or a budding off of some specialized reproductive structure—such as a potato from a potato plant. The inheritance of characteristics through the generations in asexually reproducing organisms cannot be simpler: offspring must have all the traits of their parents and nothing new.

Sexual reproduction is the rule in all organisms with which we are familiar in everyday life (although it may be actively discouraged in plants of horticultural importance, such as apples, potatoes, etc., since only asexual—or vegetative—reproduction ensures uniformity in a crop). It differs from asexual reproduction in involving *fusion* between two parents. Although pairs of the simplest animals and plants can fuse together, in all more complex organisms fusion takes place between two specialized cells called *gametes* (spermatozoa are male gametes, ova are female gametes) to

form a *zygote*. The zygote develops into a new individual with characteristics derived from both parents.

2.2 The structure and contents of cells

The cell is the structural unit of the living body. In the simplest organisms such as bacteria, yeasts, amoebae, etc. the whole body can be regarded as a single cell within which are concentrated all the means for performing the necessary functions of the organism. In more complicated organisms (what we call "higher forms of life"—fish, trees or man) there are millions of cells, many grouped into organs and specialized so as to perform some functions of benefit to the whole organism. This specialization of function usually goes with a change in appearance, so that a liver cell is as easily distinguished from a nerve cell as an oak from a beech. However, in all cells there is a *nucleus* surrounded by *cytoplasm* (although some cells may lose their nucleus. For example, mammalian red blood cells have no nucleus).

The cytoplasm is where the "work" of the cell is carried out. It may be more or less granular depending upon what and how much work is done. The most important granules are the *mitochondria*, concerned with making energy available to the cell, and *ribosomes* where proteins are synthesized. Plant cells have a wall of *cellulose* outside the cytoplasm. Many cells contain, in addition, stored food or structures especially concerned with synthesizing particular compounds. With the very high magnifications made possible by the electron microscope, it is possible to see a complicated system of membranes existing in the cytoplasm, especially at the edge of the cell.

The nucleus is usually a prominent part of any cell; genetically it is the most important. When the cell is not dividing (i.e. when it is in the *interphase state*), the nucleus normally appears as a round body bounded by a *nuclear membrane* of considerable strength. This consists of two layers perforated by very small holes. The inside of the nucleus sometimes appears to be empty, but by using ap-

propriate techniques, it is possible to see parts of the thread-like *chromosomes* which are contained within the nucleus. The chromosomes consist of simple proteins (principally *histones*) associated with coils of the "heredity substance", *desoxyribose nucleic acid* (DNA) in a way not yet fully understood.

The *interphase* nucleus is an unfavourable stage for the study of the chromosomes. When the cell divides, however, the chromosomes are usually revealed quite clearly as a number of thin threads of various shapes and sizes. We may note two characteristics of them: firstly they can be arranged in pairs, one from each pair being derived from each parent. With a few exceptions, the two members of each pair are identical in appearance, forming a *homologous pair*. Secondly, although the number of chromosome pairs varies from one to several hundred, in a given kind (species) of animal or plant, the number of chromosomes is constant (again with a few exceptions) and the chromosome set of every nucleus in the body is identical in normal circumstances.

The details of the structures of the chromosomes can be most easily observed under the microscope during cell division. In the early part of the type of division called *meiosis* (see below) the chromosomes have the appearance of strings of beads. The "beads" are called *chromomeres*, the "string" in between the *chromonema*. At one time it was thought that each chromomere was the physical basis of one *gene* (inherited factor), but this is an over-simplification which is no longer held. Treatment with dyes during interphase reveals that some parts of the chromosomes stain deeply while others do so only faintly or not at all. The former are said to be *heterochromatic*, the latter *euchromatic*. This distinction is not without genetical significance, for most of the known genes of an organism are located in the euchromatic parts. Recent work, however, has shown that the heterochromatic regions are not so genetically inert as they were once supposed to be.

Every chromosome has a *centromere*. This usually appears as a nonstainable constriction situated anywhere along the length of the chromosome except at an end. For any particular chromosome the position of the centromere is constant and two classes of chromosomes may be recognized: *metacentric* ones in which the centromere divides the chromosome into two approximately equal halves, and *acrocentric* ones where the centromere is very close to one end so that one chromosome arm is minute and the other very much longer. The centromere has an essential role in cell division in orientating its chromosome.

Chromosomes have a wide range of size (and this varies considerably during the cell division cycle). However, they are inevitably very small structures: most of the 23 pairs of chromosomes of man are only about 4–6 μ in length (a μ or micron is one thousandth of a millimetre). This smallness means that it is difficult to relate the results of breeding experiments to changes in the chromosomes, except in especially favourable circumstances. One such circumstance occurs in certain cells of some members of the insect order Diptera (midges, mosquitoes, house-flies, etc.), and in particular in cells of the salivary glands of the larvae. The nuclei of these cells contain giant *polytene chromosomes* about 100 times as long as the normal forms. These structures may perhaps be better called worm-like rather than thread-like. They have characteristic patterns of transverse bands (fig. 8) and it is possible to recognize minute structural changes (p. 67) in them. The most thoroughly investigated genetical organism, the fruit fly (*Drosophila melanogaster*) has giant polytene chromosomes, and much of our knowledge of the genetical results of changes in the chromosomes stems from work on this fly.

2.3 **Cell division: mitosis**

The vast number of cells in a sexually reproducing individual are derived by successive divisions from the single celled zygote. The original cell divides into two, the

products into four, they in turn into eight and so on. Under normal circumstances the nucleus of every cell contains exactly the same set of chromosomes as the zygote. The process of division whereby the chromosome complement of a cell comes to be repeated in the daughter cells is called *mitosis*; it is an essentially similar process in all plants and animals, from unicellular algae and protozoa to flowering plants and mammals. Mitosis can be divided, for descriptive purposes, into four stages: *prophase*, *metaphase*, *anaphase* and *telophase* (fig. 1).

Prophase.

In the interphase nucleus the chromosomes are largely invisible. At the beginning of prophase they become visible (in ordinary microscopical preparations), and each is seen to be longitudinally divided into a pair of parallel *chromatids*. Just outside the nucleus in most animals (also in some algae and fungi) is a small, darkly-staining *centrosome*. At the beginning of prophase the centrosome divides and the two halves travel round the nucleus in opposite directions until they are 180° apart. At the same time a system of rays, the *aster* forms round each of the daughter centrosomes. The nuclear membrane disappears at the end of prophase. It may be partially incorporated into the *spindle*, which appears at this time and consists of fibres radiating from the two opposite poles of the cells (marked by the centrosomes in animals).

Metaphase.

Throughout prophase the chromosomes become shorter and thicker. At the beginning of metaphase they arrange themselves on the equator of the spindle midway between the poles.

Anaphase.

The centromere splits longitudinally and the daughter centromeres move up the spindle towards opposite poles, dragging the chromatids (which may now be appropriately called daughter chromosomes) to which they

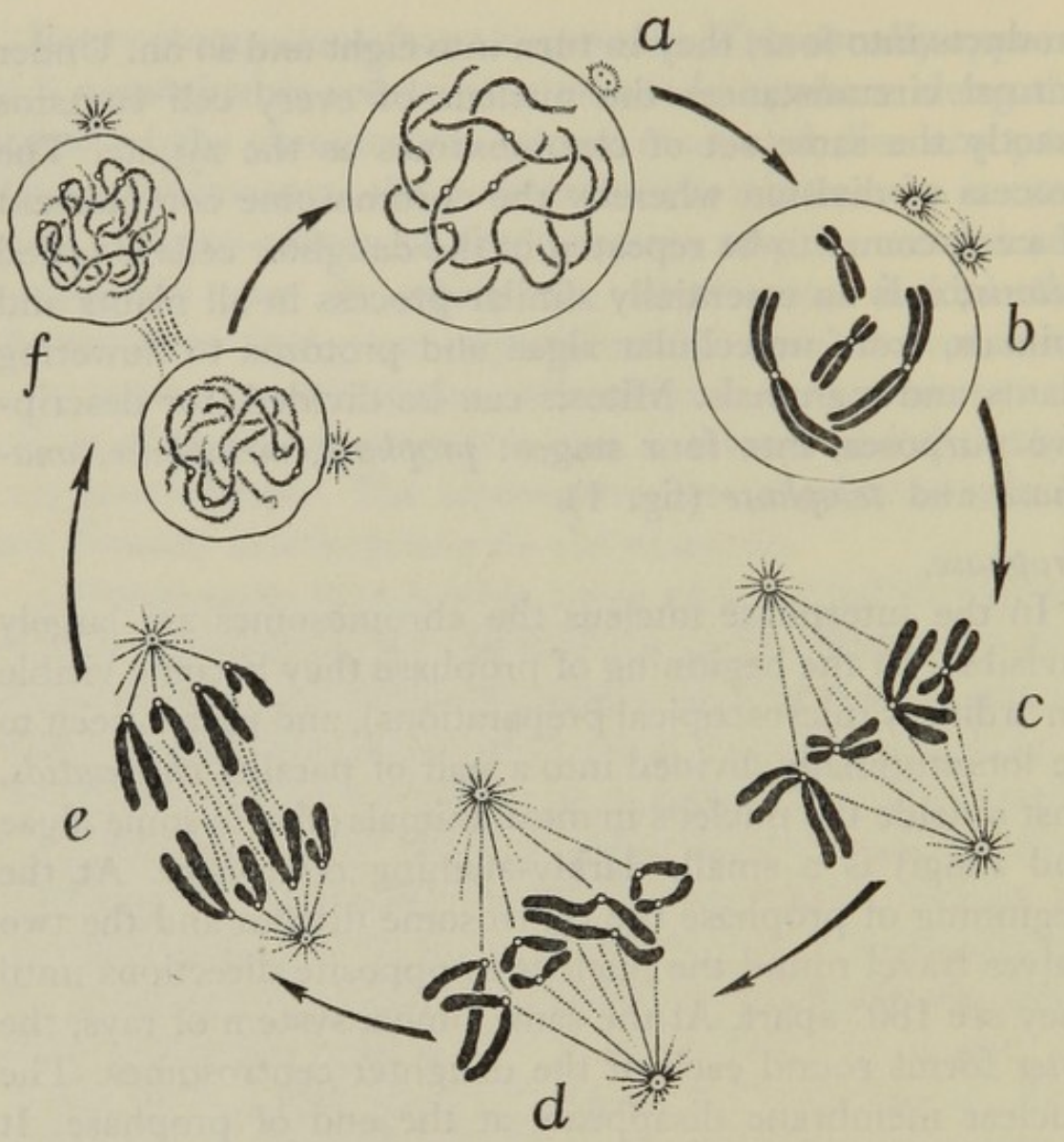


Figure 1 Diagram of cell division by mitosis illustrated by a cell nucleus containing two pairs of chromosomes.

(a) Interphase: chromosomes just visible.

(b) Prophase: chromosomes double but joined by centromeres; centrosome divides.

(c) Metaphase: nuclear membrane has disappeared, and the chromosomes are aligned at the equator of the spindle.

(d) Anaphase: the centromeres have split and are beginning to move towards the poles of the spindle.

(e) Telophase: the chromosome halves have moved to the poles, one complete set (two pairs) going to each pole.

(f) Daughter nuclei: nuclear membranes form round each chromosome set.

are attached, and so the members of each pair are separated. As the daughter chromosomes move towards the poles, the equatorial part of the spindle elongates and narrows.

Telophase.

The two groups of daughter chromosomes lose their smooth outline and come to appear as a tangled mass (as at the beginning of prophase), and a nuclear membrane forms round each group.

Thus two daughter nuclei are formed, each containing one half of the results of longitudinal splitting of the original chromosomes, i.e. the daughters are genetically identical.

2.4 Cell division: meiosis

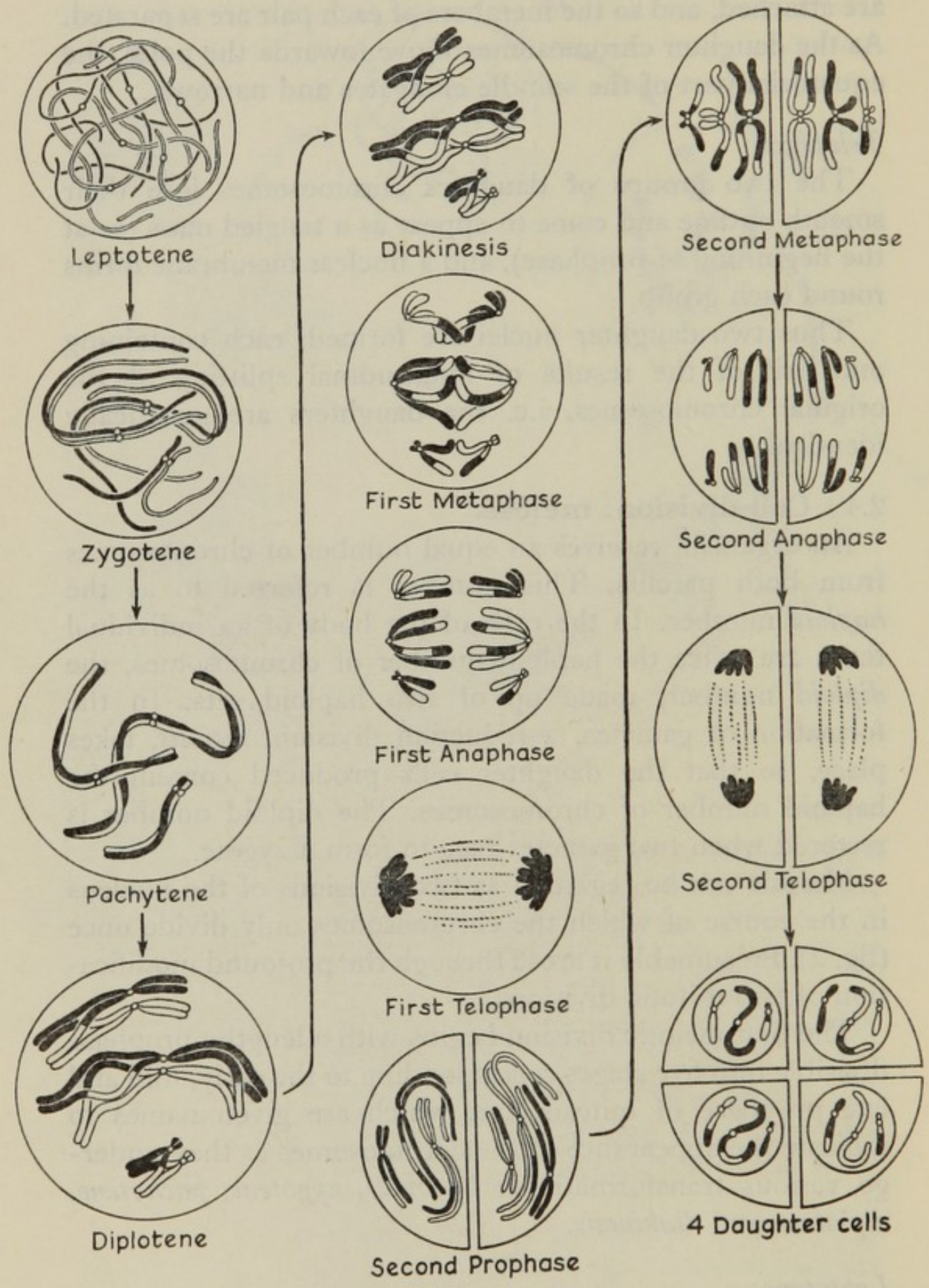
An organism receives an equal number of chromosomes from both parents. This number is referred to as the *haploid* number. In the cells of the body of an individual there are twice the haploid number of chromosomes, the *diploid* number, made up of two haploid sets. In the formation of gametes, a reduction division, *meiosis*, takes place, so that the daughter cells produced contain the haploid number of chromosomes. The diploid number is restored when two gametes fuse to form a zygote.

Meiosis can be regarded as two divisions of the nucleus in the course of which the chromosomes only divide once (fig. 2). Presumably it arose through the profound modification of two mitotic divisions.

The first meiotic division begins with a lengthy prophase divisible into five stages corresponding to the early, mid and late prophase of mitosis, but which are given names to indicate the appearance of the chromosomes as they undergo various transformations: *leptotene*, *zygotene*, *pachytene*, *diplotene* and *diakinesis*.

Leptotene:

The chromosomes become visible as long, thin, apparently undivided threads.


Leptotene
Zygotene
Pachytene
Diplotene
Diakinesis
First Metaphase
First Anaphase
First Telophase
Second Prophase
Second Metaphase
Second Anaphase
Second Telophase
4 Daughter cells

Zygotene:

Pairs of homologous chromosomes come together (*synapsis*) beginning at the ends and proceeding like a zip-fastener along the length to give very intimate and strict pairing.

Pachytene:

As soon as synapsis is complete, the degree of condensation of the chromosomes increases, so that at the end of pachytene the chromosomes are relatively thick threads. As a result of synapsis there appears to be only the haploid number of chromosomes in the nucleus, each pair (or *bivalent*) appearing as a two-stranded structure. By the end of pachytene the two constituent chromosomes of each bivalent have also become visibly two-stranded, so that the whole structure is four-stranded.

Diplotene:

The attraction of homologous chromosomes for one another apparently ceases and the members of the pairs would separate were it not for the fact that in each bivalent there are a number of places (2, 3 or 4; rarely more) where two of the four strands form an *X*-shaped association (a *chiasma*). At these places two of the four chromatids have broken and reciprocally rejoined, resulting in a pair of chromatids which have exchanged some of their material.

Figure 2 Diagram of cell division by meiosis illustrated by a cell nucleus containing three pairs of chromosomes. Chromosomes of paternal origin are shown in black, those derived from the mother in white. The first five stages (leptotene to diakinesis) together constitute the prophase of the first meiotic division. The chromosomes are seen to be double by diplotene, but the centromeres do not split until the end of metaphase of the second division. The four daughter nuclei finally produced all contain the haploid chromosome number of three.

Diakinesis:

The strands of the bivalents become yet thicker and shorter; the nuclear membrane disappears and the spindle forms.

First metaphase:

The bivalents become attached close to the equator of the spindle.

First anaphase:

The centromeres do not divide; the two centromeres in each bivalent move to opposite poles, each dragging a pair of chromatids after it. This forces the chiasmata along the bivalent (*terminalization*) until they finally slip off the ends as the half bivalents are torn asunder.

First telophase:

This does not differ essentially from the telophase of an ordinary mitosis except that the "daughter chromosomes" are each composed of two dissimilar chromatids (following the exchange—or *crossing-over*—of material between homologous chromosomes during diplotene).

Second meiotic division:

A second division may follow the first immediately or after some delay. The prophase is short and without any of the complications of the first prophase. Metaphase differs from the metaphase of ordinary mitosis in that there are only half the diploid number of chromosomes and the chromatids diverge widely from each other. The first division of centromeres during meiosis takes place during second anaphase and the four daughter nuclei which result from the original cell in second telophase all contain the haploid number of daughter chromosomes.

2.5 **Gametogenesis**

Meiosis must occur at some stage in the life cycle of any sexually reproducing organism. It takes place during the

formation of pollen and ova in higher plants; and in the production of spermatozoa and ova in animals. In the latter case the products of meiosis are gametes, and the process of their formation is *gametogenesis* (fig. 3).

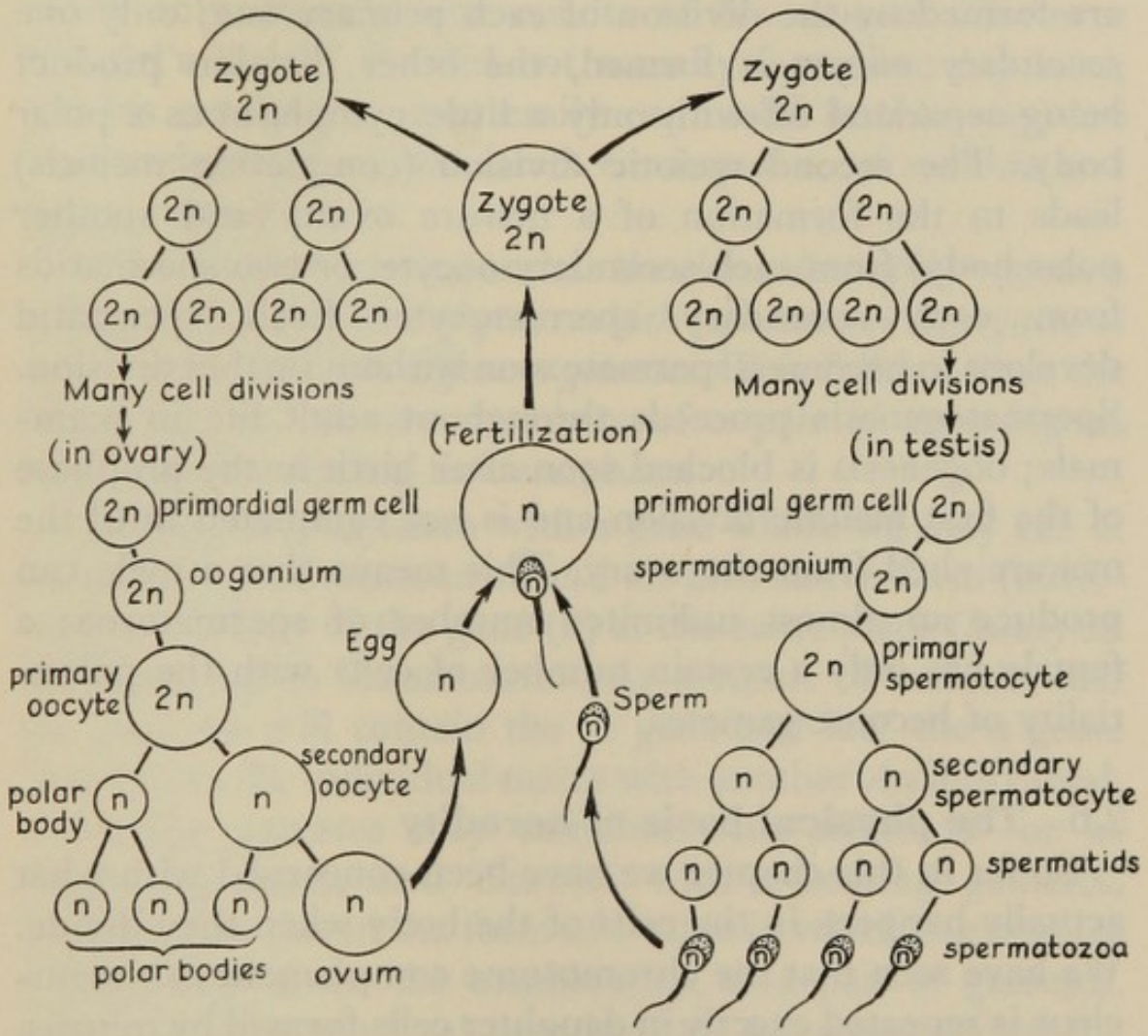


Figure 3 Gametogenesis in a mammal. The fertilized egg (the zygote) contains the diploid number of chromosomes ($2n$). This is the number present in all cells of the body except the cells in ovary and testis which undergo meiosis to form ova and spermatozoa having the haploid number (n). Fusion of an ovum and spermatozoon restores the diploid number and completes the life cycle.

The cells in the gonads (testes and ovaries) from which gametes will be formed are called *gonia: spermatogonia* in

males, *oogonia* in females. The gonia arise from sexually undifferentiated cells by mitosis. At some stage gonial cells become primary spermatocytes or primary oocytes and these undergo a first meiotic division to become secondary spermatocytes or oocytes. Two secondary spermatocytes are formed by the division of each primary one; only one secondary oocyte is formed, the other division product being separated off with only a little cytoplasm as a polar body. The second meiotic division (completing meiosis) leads to the formation of a mature ovum (and another polar body) from each secondary oocyte, or two spermatids from each secondary spermatocyte. Each spermatid develops to become a spermatozoon without further division. Spermatogenesis proceeds throughout adult life in mammals; oogenesis is blocked soon after birth in the prophase of the first meiotic division and is not completed until the ova are shed from the ovary. This means that a male can produce an almost unlimited number of spermatozoa; a female has only a certain number of cells with the potentiality of become gametes.

2.6 **The physical basis of heredity**

So far in this chapter we have been concerned with what actually happens in the cells of the body when they divide. We have seen that the chromosome complement of the nucleus is repeated exactly in daughter cells formed by mitosis, but that the daughter cells formed during meiotic division are not replicas of the parent because they contain the haploid number of reconstituted or recombined chromosomes due to chiasma formation and reduction division. Now the chromosomes carry the hereditary substance (and its associated protein), which is therefore distributed to the gametes and transmitted to the next generation. This fact, together with the events of meiosis, constitutes the physical basis of heredity. Hence, it is logical to pass on immediately to consider the genetical consequences of meiosis while we still have the details of cell division in our minds.

2.7 Mendel's law of segregation

The genetical consequences of meiosis were first realised by Mendel following breeding experiments carried out in the garden of his monastery at Brünn. At that time, the physical details of cell division were unknown and Mendel could only describe the results of his crosses. However Mendel's "laws" (he did not actually formulate any laws, but his results are most easily expressed in this way) are best understood as the direct consequence of meiosis and sexual reproduction.

Mendel's first law states that *the characters of an organism are controlled by pairs of genes which separate, or segregate, at meiosis and pass into different gametes*. This follows from the separating of the two members of a pair of homologous chromosomes during first anaphase.

Consider an organism with a gene which we may call *A* on one of its chromosomes and an alternative form (*allelomorph* or *allele*) of the gene (*a*) at the same place (*locus*) on the homologous chromosome. As a result of meiosis, half the gametes will contain the *A* gene and half the *a* gene. Now if this *Aa* individual mates with another *Aa* individual, *A*-bearing gametes may combine with either *A*- or *a*-bearing gametes, and likewise with *a*-bearing gametes. This may be put in the form of a table in which the zygotes which result from the combination of a pair of gametes, and hence the genetical constitutions (or *genotypes*) of the offspring are given in the body of the table:

		Gametes from one parent	
		A	a
Gametes from the other parent	A	AA	Aa
	a	Aa	aa

Half the offspring will be *Aa*, like their parents, having both forms of the gene; and there will be two new genotypes—a quarter of the offspring will be *AA* and the other quarter *aa*. An example may clarify this. If two pink-flowered snapdragons are crossed together they will give seeds which grow into plants with red, pink and white flowers in the ratios of 1:2:1 (i.e. $\frac{1}{4}:\frac{1}{2}:\frac{1}{4}$). Red-flowering plants crossed together are true breeding, always giving red-flowering plants, and white-flowering plants likewise breed true. The red- and white-flowering plants are genetically *AA* and *aa* respectively. However, pinks crossed either to each other or to either of the other types never give all pinks. Pink flowering plants are genetically *Aa*. A moment's reflection will show that red x white will give pink alone. In cases where the allelomorphs (alternative forms of the gene concerned) on both members of a homologous chromosome pair are the same (as with *AA* or *aa*), the organism is described as *homozygous* for that particular allelomorph. If the allelomorphs are different (as with the pink flowers which are *Aa*), the organism is *heterozygous* for those allelomorphs. We can therefore summarize the results of the five different crosses it is possible to make using red, white and pink flowering snapdragons:

(i) *red* x *red*: both plants are *AA*, both pollen and ova will carry the *A* gene, and all the progeny will be *AA*, i.e. all will have red flowers like the parents.

(ii) *white* x *white*: similarly the results of crossing two homozygous *aa* plants will be to produce all *aa* offspring. i.e. all will have white flowers like the parents.

(iii) *white* x *pink*: pink flowering plants are genetically *Aa*, and half the gametes they produce will carry the *A* gene and half the *a* gene. Since all the gametes produced by the white flowering plants will carry the *a* gene, half the progeny will have pink flowers, half white.

(iv) *red* x *pink*: similarly, half the progeny will have red flowers, half will have pink.

(v) *pink* x *pink*: both plants are heterozygous (*Aa*) and hence half the gametes produced by each will carry the *A* gene, half the *a* gene. We can tabulate the result:

		POLLEN: *proportions of different types*	
		$\frac{1}{2}A$	$\frac{1}{2}a$
OVA: *proportions of different types*	$\frac{1}{2}A$	Red 1/4AA	Pink 1/4Aa
	$\frac{1}{2}a$	Pink 1/4Aa	White 1/4aa

In other words the progeny will consist of plants with red (*AA*), pink (*Aa*) and white (*aa*) flowers in the ratios of 1:2:1.

The fact that the three genotypes of snapdragon are individually recognizable is the exception rather than the rule. More often the heterozygote is indistinguishable in appearance from one of the homozygotes. In this case the gene that is expressed in heterozygous condition is called a *dominant gene*; the alternative allelomorph which only manifests itself when it is homozygous is a *recessive gene*. When Mendel crossed pure-breeding red-flowered pea plants (*RR*) with pure-breeding white-flowered ones (*rr*), all the next generation (the F_1 or *first filial* generation) had red flowers (*Rr*). Two F_1 red-flowered plants crossed together gave red- and white-flowered plants in the next (F_2) generation in the ratio of 3 red: 1 white. This is really the same ratio as the 1:2:1 obtained by crossing pink snap-

dragons together, but the homozygous (*RR*) and heterozygous (*Rr*) red pea flowers are distinguishable only by breeding tests. The occurrence of dominance means that more than one genotype has the same appearance or *phenotype*; if a gene is dominant over its allemorph the two can be combined to give three genotypes (*RR*, *Rr* and *rr*) but only two phenotypes (red and white) since *RR* and *Rr* plants both have red flowers.

A common misconception is that the dominance of a gene means that its possessors are more vigorous or healthy than those individuals who do not carry the gene. This is not true: there is no constant relation between the dominance or recessivity of a character and its usefulness or harmfulness. Indeed we need look no further for a disproof than man, who has many serious diseases (e.g. achondroplasia) determined by dominant genes.

2.8 **Mendel's law of independent assortment**

Mendel's second law states that *when two or more pairs of genes segregate simultaneously, the distribution of any one of them is independent of the distribution of the others.* This is the result of the fact that, when the members of each pair of chromosomes separate to different poles in the anaphase of first meiotic division, the movements of any chromosome pair are independent of those of all the others. Any two non-homologous chromosomes have an equal chance of going to the same or to different poles. For example, if an organism has two pairs of chromosomes with the allelomorphic genes A^1 and A^2 on opposite members of one pair, and B^1 and B^2 on the members of the other, then four different daughter cells can be formed in equal numbers following meiosis. Each daughter cell will have two chromosomes, and the four different sorts of cell will differ in the genes thereon: $A^1\ B^1$, $A^1\ B^2$, $A^2\ B^1$ and $A^2\ B^2$.

Mendel crossed a pea plant pure breeding for round yellow seeds (*RRYY*) with one pure breeding for the alternative expression of these characters—wrinkled green

seeds (*rryy*). All the F_1 plants had round yellow seeds. They must have been doubly heterozygous (*Rr Yy*): hence round is dominant over wrinkled, and yellow over green. Now if the *R* and *Y* loci segregate independently of each other, four genetically different types of pollen grain will be produced in equal numbers (*RY*, *Ry*, *r Y*, *ry*), and likewise four types of ova. Assuming that this occurs, the relative proportions of different phenotypes among the progeny of a cross between two F_1 plants can be predicted:—

Genetical constitution of ova	*Genetical constitution of pollen grains* RY	Ry	rY	ry
RY	RRYY round yellow	RRYy round yellow	RrYY round yellow	RrYy round yellow
Ry	RRYy round yellow	RRyy round green	RrYy round yellow	Rryy round green
rY	RrYY round yellow	RrYy round yellow	rrYY wrinkled yellow	rrYy wrinkled yellow
ry	RrYy round yellow	Rryy round green	rrYy wrinkled yellow	rryy wrinkled green

There are 16 genotypic classes but only four phenotypic ones. It would be expected that there would be 9 round yellow plants to every 3 round green, 3 wrinkled yellow, and 1 wrinkled green. In an actual experiment Mendel obtained 315 round yellow plants, 108 round green, 101 wrinkled yellow and 32 wrinkled green. Clearly these figures come close to the predicted ratios of 9:3:3:1 for the different classes.

Independent segregation only holds between genes on different chromosomes: genes which are situated on the same chromosome are said to be linked (Chapter 4) and do not segregate independently.

2.9 Genes and chromosomes

Mendel's success in elucidating the rules of hereditary

transmission was due in a large measure to his choice of simple characters and to confining his attention to the presence or absence of these characters. He knew nothing of the physical explanation of his results. However, if we accept the premise that the genes are located on the chromosomes (and we shall consider some of the evidence for this in Chapters 4 and 8), and when we understand what happens to the chromosomes during meiosis, Mendel's "laws" come to seem very simple statements. Many people regard genetics as an almost mystical subject (as when individuals are said to "share blood" or possess "bad blood"); if gene transmission is thought of as a necessary consequence of the events of cell division much of its confusing nature disappears.

CHAPTER 3

SEX

Most organisms with which we are familiar exist in one or other of two different forms—male or female. This sexual differentiation is an example of *discontinuous variation* (i.e. variation in which the different classes do not overlap each other) which is so widespread as to escape comment as an aspect of genetical variability. Nevertheless, sex is basic to genetics and it is as well to understand the mechanisms by which it may be determined as a background to more general problems of inherited variation. The necessity for this understanding becomes more compelling when we consider that Aristotle believed—and he was not alone in this—that the sperm in itself had the power to form all parts of the body: "the male gives *form*, the female *substance*, just as the artist imparts shape and form to the material by means of the motion he sets up." Although the male reader may feel there is much to be said for this view, to accept it would be to render irrelevant much of what follows in this book. Anyway the fusion of sperm and ovum nuclei following fertilization was observed in 1875 and we cannot now doubt the respective roles of male and female.

3.1 **Sex chromosomes**

In the vast majority of animals and higher plants sex determination is effected by *sex chromosomes*.

The human male has 22 pairs of homologous chromosomes (the *autosomes*), one of each pair being contributed by the father, one by the mother. He also has a single, dissimilar pair of sex chromosomes. Females have a like pair of the larger sex chromosomes, the *X* chromosome; they do not possess the smaller one, the *Y*. Hence men have

22 pairs of autosomes, plus XY; women have 22 pairs of autosomes, plus XX. The gametes, spermatozoa and ova, carry half this number of chromosomes. All ova have 22 autosomes plus a single X chromosome; there are two sorts of sperm, half having 22 autosomes + X, the other half 22 autosomes + Y. An ovum fertilized by an X-bearing spermatozoon will give rise to a woman; one fertilized by a Y-bearing spermatozoon to a man. Since half the sperm carry an X, half a Y, there will be an approximately equal number of both sexes in the population (actually the Y-bearing spermatozoa seem to be more efficient at fertilization than the X-bearing ones, and more boys are conceived than girls).

The type of sex determination in which one sex has two X chromosomes and the other one has one X and one Y (or one X only) is very widespread. It has been found in many insects and other invertebrates, in some fish and in all birds and mammals studied. Generally speaking, mammals and most insects have XX females and XY or XO (i.e. absence of a second sex chromosome) males; birds have XY females and XX males.

3.2 Genic balance and inter-sexes

For a long time it was believed that the sex into which a zygote would develop was controlled by some sort of balance between autosomes and sex chromosomes (p.97). In the fruit fly *Drosophila melanogaster* individuals are occasionally found which have "too many" sets of autosomes, or "too many" sex chromosomes. These chromosomally abnormal flies are usually either sterile, or *intersexes*, intermediate between male and female. From a study of these flies it seemed that sexual development was due to the simultaneous action of two opposed sets of genes, one set tending to produce male characters and one female characters. The male-tendency genes on the autosomes appeared to be more numerous or more effective than those on the X chromosome, while the net effect of genes on the X

chromosome was a tendency to the production of female characters. The *Y* chromosome seemed to be of little importance: individuals with two *X*s and a *Y* are normal females, and individuals with one *X* and no *Y* are morphologically normal, though sterile males.

This balance explanation does not hold true for mammals. Humans having a normal set of autosomes plus four *X*s and a *Y* are fairly normal males in appearance, albeit sterile. *XXY* individuals are similarly sterile males (unlike *XXY* flies which are normal-appearing fertile females.) They are described as suffering from Klinefelter's syndrome. *XO* (i.e. possessing only a single sex chromosome) individuals are underdeveloped females (Turner's syndrome). These differences between flies and mammals may be due to the fact that only one of the *X* chromosomes seems to function in any mammalian cell (see p. 58) which means that sex determination is effectively dependent on the presence or absence of a *Y*.

3.3 **Regulation of the sex ratio**

While the system described with two sex chromosomes is the commonest, many other sex-determining systems exist. Males and females of the mosquito *Culex molestus* differ by only a single gene; other organisms have many sex chromosomes. The extreme seems to be a Palestinian beetle in which the males have 12 *X* chromosomes and 6 *Y*, while the females have 22 *X* chromosomes. Multiple sex chromosomes are often found among fish.

These systems are all geared to the production of equal numbers of males and females; on the other hand there are organisms which can regulate their sex ratio. Many Hymenopteran insects (such as the honey bee) are well known examples of this. Thus the queen honey bee lays all the eggs in a hive: fertilized eggs develop into workers (females); unfertilized eggs, possessing only the haploid number of chromosomes, develop into drones (males). Aphids produce a sexual generation only at the end of the breeding season,

but throughout the summer generations of females hatch from unfertilized eggs (*pathenogenetically*), ensuring that there is no waste of either eggs or adult flies. There is an *XX*:*XO* sex chromosome system in these flies but for most of the breeding season it is not employed; reduction division only takes place prior to the formation of the sexual generation at the end of the summer. Some forms prevent wastage of males (in the sense of failing to find a mate), by a purely environmental determination of sex. Thus the marine sessile worm *Bonellia viridis* has a sexually undifferentiated larval form. A larva which settles by itself becomes an adult female secreting a hormone so that any other larvae settling in the vicinity turn into males. Some oysters begin life as males, and then have a series of alternating sex phases throughout life. There is never a permanent change to female, but always a reversion to male after eggs have been shed. There are higher plants (e.g. dandelion, blackberry) which rarely or never reproduce by crossing with another plant. They are self-fertilized, or undergo parthenogenetic development. This means that they can rapidly establish themselves without a wastage of either gametes or unsuitable genetical types that might arise from a sexual union. Many weeds reproduce in this fashion.

3.4 **Out-crossing**

In species like our own where there are approximately equal numbers of either sex, any individual can mate with any from about a half, and only a half, of his or her fellows. This *out-crossing* or *out-breeding* means that there is a frequent mixing of genetical characters and the ever-present possibility of new, favourable combinations occurring. The positive advantage of out-crossing has to be compensated against the fact that many less advantageous genetical combinations will also be formed. It is for this reason that the weeds mentioned in the last section have foregone sexual reproduction. However, cross-fertilization is the rule among both animals and plants and in those forms which are

hermaphrodite (i.e. having the reproductive organs of both sexes present in one individual) complex mechanisms often exist to lessen the chance of self-fertilization and correspondingly increase the amount of out-breeding.

Thus the colour, scent and nectar of flowers are "inducements" to insects to visit the flower and thus to serve as agencies for the transfer of pollen between different plants. In addition physiological "self-incompatibility" systems may provide an additional protection against self-pollination. A common version of such a system (found, for example, in red clover and wild cherry) involves a gene which has the effect that pollen carrying it will grow very slowly on a style possessing the same gene, and hence will be unlikely to reach an ovule in time to effect fertilization. Now this incompatibility gene apparently exists in a great number—perhaps several hundred—different forms or *allelomorphs*. Any two plants are relatively unlikely to carry the same allelomorph if there are so many of these, and they will therefore be inter-fertile although self-sterile.

3.5 Some alternatives to sex

Sexual differentiation is found in all groups of organisms down to unicellular animals and plants. Thus simple algae such as *Chlamydomonas* or *Spirogyra*, exist as "positive" and "negative" mating-types such that plus never unites with plus or minus with minus. In such organisms meiosis takes place in the normal way. However, there are methods of reproduction following *conjugation* (i.e. coupling) in fungi, bacteria and viruses which are so unlike sexual recombination that they must be treated separately. A complicated terminology has grown up in this branch of genetics. This can be very confusing and some readers may prefer to omit the rest of this chapter.

3.5.1 Parasexuality : heterokaryosis

In the rust fungi the nuclei from different strains do not fuse after conjugation; nuclei from different sources may

coexist in the fungal cytoplasm and divide synchronously, for many generations. The fungal strand (*hypha*) containing the different nuclei is known as a *heterokaryon*. The nuclei complement each other as if they were already fused to form a single diploid nucleus. There are other fungi in which the nuclei sometimes fuse to form diploids. For example, one mutant strain of the green fruit or soil mould *Aspergillus* may be unable to synthesize the amino-acid adenine while another cannot make biotin. Despite the fact that neither will grow on a medium containing neither of these substances, a heterokaryon formed from them can do so. Any one of the nuclei may divide to form asexual reproductive *conidiospores*; the fusion of the haploid nuclei to form a diploid is a much rarer event. If it does happen, interchange of genetical material between homologous chromosomes (see Chapter 2) in the diploid nucleus can take place without being immediately followed by a reduction division as in normal meiosis. Thus, these fungi have a *parasexual* process differing from the true sexual process in the absence of the regular time sequence of fertilization, meiosis and reduction of the diploid to the haploid chromosome complement.

3.5.2 **Bacterial recombination**

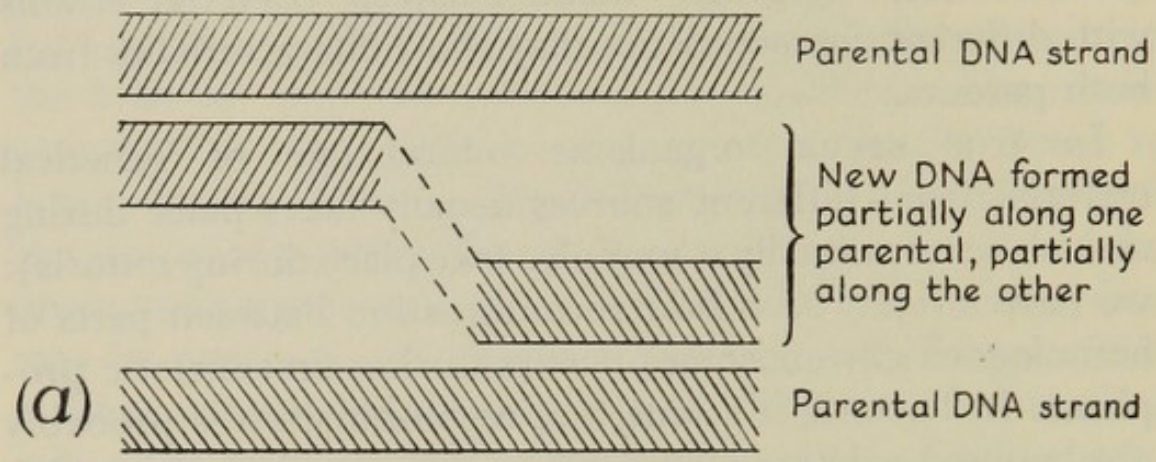
A form of sexual reproduction occurs in bacteria. Conjugation can take place between (e.g.) two colon-living bacteria (*Escherichia coli*): a cytoplasmic bridge is formed between the pair and genetical material is then transferred from one cell to another. The conjugating bacteria can be separated by agitation and the amount of genetical material transferred is proportional to the time they were in contact. Bacterial cells possess microscopically visible "nuclei" containing the same hereditary material as in higher organisms (desoxyribose nucleic acid, DNA) and this behaves as if it were on a single chromosome. Although there must be some distinctive mechanism for division of the cells, nothing akin to mitosis or meiosis has ever been recognized.

Nevertheless, "hybrids" made between bacterial strains with different characteristics may show characteristics from both parents.

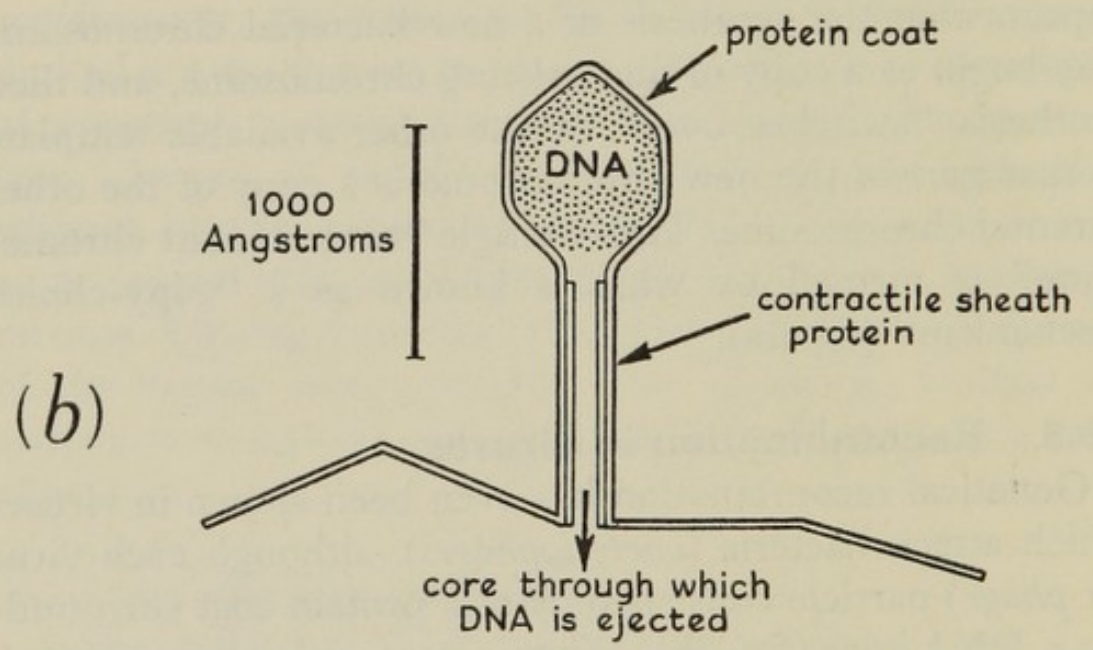
In true sexual organisms interchange of genetical material from different sources usually takes place during meiosis (exceptionally it may also take place during mitosis): we have already seen how recombination between parts of homologous chromosomes occurs during first meiotic prophase. In bacteria it seems that recombination is probably not between existing structures in this way, but rather that "recombinant chromosomes" are formed as they are synthesized as replicas of the parental genetical material. It appears that the synthesis of a new bacterial chromosome may begin as a copy of one existing chromosome, and then synthesis "switches over" to the other available template so that part of the new chromosome is a copy of the other parental chromosome. Thus a single "recombinant chromesome" is formed by what is known as a "copy-choice mechanism" (fig. 4a).

3.5.3. **Recombination in viruses**

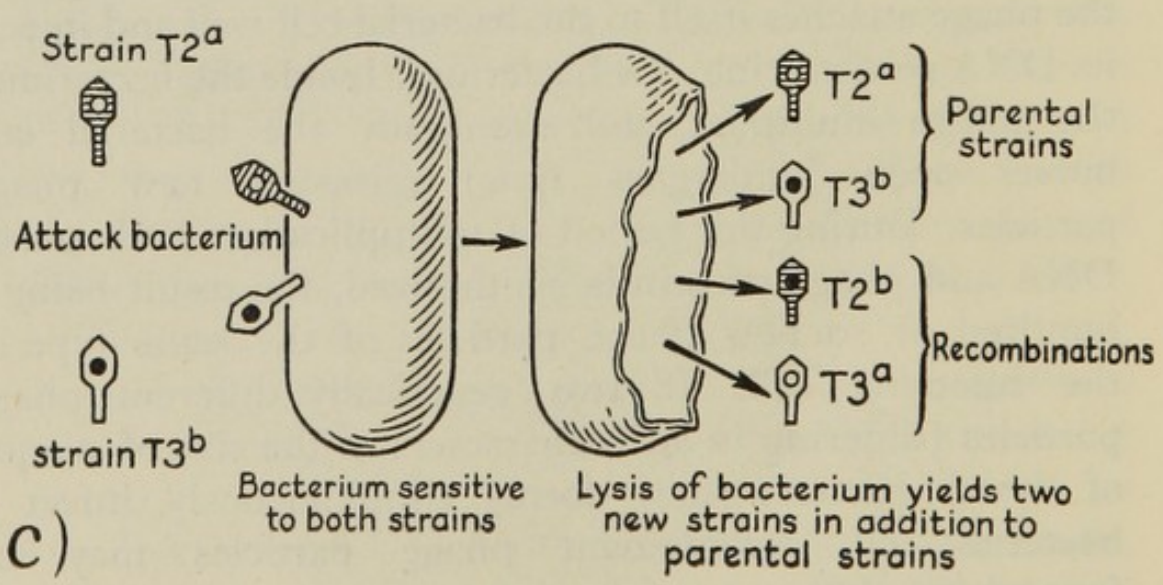
Genetical recombination has even been shown in viruses which attack bacteria (*bacteriophages*), although each virus (or *phage*) particle consists only of a protein coat surrounding a DNA core (fig. 4b). When a bacterial cell is infected, the phage attaches itself to the bacterial cell wall and injects its DNA contents into the bacterium. Inside the bacterium, the phage multiplies and eventually the bacterial cell bursts open (undergoes lysis) releasing new phage particles. During the period of multiplication both phage DNA and phage protein is synthesized, the result being a hundred or so new phage particles of the same type as the infecting cell. If two genetically different phage particles (differing in such characters as the size of plaque of lysed bacteria they form) simultaneously infect a bacterial cell, recombinant phage particles may be formed (fig. 4c).


Parental DNA strand
New DNA formed partially along one parental, partially along the other
Parental DNA strand

(a)


protein coat
DNA
1000 Angstroms
contractile sheath protein
core through which DNA is ejected

(b)


Strain T2a
Attack bacterium
strain T3b
Bacterium sensitive to both strains
T2a
T3b
Parental strains
T2b
T3a
Recombinations
Lysis of bacterium yields two new strains in addition to parental strains

(c)

3.5.4 Transduction and transformation

A temperate phage (i.e. one which may exist in a strain of bacteria without killing too many) can carry over genetical characters of its host (such as streptomycin resistance, or the capacity to utilize a particular sugar) from one bacterial strain to another. In the course of its DNA synthesis the phage may incorporate some of the genetical material of the host bacterium. When the phage infects another bacterium, this genetical material has a chance of being incorporated into the genotype of the new host. This *transduction* is a special sort of genetical recombination involving an infectious rather than a sexual process (cf. p. 00). *Transformation* is a comparable process whereby DNA (the *transforming principle*) extracted from one strain of bacteria can "transform" some of the genetical characteristics of a second strain to which it is added. For example the bacteria that cause pneumonia can be changed (or transformed) from a relatively non-dangerous type to a much more virulent one by the addition of DNA extracted from the

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Figure 4 Genetical processes in bacteria and bacteriophage.

(a) A copy-choice mechanism for the replication of DNA. The "new" (replicating) DNA is formed partially as a copy of the parental strand and partially as a copy of the introduced DNA strand.

(b) Diagram of a bacteriophage particle. This attaches itself to a bacterium, and the DNA is extruded as the contractile sheath contracts.

(c) Recombination in bacteriophage: when the bacterial host bursts, both types of bacteriophage which were introduced are liberated, together with two "recombinant" strains. *Based on a figure which appeared in* ELEMENTARY GENETICS *by Singleton, published by Van Nostrand*

virulent form. The introduced DNA is incorporated into some of the new bacteria formed, and these have the characteristics of the cells whence the extracted DNA came. This direct effect of DNA was one of the earliest proofs that the genetical material is composed of DNA (p. 79).

One reason for the importance of the genetics of micro-organisms, with their extremely high rate of reproduction as compared with higher organisms, and vast, easily estimated numbers, is that it has provided the key to a true understanding of the internal complexities of the gene (Chapter 8).

CHAPTER 4

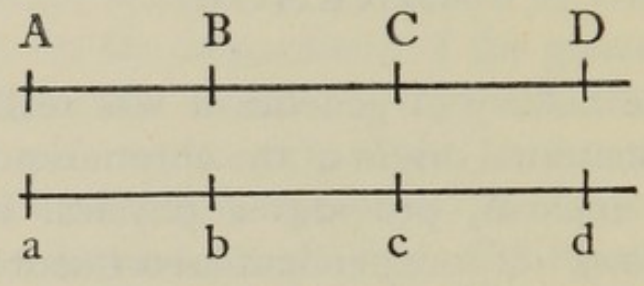
LINKAGE

EARLY in the history of genetics it was realized that the paternal and maternal origin of the chromosomes, and their behaviour at meiosis, provides a physical basis for the Mendelian "laws" of independent assortment and segregation of the inherited factors, i.e. it seemed reasonable to suppose that the chromosomes that can be seen under the microscope were, or carried, the inherited factors. It soon became apparent in genetically studied organisms that there are many more genes than chromosomes, whence it was argued that the inherited factors (genes) are located and linked together on the chromosomes. The direct proof of this *chromosome theory of heredity* came first from the study of microscopically visible chromosomal aberrations (deletions, duplications, etc.) which produced genetical effects and could be followed from generation to generation, and more recently from chemical studies, particularly on desoxyribose nucleic acid, DNA (p. 79). The number of groups of linked genes has been shown in a few organisms to be the same as the number of chromosome pairs, and in *Drosophila* at least, the number of genes in the different linkage groups is approximately related to chromosome size.

4.1 Coupling and repulsion

The fact that each chromosome carries many genes means that these genes will be inherited together. Genes on the same chromosome will always occur together and be transmitted together (with the important exception discussed in the next paragraph). They are said to be in *coupling*. Genes on opposite members of a chromosome pair (i.e. coming from different parents) will always separate into different gametes when homologous chromosomes segregate in

meiosis, and are said to be in a state of *repulsion*. Thus, if a chromosome carries 4 genes *A*, *B*, *C*, *D*, and their allelomorphs *a*, *b*, *c*, *d*, are carried on the homologous chromosome,



A and *B* are in coupling and *B* and *b*, etc., are in repulsion. This physical linkage of genes together is the most important exception to the simple facts of heredity as discovered by Mendel.

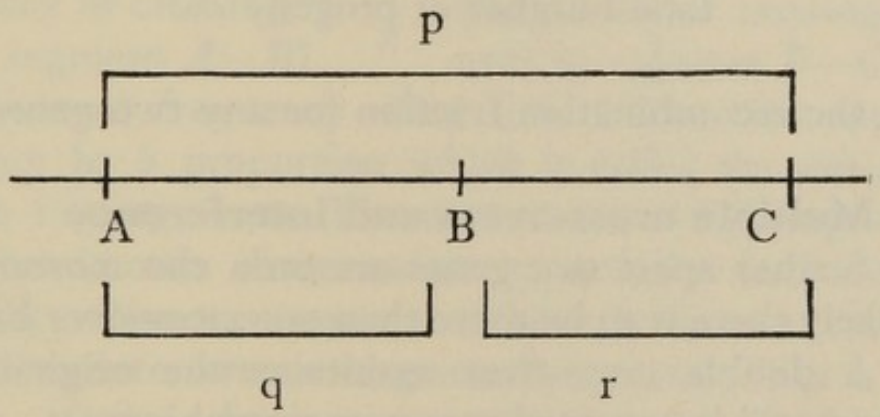
4.2.1 **Recombination**

However, the statements of the last paragraph are oversimplications: linkage of genes on the chromosomes is complicated by the fact that it is not complete. Genes are exchanged between homologous chromosomes so that they undergo a limited amount of *recombination* during the first meiotic division. Hence genes in coupling on a chromosome may *cross-over* to become separated on opposite members of a homologous chromosome pair, and vice versa. The basis of this genetical recombination is the physical exchange of chromosomal material between homologous chromosomes which take place when the members of a pair meet each other in the zygotene phase of first meiotic division. At about the time when the chromosomes are first seen to be divided, the chromatids establish one or more exchanges (*chiasmata*) per chromosome pair. At each chiasma, two of the four chromatids become broken and then rejoin so that new chromatids are now compounded of sections of the old ones. Despite much speculation the mechanism of breakage and rejoining of chromatids remains unknown. However, the facts of recombination are incontravertible and of great importance in all genetical interpretation. Re-

combination is a concept which recurs repeatedly in this book.

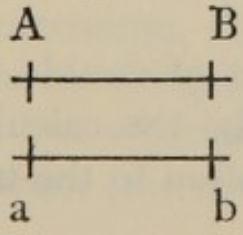
4.2.2 Recombination fraction

Because of the occurrence of recombination, linkage is not complete. However, it is not an entirely random process: the frequency with which two genes on the same chromosome undergo recombination is constant under normal conditions and the amount of recombination between genes *A* and *C* in a segment of chromosome carrying the genes *A*, *B*, *C*, is approximately the sum of that between *A* and *B*, and *B* and *C*. If we take such a section of a chromosome:

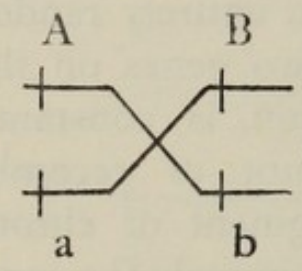


we can define *p*, *q* and *r* as expressions of the frequency of recombination between the respective pairs of genes (*recombination fractions*), so that $p = q + r$. The additiveness or recombination fractions constitutes the simplest evidence that genes are arranged in a linear order along the chromosome. Indeed one can go a stage further and state that the extent of recombination between any two genes on a chromosome is an expression of their physical distance apart along the chromosome.

Example—An organism heterozygous for both of two linked genes, *A*, *a*, and *B*, *b* such that *A* and *B*, are in coupling, will have a genotype:



It will produce four types of gametes: equal numbers of the parental, non-recombinant types A——B and a——b and equal numbers of the recombinant types produced by a cross-over between A and B



giving A——b and a——B

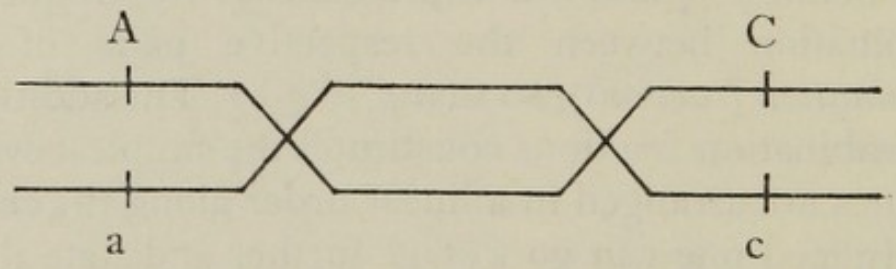
The ratio

$$\frac{\text{number of individuals showing recombination}}{\text{total number of progeny}}$$

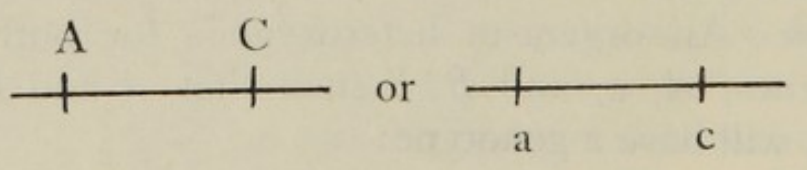
defines the recombination fraction for any two genes.

4.2.3 **Multiple cross-overs and interference**

The further apart two genes are on a chromosome, the more likely there is to be more than one cross-over between them. A double cross-over maintains the original gene order and will be counted as a non-recombinant:

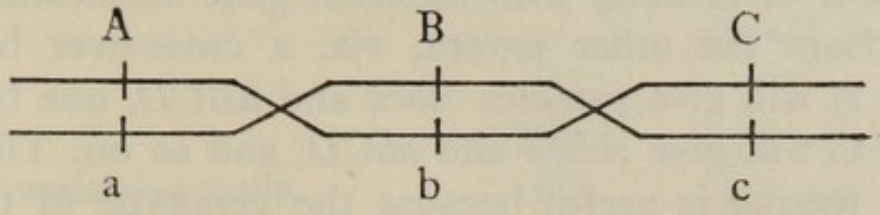


i.e. both parental and (double) recombinant types have the genotype



The greater the number of double, quadruple, etc., cross-overs the smaller will be the calculated, apparent recombination fraction in relation to the true one.

If a gene *B* lies between *A* and *C*:



it will be possible to recognize a proportion of double cross-overs by such types as *AbC*, *aBc*. On the assumption that a cross-over between *A* and *B* occurs independently of one between *B* and *C*, the expected frequency of double cross-overs would be:

(frequency of crossing-over in segment *A*—*B*) × (frequency of crossing-over in segment *B*—*C*)

The observed frequency often falls below this expected frequency by a proportion which is called the *coincidence* between the segments. The occurrence of crossing-over at one point in the chromosome apparently decreases the probability of its occurrence elsewhere in the same chromosome. This interference is generally greatest over a short distance of the chromosomes (presumable due to the natural rigidity of the chromosomes) so that within a certain minimal distance there is no double crossing-over (coincidence = 0).

4.2.4 **Numerical example of linkage**

The most informative mating from the point of view of linkage is one in which a multiple heterozygote is *back-crossed* to the multiple recessive homozygote, i.e. where the parents in the cross can be represented as

$$\frac{A\ B\ C\ D}{a\ b\ c\ d} \text{ and } \frac{a\ b\ c\ d}{a\ b\ c\ d}$$

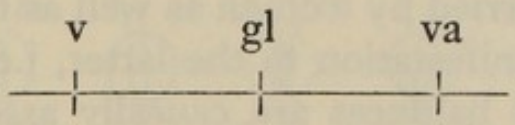
where *A*, *B*, *C*, *D* are genes on the same chromosome. Interchange of material will take place between the homologous chromosomes during meiosis in both parents but whereas all the gametes produced by the second parent (the multiple recessive homo-

zygote) will be the same (carrying the chromosome *a b c d*), a number of gametes with different gene consitutions will come from the other parent, viz. a cross-over between *A* and *B* will give gametes *Abcd* and *aBCD*, one between *B* and *C* will give *ABcd* and *abCD*, and so on. This particular mating is useful because the genotype of the offspring for the characters under consideration can be recognized from the phenotype, since all the dominant genes contributed by the heterozygous parent will be present as heterozygotes and all recessives as homozygotes. Thus an organism which is genetically $\frac{A\ b\ c\ D}{a\ b\ c\ d}$ will look like (i.e. appear phenotypically as) *AbcD*.

We may take as an example an actual three-point (involving three characters) back-cross carried out in maize. If the inflorescence of a maize plant is pollinated with pollen from a single plant, every kernel which results on the "cob" represents a single offspring of the cross. These kernels can be grown separately and the different phenotypes in the "family" counted. The cross described involved the linked recessive genes virescent (symbolized *v*: plants begin life as albinos, but gradually become yellow-green), glossy leaves (*gl:* leaves have a particularly glossy appearance), and variable sterile (*va:* characterized by irregular distribution of chromosomes at meiosis). The cross was between a normal appearing plant which was heterozygous for the dominant (sometimes called the normal or wild-type) genes (symbolized +) and the recessive genes *v*, *gl* and *va*; and one homozygous for the three recessives (and hence virescent, glossy and variable sterile in phenotype). Each offspring will receive the same $\underline{gl\ va\ v}$ chromosome from the second parent, and it is thus possible to recognize the genotype of the gamete coming from the heterozygous or hybrid parent. In the experiment the numbers of offspring were as follows (*data of Emerson, Beadle & Fraser*):

Phenotype	Number	Genotype of gamete from hybrid parent		
normal	235	+	+	+
glossy, variable sterile	62	gl	va	+
variable sterile	40	+	va	+
virescent, variable sterile	4	+	va	v
virescent, glossy, variable sterile	270	gl	va	v
glossy	7	gl	+	+
virescent, glossy	48	gl	+	v
virescent	60	+	+	v
total	726			

The parental, non-recombinant (commonest) types and double cross-over (rarest) types can be picked out easily. Now the knowledge that three genes are linked does not tell us anything about their order along the chromosome. We can learn this from the double cross-over types. Since the double cross-over gametes involve the transposition of *gl*, this must lie between the other two genes on the chromosome, i.e. the order of genes on the chromosome is



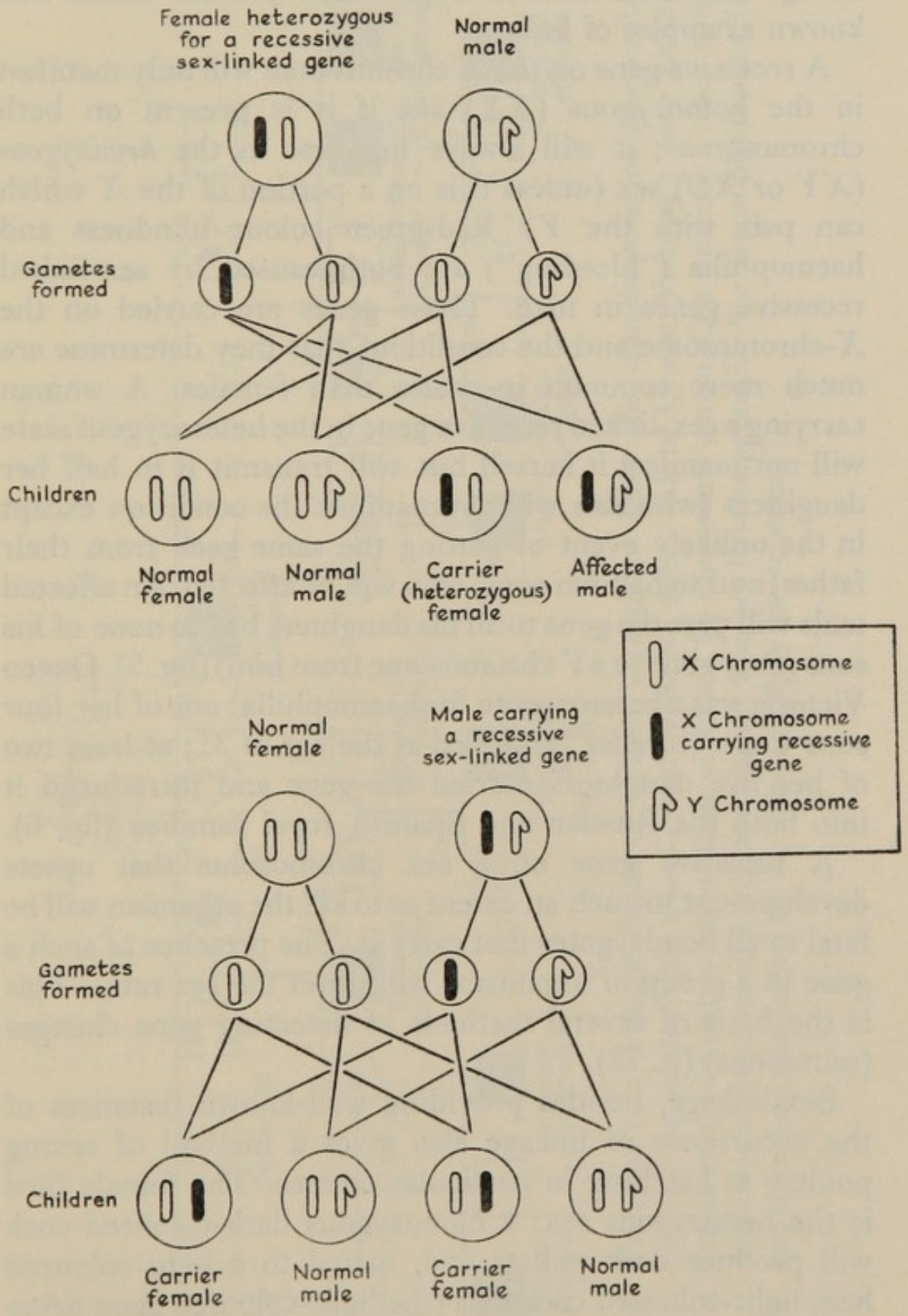
The number of single cross-overs between *v* and *gl* is 60 + 62; between *gl* and *va* it is 40 + 48 (note the approximate equality of reciprocal cross-over types). Hence the total number of cross-overs between *v* and *gl* is 60 + 62 + 7 + 4 = 133, and the frequency of recombination in this segment is 133/726 = 18·3% = recombination fraction. Similarly between *gl* and *va* there are 40 + 48 + 7 + 4 =99 cross-overs, giving a recombination fraction of 13·6%. Note that 232 cross-overs have been counted (or scored) between *v* and *va* giving a recombination frequency of

31·9%, the sum of the frequencies in the two segments. If the cross had only involved *v* and *va*, the double cross-overs would have appeared as parental types and the frequency of recombination would then be calculated as 210/726 = 28·9%. If the chance of a cross-over between *v* and *gl* is independent of one between *gl* and *va*, the expected probability of a simultaneous cross-over in both segments (a double cross-over) would be 18·3% × 13·6% = 2·5% but only 11/726 = 1·5% double cross-overs were found. Hence the coefficient of coincidence (= strength of interference) = 1·5/2·5 = 0·6.

4.3 Sex Linkage

Linkage is not a phenomenon readily noticeable in everyday life: two genes which can occur on the same chromosome together (in coupling) in some people may equally well be separated on opposite members of a homologous chromosome pair (in repulsion), in others. In the latter case they would be distributed to different gametes at meiosis. (A phenomenon which is often confused with linkage is the *association* of characters. For example the fact that very few women are bald does not mean that the gene for baldness is linked to one causing maleness. The dominant gene causing frontal baldness in relatively young people can be carried by women as well as by men, but it is *limited* in its manifestation to the latter, i.e. the characters of maleness and baldness are causally associated through the effect of the male hormones, not genetically linked). However, the particular type of linkage known as *sex*

Figure 5 Sex linkage: half the sons of a woman carrying a sex-linked recessive gene will carry and be affected by the gene, because they do not possess a second *X* chromosome to "mask" the effects of the gene; half her daughters will carry but not manifest the gene. An affected man married to a normal woman will produce all normal children, but all his daughters will carry the gene.


Female heterozygous for a recessive sex-linked gene
Normal male
Gametes formed
Children
Normal female
Normal male
Carrier (heterozygous) female
Affected male
X Chromosome
X Chromosome carrying recessive gene
Y Chromosome
Normal female
Male carrying a recessive sex-linked gene
Gametes formed
Children
Carrier female
Normal male
Carrier female
Normal male

linkage manifests itself in ways which provide some well known examples of linkage.

A recessive gene on the *X* chromosome will only manifest in the homozygous (*XX*) sex if it is present on both chromosomes; it will always manifest in the *hemizygous* (*XY* or *XO*) sex (unless it is on a portion of the *X* which can pair with the *Y*). Red-green colour blindness and haemophilia ("bleeding") are both caused by sex-linked recessive genes in man. These genes are carried on the *X*-chromosome and the conditions that they determine are much more common in males than females. A woman carrying a sex-linked recessive gene in the heterozygous state will not manifest it herself but will transmit it to half her daughters (who also will not manifest the condition except in the unlikely event of getting the same gene from their father) and to half her sons, who will be affected. An affected male will pass the gene to all his daughters but to none of his sons (they receive a *Y* chromosome from him) (fig. 5). Queen Victoria was a heterozygote for haemophilia: one of her four sons was a "bleeder" and died at the age of 31; at least two of her five daughters carried the gene and introduced it into both the Russian and Spanish royal families (fig. 6).

A recessive gene on a sex chromosome that upsets development to such an extent as to kill the organism will be fatal to all hemizygotes that carry it. The presence of such a gene in a group of organisms will upset the sex ratio. This is the basis of several methods of detecting gene changes (mutations) (p. 72).

Sex-linkage, besides providing well-known instances of the occurrence of linkage also gives a method of sexing poultry at hatching in particular crosses. The female bird is the hemizygous sex: a homozygous dark-coloured cock will produce dark pullets and, mated to a light-coloured hen, light-coloured cockerels (the light-coloured gene being dominant to the dark one). Similarly, if the hen's *X* chromosome carries the dominant gene for barred colour (as in the Plymouth Rock), all the male chicks will be barred (fig. 7).

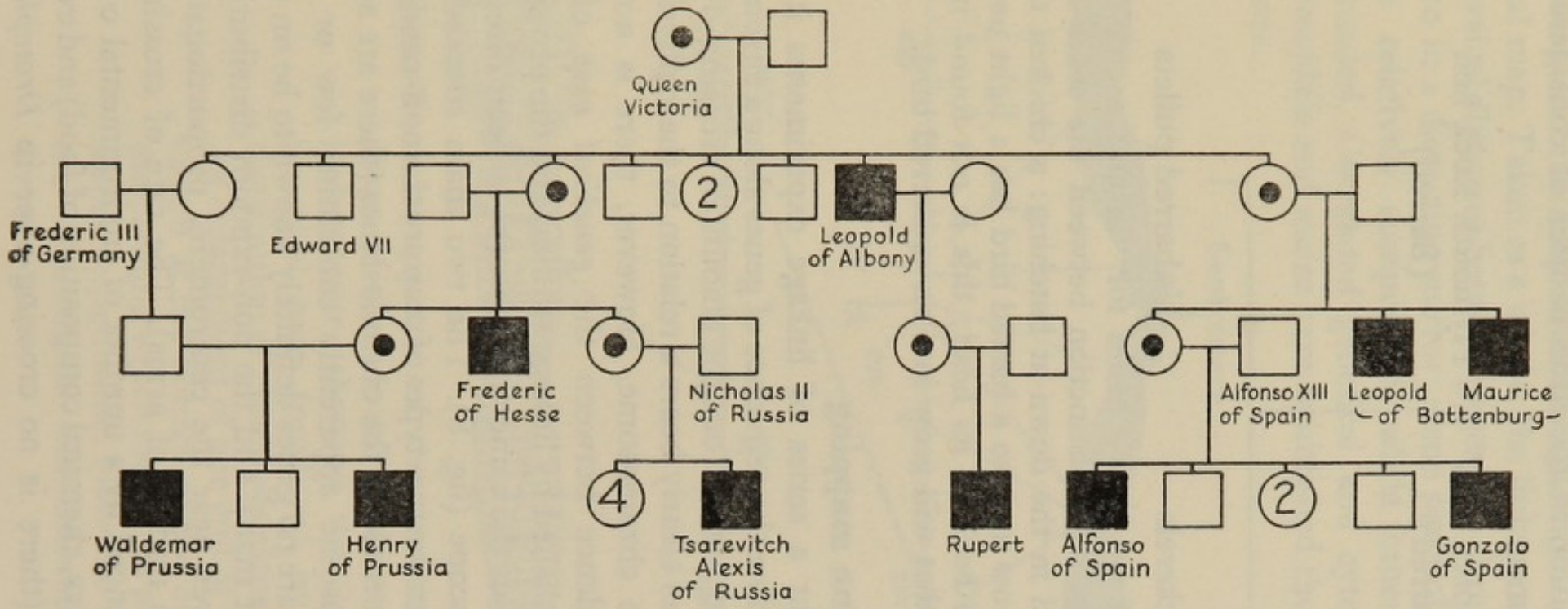


Figure 6 Pedigree of the descendants of Queen Victoria to show the transmission of haemophilia (a trait determined by a sex-linked recessive gene). All of Queen Victoria's own children are shown, but only some of their children. □ represents a man, ○ a woman; a black square indicates a haemophiliac; ⊙ are women who are heterozygous for the haemophilia gene (and are therefore unaffected by it, although they are 'carriers').

This early recognition of the sexes is often of considerable economic importance.

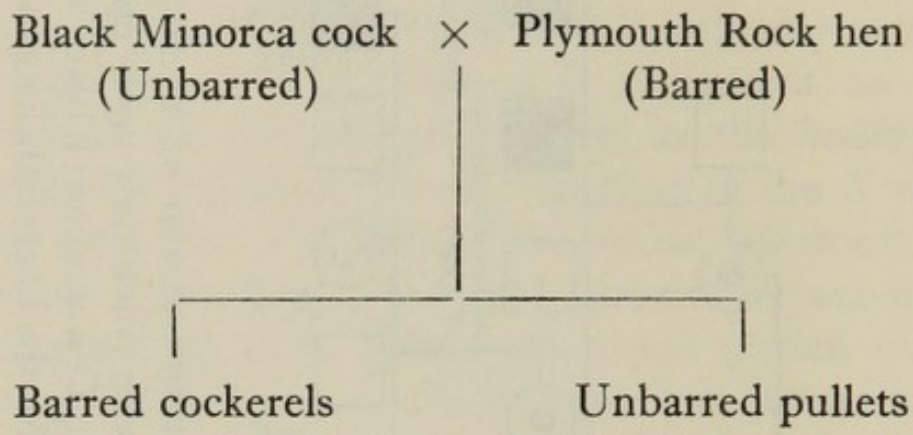


Figure 7 Use of sex-linked genes for "instant sexing" of poultry. The distinction between the sexes can be told in the down at hatching: a chicken that will grow up into a barred bird has a light patch on the back of its head; this is not found in a chick that will grow into an unbarred bird.

4.4 Chromosome mapping

By carrying out a series of linkage experiments it is possible to determine the sequence of genes along a chromosome. As has been pointed out the amount of crossing-over between two genes clearly bears a relation to their physical separation on the chromosome. However, there is not a direct correspondence between the *genetical map* of a chromosome established by linkage studies, and the physical or *cytological map* of the same chromosome as seen directly under the microscope (fig. 8). The two main sources of differences between the two types of map are the non-random distribution of genes along the chromosomes (there are segments of chromosome apparently containing few or no genes; thus there are no genes definitely known to be on the *Y* chromosome of man), and the non-random distribution of chiasmata (fewer near the centromere, proportionately more towards the middle of arms). The rate of crossing-over can be influenced by a number of environmental conditions (heat, X-rays, chemical composition of food) and even genetical factors (there is no crossing-over in *Drosophila*

males), and this may affect the spacing of genes on the genetical map. Taken as a whole, the linkage maps represent the physical distances between genes on a chromosome as though seen in a distorting mirror; some parts of the chromosomes are relatively compressed, while other parts are over-extended. Correlated genetical and cytological studies in *Drosophila* and maize have established the situation of many genes.

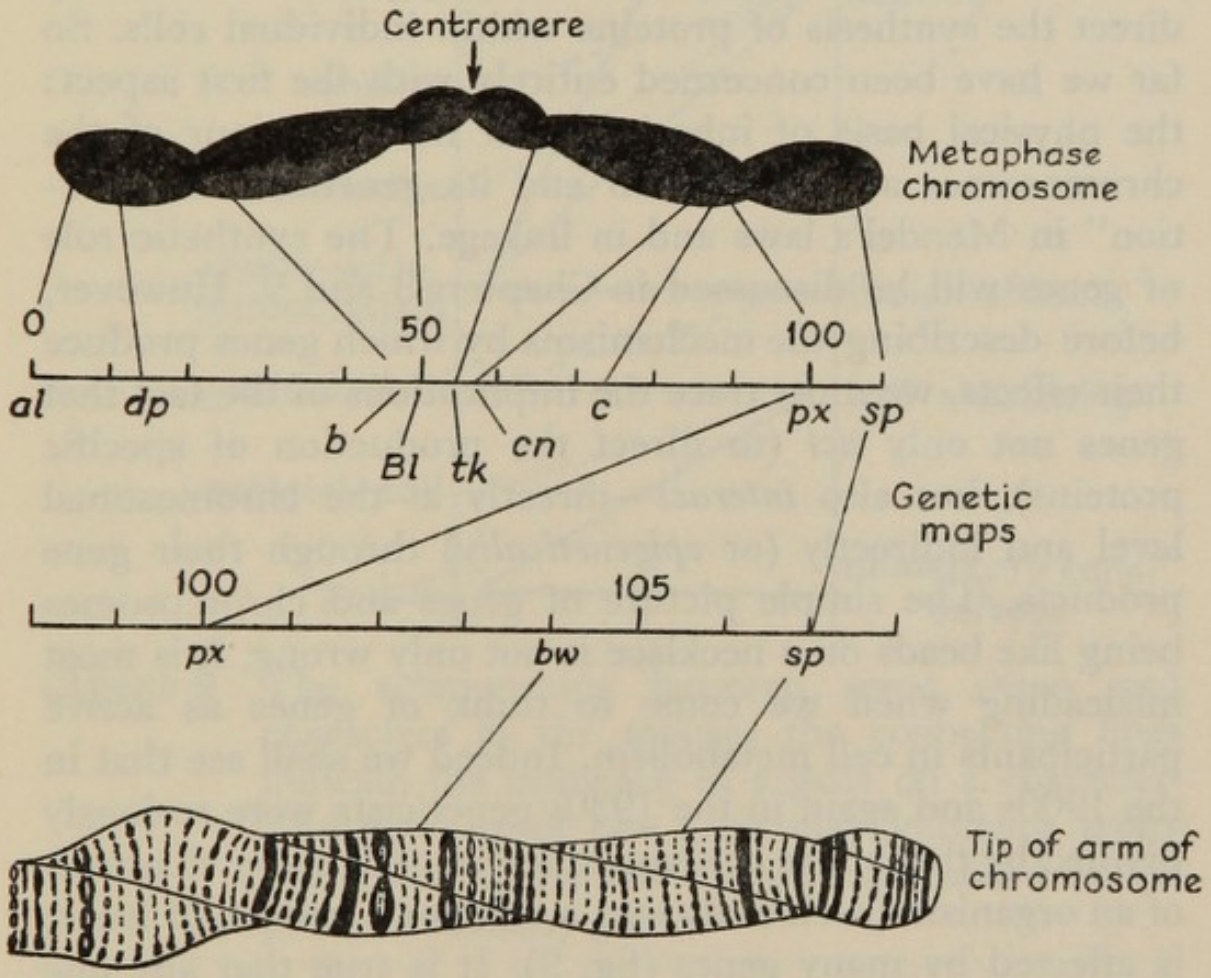


Figure 8 A comparison of the genetical and cytological maps of the second chromosome of *Drosophila melanogaster*, showing the "distortion" of the genetical map (produced by the non-random distribution of chiasmata along the chromosome). An enlargement of one end of the chromosome is shown at the bottom of the diagram, illustrating the banding which makes the parts of the chromosomes recognizable. Note the accurate pairing of the homologous chromosomes. *Redrawn from* CYTOLOGIA.

CHAPTER 5

INTERACTION OF GENES

GENES do two things: they replicate themselves and hence have a continuity from generation to generation, and they direct the synthesis of proteins within individual cells. So far we have been concerned entirely with the first aspect: the physical basis of inheritance in the behaviour of the chromosomes at cell division and its genetical "explanation" in Mendel's laws and in linkage. The synthetic role of genes will be discussed in Chapters 8 and 9. However, before describing the mechanisms by which genes produce their effects, we must trace the implications of the fact that genes not only *act* (to direct the production of specific proteins), but also *interact*—directly at the chromosomal level and indirectly (or *epigenetically*) through their gene products. The simple picture of genes and chromosomes being like beads on a necklace is not only wrong, it is most misleading when we come to think of genes as active participants in cell metabolism. Indeed we shall see that in the 1900s and again in the 1930s geneticists were seriously divided by the failure of some to realize that every character of an organism (such as an eye, a wing or a pattern of hairs) is affected by many genes (fig. 9). It is true that any one character is influenced more strongly by one or a few genes (which are described in "shorthand" language as 'determining' or 'being responsible for' that character) but there are a great number of other genes which in some way *modify* the character under consideration. Thus there is in the mouse a gene, the effect of which varies from 'causing' a slight shortening of the tail to 'causing' the early death of its carrier through abnormalities of the kidneys—the variation depending on other genes that are present in the genotype.

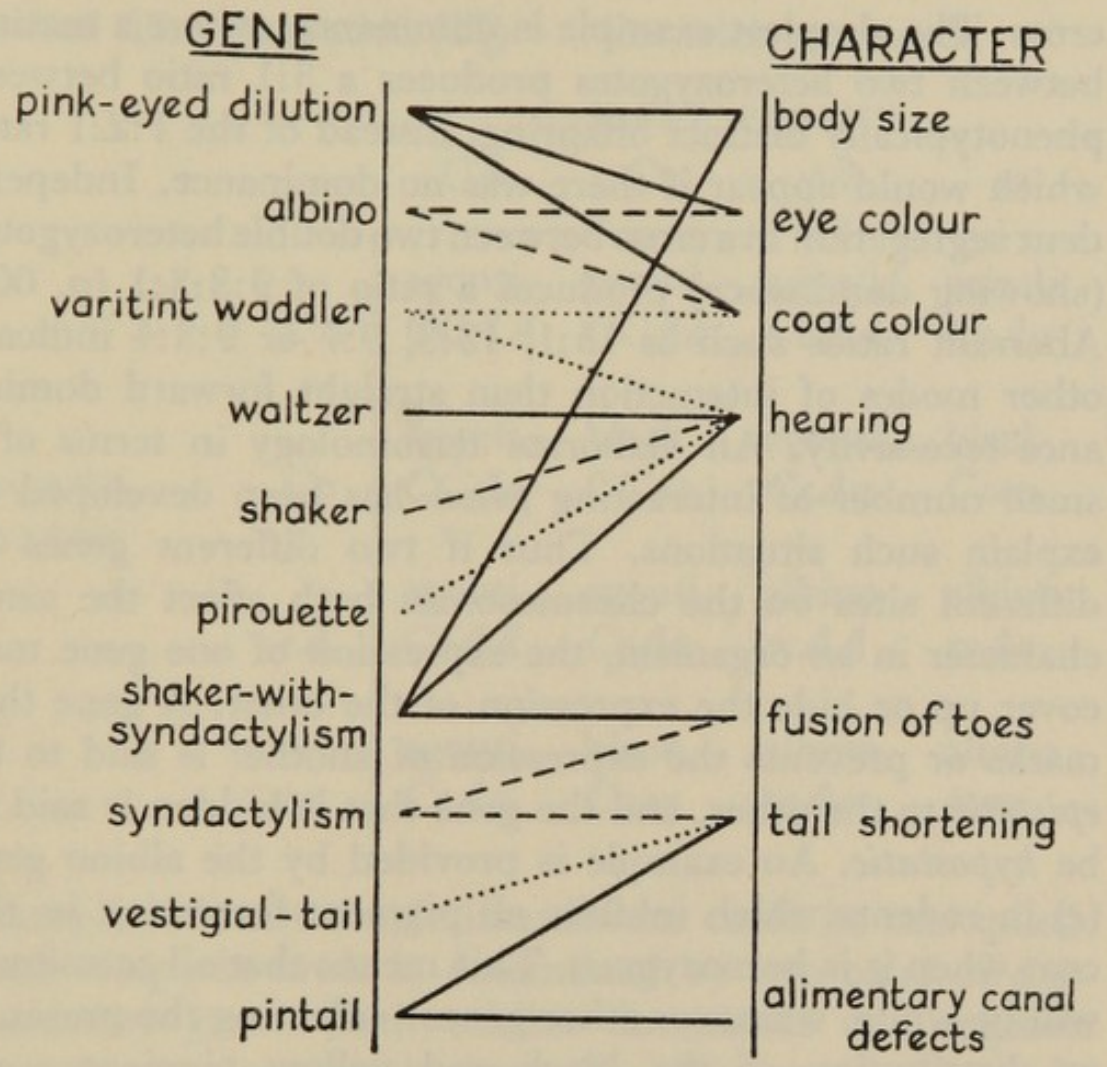


Figure 9 The relationships between some genes and characters in the mouse; the connecting lines indicate the influence of a gene on a character. The product of one gene may influence many characters; a character may be influenced by the product of many genes.

Genic interactions can be understood most easily if only two or a few genes are involved and we shall first present examples of this state of affairs. However, we then have to go on to consider the whole phenotype, in order to appreciate the full range and importance of interactions between genes.

5.1.1 **Interaction between specific loci**

One effect of gene interaction is to lead to the modification of the ratios of different phenotypes produced in a

cross. The simplest example is dominance, where a mating between two heterozygotes produces a 3:1 ratio between phenotypically distinct offspring, instead of the 1:2:1 ratio which would appear if there was no dominance. Independent segregation in a cross between two double heterozygotes (showing dominance) produces a ratio of 9:3:3:1 (p. 00). Aberrant ratios such as 15:1, 13:3, 9:7 or 9:3:4 indicate other modes of interaction than straight forward dominance-recessivity. An elaborate terminology in terms of a small number of interacting genes has been developed to explain such situations. Thus if two different genes at different sites on the chromosomes both affect the same character in an organism, the expression of one gene may cover up or hide the expression of the other. A gene that masks or prevents the expression of another is said to be *epistatic* to the other, and the gene that is hidden is said to be *hypostatic*. An example is provided by the albino gene (*c*) in rodents which inhibits all pigment formation in the coat when it is homozygous. This means that all *cc* animals will be white, whatever other genes—affecting the presence or distribution of the black and yellow pigments—are present. If we consider only two loci, the albino (*C*,*c*) and the agouti (*A*,*a*) (which is responsible for the banding of black and yellow pigments in the hair), an animal which is *aa* will be black if it also carries the *C* gene, whilst an animal which is homozygous for *c* will be white whether it is *AA*, *Aa* or *aa*. Hence a cross between a black (*CCaa*) and an albino (*ccAA*) mouse will give all agouti (normal mouse colour) mice (*CcAa*) in the F_1, and these mated amongst themselves will produce a ratio of 9 agouti: 3 black: 4 albino in the F_2.

Thus:

Parental generation (P_1)	black	×	albino
	CCaa		*ccAA*
First filial generation (F_1)	agouti		
	CcAa		

Second filial generation (F_2) Gametes produced:

		FIRST PARENT			
		CA	*Ca*	*cA*	*ca*
SECOND PARENT	*CA*	agouti *CCAA*	agouti *CCAa*	agouti *CcAA*	agouti *CcAa*
	Ca	agouti *CCAa*	black *CCaa*	agouti *CcAa*	black *Ccaa*
	cA	agouti *CcAA*	agouti *CcAa*	albino *ccAA*	albino *ccAa*
	ca	agouti *CcAa*	black *Ccaa*	albino *ccAa*	albino *ccaa*

Examples of such simple interactions could be multiplied: comb shape in fowls is determined by two pairs of *complementary genes*. Both exhibit dominance and together produce a walnut comb shape (fig. 10); one dominant by itself produces a pea or rose comb; the double recessive gives a single comb. The seeds of some strains of maize are purple due to anthocyanin pigment in the outer (aleurone) layer. The pigment is formed by the interaction of dominant genes at three or more different sites on the chromosomes (*loci*). The action of these dominant genes is complementary and each one controls a step essential for the production of pigment. The absence of any one of them throws the whole anthocyanin-forming machinery of the plant out of order.

Genes are known which have little or no effect themselves on a particular character, unless some specific "main" gene is present, when they modify its effect. Thus there is a gene (*W*) in the mouse which is lethal (due to a severe anaemia) when homozygous, and produces white spotting in the heterozygote. The amount of spotting varies from a very small amount to an almost completely white coat, depending

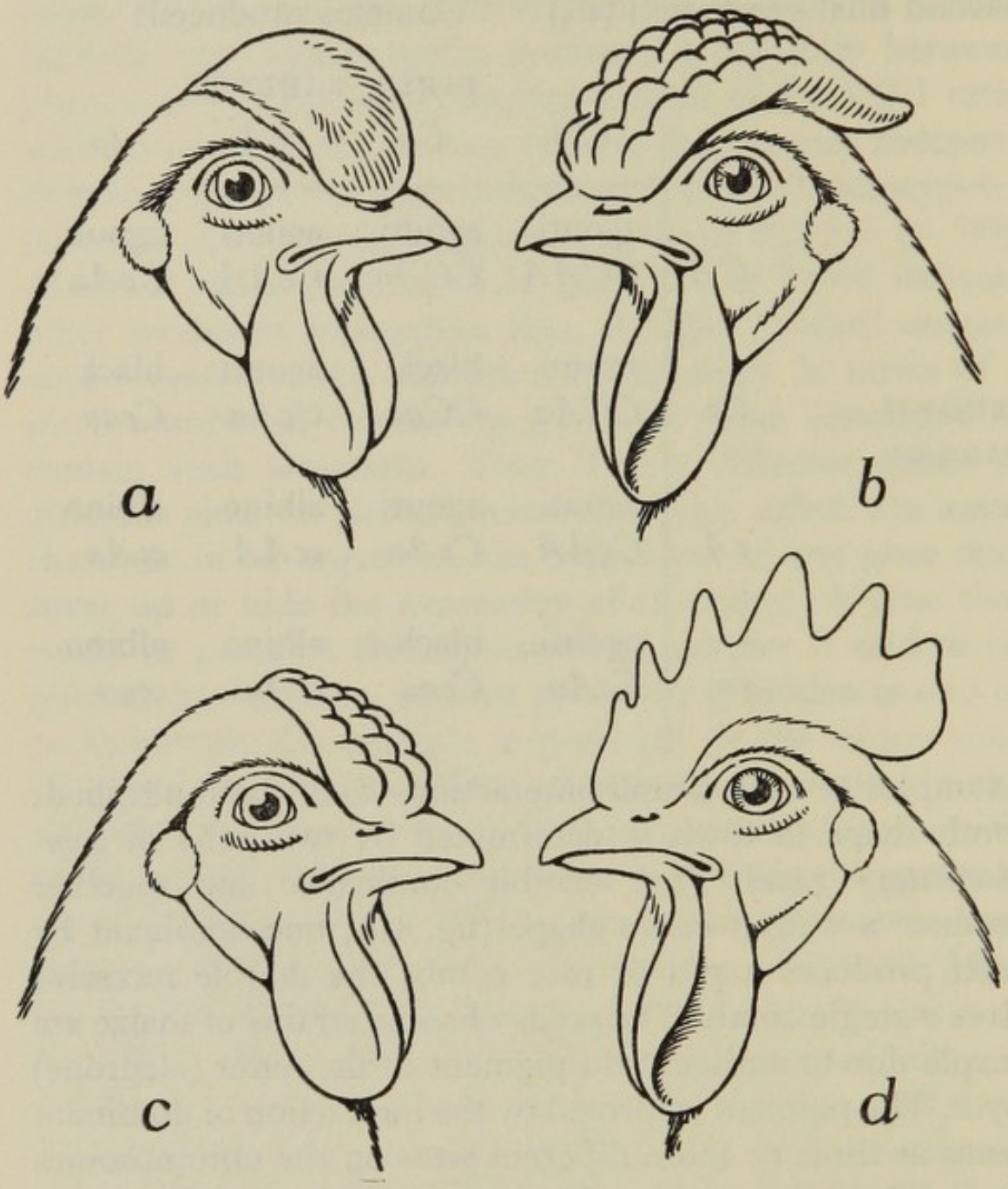


Figure 10 Comb shapes in poultry illustrating complementary gene action. (a) walnut (b) rose (c) pea (d) single. Pea and rose are each due to a separate gene both of which are dominant to single, which is the double recessive. Walnut is the double dominant.

on a number of modifying genes. Yet a normal (*ww*) mouse with many of these modifying genes present has no sign of white spotting; the animal is unspotted unless *W* is present. Other genes have been recognized whose sole known

phenotypic effect is to *suppress* the manifestation of another gene (p. 89).

The action of genes may be dependent on their relative positions to one another on chromosomes, or their position relative to the more genetically inactive and more densely staining portions of the chromosomes (the heterochromatic regions)—the *position effect* (p. 69). However, cases of genic interaction due to physical relationships along the chromosomes appear to be in the minority. The integration of physiology and development is not based on gross chromosomal architecture as was believed during the early period of cytogenetics. Indeed, it is probable that genes which interact and which are linked may have been secondarily brought together on the same chromosome through translocation (p. 70).

It is perhaps best to use some such general term as *epistatic interactions* to indicate interactions between different loci either on the same or on different chromosomes. Specialized terminology becomes inapplicable as it is discovered that more and more loci are involved in most interactions. It is becoming increasingly evident that a gene is characterised not only by the chemical nature of its product, but also by the period in the developmental process when it is active, and by the quantity of its product (see Chapter 9). Jacob and Monod's model of gene action (p. 89) has emphasized a new level at which genic interactions can take place. The abandonment of the concept of the gene as a bead on a string has rendered meaningless the older, more naive understanding of gene interaction, while extending the range and importance of the subject.

5.1.2 **Dominance of genes in man**

The majority of "abnormal" genes are recessive in most organisms. Man is peculiar in that most of the abnormal (or *mutant*) genes known in him are dominant to the normal ones (this is partially an adjunct of the clinical care of individuals which means that genetically produced variations too small

to be noticed in an animal are recognized. Although many conditions are described as being dominantly inherited in man, it would be more correct to describe them as exhibiting "intermediate inheritance" or "no dominance", since the homozygote (when known) is almost invariably much more severely affected than the heterozygote). These small dominantly-inherited variations can provide instructive examples of gene interaction. For example a mild, dominantly inherited trait such as gout which has been inherited in a family for generations, may become suddenly more serious and acute in certain members, or, alternatively, "skip" a generation by failing to appear as a disease in an individual who is carrying the gene (as shown by biochemical tests, or by his transmitting the gene to his children). These variations in the *expressivity* and *penetrance* of genes are almost certainly a consequence of other genes at different places on the chromosomes (i.e. *non-allelomorphic*) which interact with the mutant gene and modify the manifestation of the condition in question. In a species such as the human one where individuals tend to actively avoid marrying close relatives, different combinations of genes are continuously being formed (probably about 30% of all gene sites (*loci*) in a single individual are heterozygous), and this means that different individuals are liable to have a trait affected by different allelomorphs of genes. Hence there is much potential variation.

Man is, of course, in no sense unique in showing variation in the expression of dominance: we shall discuss several cases in other animals in Chapter 10. The point to be made here is that some of the apparently inconstant features of human heredity are a consequence of gene interaction; the reduction of variability that is found in, for example, thoroughbred dogs is an artificial result of consciously selecting for constant features.

5.2 Multifactorial inheritance

We have already mentioned two examples of complemen-

tary gene action. To these may be added the determination of skin colour in man, where it is alleged that all the varieties of colour of mulatoes, quadroons, etc., that emerge from "mixed" marriages can be accounted for in terms of two gene loci (*A* and *B*) each with two allelomorphs (A^1, A^2 and B^1, B^2) which exhibit no dominance, together with the "minor" genetical factors that cause variation within individual races. The assumption of two loci with two allelomorphs at each makes 9 different genotypes possible, and, if the genes are perfectly additive (e.g. if every gene not possessed by a white man increases the pigmentation equally), these fall into five phenotypic classes:—

		$A^1A^1B^2B^2$		
	$A^1A^1B^1B^2$	$A^1A^2B^1B^2$	$A^1A^2B^2B^2$	
$A^1A^1B^1B^1$	$A^1A^2B^1B^1$	$A^2A^2B^1B^1$	$A^2A^2B^1B^2$	$A^2A^2B^2B^2$
White				Negro

The next more complicated case is where there are three-loci (*A*, *B* and *C*) each with two allelomorphs. Here there will be 8 different gametes ($A^1B^1C^1$, $A^2B^1C^1$, $A^1B^2C^1$, $A^2B^2C^1$, $A^1B^1C^2$, $A^2B^1C^2$, $A^1B^2C^2$, $A^2B^2C^2$) and, assuming additiveness of the gene effects, they will combine to produce 7 phenotypic classes in the ratios 1:6:15:20:15:6:1. The more loci and allelomorphs involved, the more classes will result, and the greater will be the number of genotypes and individuals in the middle class. Furthermore, the more classes there are, the less will be the difference between adjacent classes; it may be impossible to separate classes on phenotypic appearance alone. In such a case the character (e.g. size, intelligence) has to be described by measurement and is spoken of as a quantitative rather than a qualitative character.

In the nineteenth century, the *biometricians* (i.e. those who measure biological material) led by Galton and Weldon, argued that there is a fundamental difference between the inheritance of discontinuous, qualitative charac-

ters and continuous, quantitative ones. This claim resulted from the difficulty of applying Mendel's methods of analysis to continuously varying traits because they seem to mix or blend, instead of segregating, in the offspring of hybrids. Galton found it possible to determine the degrees of likeness between relatives by means of the method of correlation. His statistical methods need not concern us; it suffices to say that for any particular character, a correlation coefficient of one between two individuals would imply perfect resemblance, whereas zero correlation would mean no likeness and, by implication, no hereditary influence. A parent and a child, or a brother and a sister have half their genes in common; the correlation coefficients between them for height are both about 0·5. Identical twins (formed from the division of one fertilized egg and, hence both possessing exactly the same genes) have a correlation coefficient of about 0·95 even when reared apart, suggesting that this resemblance is almost entirely genetically determined and not due to a common environmental factor such as diet. Now if the heights of everyone in a population are plotted on a graph, a symmetrical curve is obtained with most people being of an intermediate "average" height (fig. 11b). This curve is basically the same as the histogram of distribution of different phenotypic classes assuming a number of different loci and allelomorphs. In other words, quantitative "blending" inheritance can be accounted for by supposing that continuously varying traits are due to the joint action of several or many genes. There is no need to postulate a different sort of inheritance. Moreover, since the greater the number of genes segregating, the fewer will be the proportion of individuals manifesting the extreme expression of the character in question, it is possible to estimate the number of loci involved in a *multigenic system* from the proportion of extreme individuals found. Using this method (and bearing in mind the discussion at the beginning of this chapter), it has been calculated that many quantitative characters represent the composite influence of

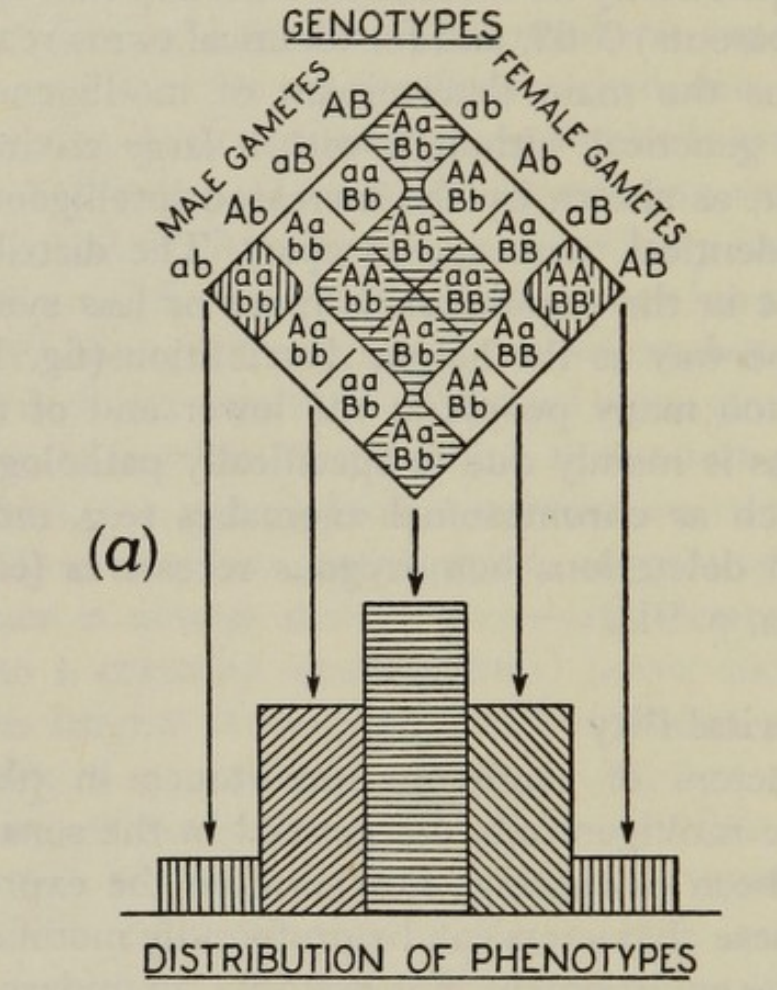
genes at more than 10 and sometimes as many as 200 loci.

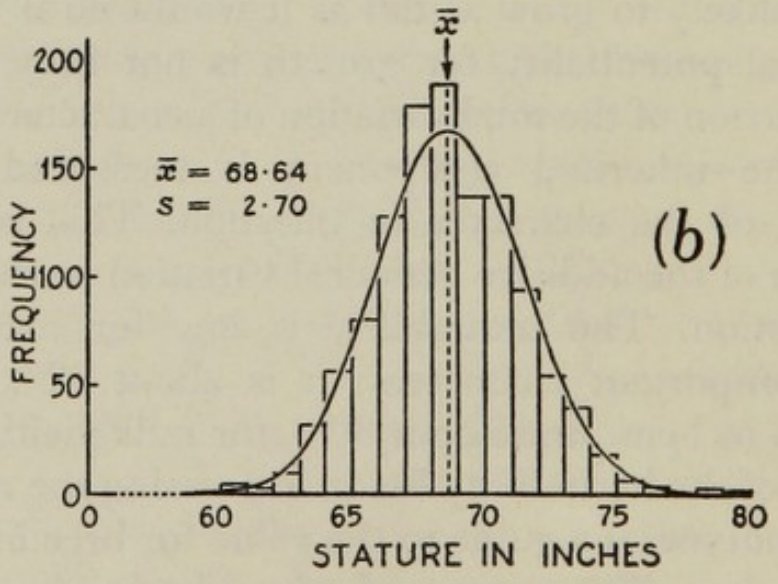
In man, many socially and culturally important characteristics are inherited in the same way as height. For example, the correlation coefficients between identical twins for intelligence quotient (I.Q.) is 0·88, for non-identical twins (who are genetically no more alike than any two children of the same parents) 0·63, and for identical twins reared apart 0·77. Thus the main determinant of intelligence is undoubtedly genetical, although with a large environmental component, as shown by the increased intelligence differential of identical twins reared apart. The distribution of intelligence in the population is more or less symmetrical in the same way as the height distribution (fig. 11b), but there are too many people at the lower end of the scale. This excess is mainly due to specifically pathological conditions such as chromosomal anomalies (e.g. mongolism, p. 68) and deleterious homozygous recessives (e.g. phenylketonuria, p. 91).

5.3.1 **Heritability**

Most factors of economic importance in plants and animals are multigenically determined in the sense that we have just been discussing. Furthermore the expression of many of these characters can be profoundly modified by the action of the environment. For example, an undernourished child is unlikely to grow as tall as it would do if well fed; its genetical potentiality for growth is not fully realized. The proportion of the total variation of a character attributable to the inherited component is measured by the *heritability* of the character in question. This is defined as the ratio of the additive genetical variation to the phenotypic variation. The heritability is low for many commercially important characters: it is about 32% for egg production in hens, and about 30% for milk yield in cattle. The value of the heritability lies in expressing the reliability of the phenotype as a guide to the value for breeding of the animal or plant. The success of a breeder in changing the

characteristics of a population (by *selecting* for desirable traits in the organisms he breeds from) can be predicted from a knowledge of the heritabilities of the characters concerned.





5.3.2 **Polygenic inheritance**

As is usual, much research is carried out on any problem involving economic advantage, and the nature of the genes concerned with commercially valuable characters come under this heading. In the early days of genetics it was thought that all recognizable characteristics could be attributed to "major" genes whose expression was affected by "modifying" genes. More recently Mather has suggested that there is a difference in principle between genes with conspicuous, discontinuous (i.e. non-overlapping) con-

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Figure 11 Multifactorial inheritance.

(a) The relationship between genotypes and the distribution of phenotypes when the phenotype is determined by two gene loci each with two equally common and additive allelomorphs. Assuming no dominance, the expression of any of the phenotypes will be proportional to the number of capitals (0, 1, 2, 3 or 4). The more genes that are involved, the greater will be the number of phenotypic classes, and the less the difference between adjacent ones.

(b) Histogram of the distribution of height of 1,164 men grouped into one inch classes. Superimposed on the height distribution is a *normal distribution curve* which would apply if stature is determined by a large number of genes with an additive effect. The mean height of the group ($\bar{x}$) was 68·64 inches, and the distance of the mean from the points of maximum slope of the curve (the standard deviation, s) was 2·70 inches. The mean and standard deviation characterize any normally distributed variable.

Based by permission on a figure in THE ELEMENTS OF GENETICS *by Darlington and Mather, published by George Allen & Unwin Ltd.*

tributions to the phenotype (which he cells *oligogenes*), and genes with slight contributions resulting in the sort of continuous variation exemplified by height or intelligence (*polygenes*). Modern opinion tends not to support this distinction: every character is affected by numerous genes and is therefore polygenically determined, and hence virtually every gene is a polygene. On the other hand, there are nearly always a relatively few genes that make the major contribution to the determination of a character. The fewer these major genes and the larger their individual contributions the more discontinuous will the variation appear. However, continuous variation is often loosely called polygenic variation nowadays. The use of the term may perhaps be justified in emphasizing the complex nature of the genetical determination of such traits.

5.4 **Further types of interaction**

So far we have considered normal genic interactions. There are a number of further phenomena which must be included here. As knowledge of the structure of the genotype progresses many more such complications will undoubtedly be discovered. Until our understanding is more complete, we cannot evaluate their relative importance.

Lyonisation of the X-chromosome

In a number of mammals, including man, if there is more than one *X* (sex) chromosome, all but one of them in each nucleus become non-functional and condensed forming *sex chromatin*. In any cell or group of cells the *X*-chromosome which is "lyonised" in this fashion seems to be random, although chromosomes carrying a mutant gene may suffer the fate more readily than normal ones.

Unequal segregation

In several species of *Drosophila* there is a gene which leads to degeneration of *Y*-bearing spermatocytes. This is compensated for by a double division of the *X*-bearing

spermatocytes. As a result, the normal number of spermatozoa is produced, but all produce females (since they carry the *X*-chromosome) and all carry the sex-ratio gene. Mice carrying a certain gene, which is frequently lethal when homozygous, nevertheless produce sperm about 90% of which carry the gene, apparently due to some prezygotic advantage. Similarly, the sex-ratio in man is approximately 1·6:1 in favour of males at conception, presumably due to the greater activity or efficiency of *Y*-bearing sperm.

Affinity

Cases have been reported of failure of independent assortment of genes in meiosis leading to pseudo-linkages, apparently due to attraction between some of the centromeres of chromosomes derived from the same parent.

5.5 **The coherence of the genotype**

We cannot conclude this chapter without a mention of the consequence of interactions on whole organisms rather than on specific characters. For example, one of the features of experiments where an organism is selected for greater (or less) expression of some character is the tendency of the phenotype to return to the original condition when selection is relaxed, whether it be for increased bristle number or body size in *Drosophila*, or increased egg size in the domestic fowl. This phenomenon has been named *genetical inertia* or *genetical homeostasis* and defined as the "property of a population to equilibrate its genetical composition and to resist sudden changes." It is a direct consequence of the fact that the development of an organism is a finely adjusted and linked system, and juggling with the components must have repercussions at many stages. The genotype should be thought of as a unity controlling the functional integration of development. This unity is an immensely conservative force serving as a brake on all forms of genetical change. Even a change which leads to an improvement in the phenotype may have difficulties in fitting into such a system. For

example, lengthening of teeth in fossil horses took place at the rate of about one millimetre per million years. To be of real value an improvement in the teeth has to be correlated with a strengthening of the upper and lower jaws, and with numerous other readjustments of the skeleton, the muscles and, presumably, even the digestive and nervous systems .It is unlikely that any structure is so independent of its fellows that it is able to change without a consequent change in other structures.

The definition of genetical homeostasis mentions "the population." Integration of the genotype within interbreeding populations is a necessary—albeit more complicated—corollary of the integration of individual development. Crossing-over between chromosomes (recombination) produces in every generation new assortments of genes (new genotypes), which in turn have to form viable phenotypes. This means that there must be harmony among all the genes which a population contains. This internal cohesion of a population genotype is of practical importance in the discussion of the impact of raised mutation rates on a population (p. 143).

CHAPTER 7

CYTOPLASMIC INHERITANCE

THE inherited characters of an organism in the normal sense are carried by the chromosomes in the nuclei of cells. Of this there can be no question. However, the major part of any individual is extra-nuclear material: even gametes whose sole function is to act as vehicles of nuclei contain some cytoplasm. Now cytoplasm contains many particles and it is perhaps not surprising that some of these may occasionally be transmitted from one generation to another. Such *cytoplasmic inheritance* is not subject to the same regular rules as nuclear inheritance, but in some cases it seems to be of importance.

The most direct way of investigating the relative genetical roles of nucleus and cytoplasm is to separate the two. If the nucleus of an egg of a sea urchin or amphibian is removed, the cytoplasmic mass which remains undergoes "cell division", although this comes to an end before any of the cell movements that take place in early development (*gastrulation*). More information can be obtained from removing the nucleus from an egg, and replacing it with the nucleus from another species. The early cell divisions of such a *merogon* are normal and can in some cases be shown to follow the pattern of the species from which the cytoplasm is derived. However, there is soon a crisis (usually in the early gastrula stage) and development stops. It is presumably at this time that the genetical factors take over control of development. Development proceeds to more advanced stages in combination between more closely related species than in "distant" combinations. Where development proceeds, the structures that develop are the ones characteristic of the species contributing the nucleus.

6.1 Differences in reciprocal crosses

A large number of cases of inheritance through the cytoplasm have been described. They may perhaps be more accurately described as *non-chromosomal* inheritance. They are identified primarily by their non-segregation at meiosis, so that crosses between two contrasting parents give rise to progeny exclusively of one parental type—the type of the parent that contributes most cytoplasm to the zygote. For example, streptomycin resistance is transmitted solely by the "positive" mating partner in the ciliate *Chlamydomonas*; in the bread mould *Neurospora* the slow-growing characteristic of a strain called *poky* crossed with a normally growing one shows non-segregation in meiosis, inheritance through one parent alone and, a direct corollary, the impossibility of placing the "gene" on the chromosome map.

An elegant example of the effect the cytoplasm can have is provided by the direction of shell coiling in the water snail *Limnaea peregra*. This is determined by a single gene pair, and right hand coiling is dominant to left hand coiling. However, the direction of coiling is controlled not by an individual's own genes, but by those of its mother: it is, in fact, dependent upon the orientation of the second (possibly the first) division of the fertilized egg. This in turn is determined by the influence of the mother's genes on the ovary (fig. 12). Although this is strictly speaking an example of maternal predetermination of a tendency rather than of a particle transmitted through the cytoplasm, nevertheless it illustrates the importance of the cytoplasm in the "inheritance" of a characteristic.

6.2 Chloroplast heredity

Many chromosomally located genetical changes (mutations) are known which affect chloroplasts (the chlorophyll containing structures in the leaves of green plants). There have been over fifty described in maize alone. There are also many cases of cytoplasmic inheritance of chloroplast mutations, the easiest to study being striped or "variegated"

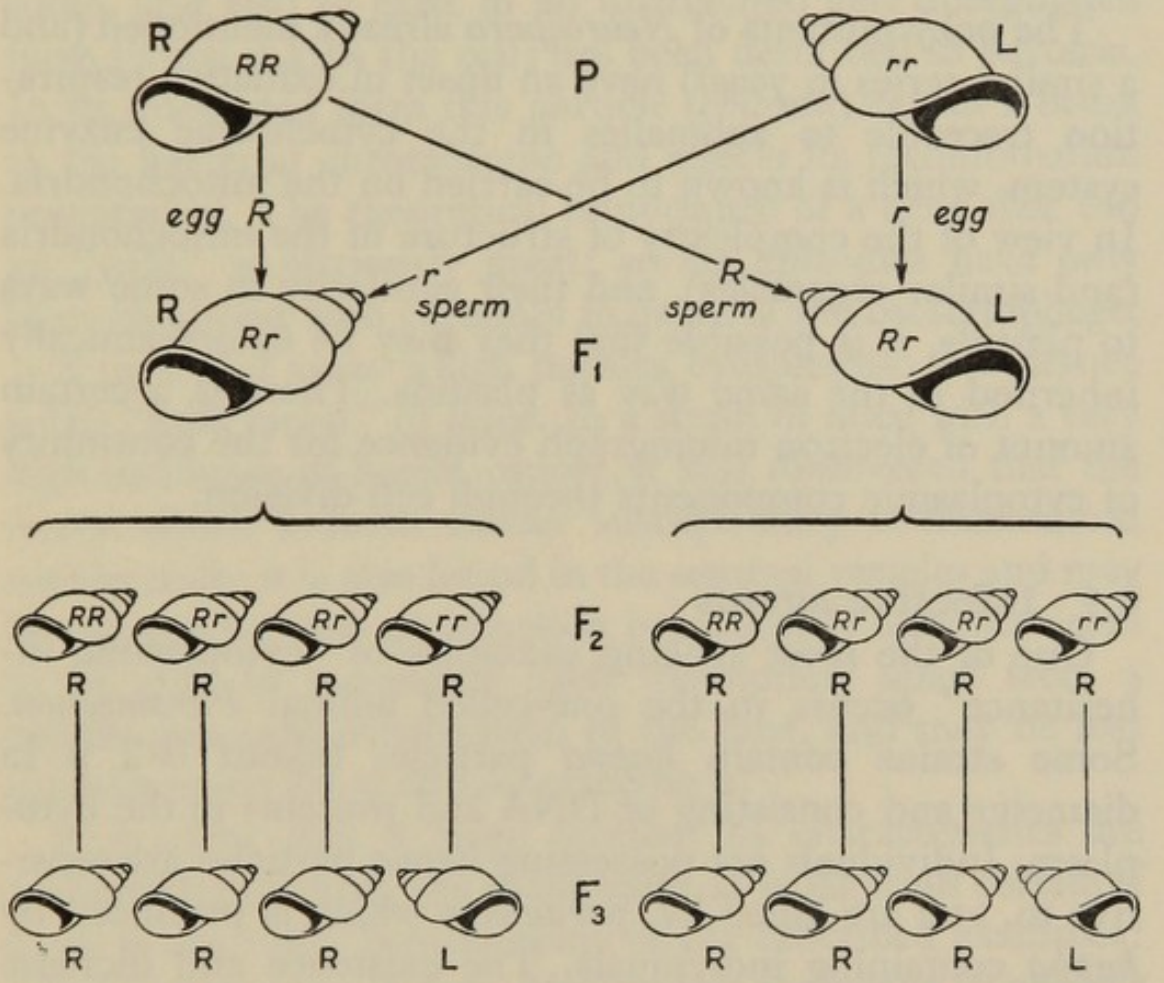


Figure 12 Inheritance of the direction of shell coiling in *Limnaea peregra*; the phenotype is determined by the genotype of the mother. R = right-hand coiled phenotype, L = left-hand coiled phenotype; *R* is the dominant gene for right-hand coiling, *r* is the recessive allelomorph. The species is hermaphrodite and can be either cross or self-fertilized.

plants. The egg alone is responsible for transmitting either normal or pale chloroplasts, the pollen has no effect. Thus, flowers on green branches always give rise to green progeny, those on pale to pale, while those on mixed branches may give pale, green or variegated progeny.

The evidence does not reveal what or where is the chloroplast determinant: it could be anywhere in the cell except on the chromosome; it does not seem to be in the plastid (i.e. the chloroplast) itself.

6.3 Mitochondrial heredity

The poky mutants of *Neurospora* already mentioned (and a similar series in yeast) have an upset in oxidative respiration traceable to anomalies in the cytochrome enzyme system, which is known to be carried on the mitochondria. In view of the complexity of structure of the mitochondria (and similar organelles), and their similarity in some ways to plastids, it is possible that they may be cytoplasmically inherited in the same way as plastids. There is a certain amount of electron micrograph evidence for the continuity of cytoplasmic components through cell division.

6.4 Infective agents

One of the most striking examples of "cytoplasmic inheritance" occurs in the one-celled animal *Paramecium*. Some strains contain *kappa* particles (about 0·2 μ in diameter and consisting of DNA and protein) in the cytoplasm. Individuals not possessing *kappa* particles are sensitive to, and are killed by, *paramecin* which is produced by *kappa* containing individuals. The existence and increase of *kappa* particles is determined by the possession of a nuclear dominant gene, *K*. However, this gene cannot initiate *kappa* production; individuals must be "infected" with at least one particle, which can then increase. Conversely, a *kk* individual may contain *kappa* particles in its cytoplasm, although this state is unstable and eventually the particles disappear. *Kappa* is an extreme example of a class of genetic determinants which are not essential cell constituents, but which produce new traits in the host organism when they are present. Another example of the same thing is the heat-labile *sigma substance* in *Drosophila* which greatly increases the sensitivity of its carriers to carbon dioxide. It is almost always transmitted matroclinally (through the female); very occasionally it may be passed *via* sperm. Once *sigma* has entered a female, it becomes included in the gametes and subsequently transmitted.

A virus-like particle with the most curious property of

being able to be integrated (and mapped) on the chromosome, and also to exist in an unattached and unregulated form (when it kills the cell) has been described in bacteria. In its integrated form this particle (*episome*) causes a break in the bacterial chromosome and affects its recombination potentiality. The theoretical importance of a gene that can go "wild" is obviously great; so far episomes have only been identified with certainty in bacteria and bacteriophage.

A case of a virus which mimics cytoplasmic inheritance is the "milk factor" of mice. In a strain of mice with a very high incidence of breast cancer, it was discovered that the factor which induces cancer susceptibility is transmitted *via* the milk; it is also found in the seminal vesicles and may be transmitted like an infection by males. It does not seem to be able to reproduce itself indefinitely apart from a certain genetical constitution of the host, and may be lost spontaneously from strains carrying it.

It is clear that a large number of characteristics are transmitted through the cytoplasm. It is far from certain if there is any unity behind many of the described examples: whether there are, in fact, *plasmagenes* analogous to nuclear genes. In particular, we are almost totally ignorant about the nuclear control of cytoplasmic organization (which may be very complex), which could bear greatly on the chance of transmission of any given cytoplasmic body.

CHAPTER 7

MUTATION

DE VRIES (one of the re-discoverers of Mendel's work) in the early 1900s was struck by the unusual variability shown by the evening primrose (*Oenothera lamarckiana*) which he found growing as a weed in Holland. When he grew it in his garden it produced a number of striking *mutants*: large discrete changes of organization (e.g. of size, colour or shape of different parts, etc.) which, thereafter, bred true. De Vries, impressed by these genetical changes ("mistakes") or mutations, propounded a hypothesis of organic change (evolution) based upon them. However, the situation is not as simple as De Vries believed. It has since been shown that what he described as mutations represent a variety of changes. For example, some plants had an extra chromosome, one had all the chromosomes duplicated, and so on. However, De Vries introduced the idea of the origin of new genetical variability by distinct "mutations" and the study of the mutagenic process has been a central problem in genetics ever since.

7.1 **The characteristics of mutations**

From the earliest days of laboratory genetics mutations were occasionally noticed but their origin and effect seemed purely fortuitous, i.e. mutation is *spontaneous* and *random* in effect. Both of these statements are confessions of ignorance.

Mutations may occur in any cell at any stage of the life of an organism, but only those arising in (or including) the germ cells (sperm, ova, etc.) will be transmitted to future generations. For example, the fatal cancer of the blood, chronic myeloid leukaemia, arises as a "somatic" (that part of the body not concerned with reproduction) mutation, and hence it is not inherited in the normal sense.

A mutation may be dominant or recessive; viable or lethal. If it produces a deleterious effect which is expressed before the end of the breeding life of the organism, the fertility of the organism may be reduced and there will be *selection* against the mutant gene being transmitted.

7.2 Gene and chromosomal mutations

Many mutations can be detected cytologically in the chromosomes. Some (gene or "point") mutations are not so detectable. In the past it has been a matter of some dispute whether these "invisible" mutations are in fact distinct from the others, or whether they are only quantitatively different, e.g. it has been suggested that a broken chromosome which then rejoins will bear a scar which might alter the function of the gene in that place, i.e. bring about a mutation. There is a growing body of evidence, largely based on the relative efficiencies of certain chemicals and ionizing radiations in breaking chromosomes, that a chromosomal break is not a prerequisite of mutation, i.e. there is such a thing as a true "point" mutation (p. 140).

In some organisms (particularly those, such as *Drosophila*, with a few large chromosomes) chromosomal mutations are readily classifiable on cytological grounds:

(i) Whole chromosome sets may be involved leading to haploidy (p. 11) (usually lethal) or, by the addition of whole sets, various degrees of *polyploidy*. The fertility of polyploids is usually reduced because each chromosome has more than one homologue to pair with in meiosis. As a consequence, multivalent associations are formed, followed by difficulties in division. Polyploids are sometimes stronger and more vigorous than the corresponding diploids, and of economic importance in agriculture and horticulture, e.g. cultivated wheat, clovers, many varieties of roses.

(ii) There may be loss (*monosomy*) or gain (*polysomy*) of one or more chromosomes. The most usual mechanism of such *aneuploidy* (*lit.* variation from the true

number of chromosomes) is *non-disjunction*: during cell division one or more pairs of homologous chromosomes, instead of separating to opposite poles, both go to a single pole, resulting in daughter cells one of which lacks a chromosome, and one of which has an additional one. Monosomic organisms are, usually, inviable unless the chromosomes involved are the sex chromosomes: an *XO Drosophila* is a sterile male, an *XO* human is a sterile female (and is said to suffer from Turner's syndrome). The addition of chromosomal material in trisomy has variable, usually deleterious, results. The classical example concerns the American thorn-apple, *Datura stromium*, which normally has 12 pairs of chromosomes. Any one of these twelve may be triplicated and the resulting 12 trisomics can all be distinguished by the shape of the seed capsule. Seventy-five per cent of cases of the commonest single cause of mental defect in man, mongolism, follow non-disjunction during meiosis resulting in trisomy of one of the smallest chromosomes. The probability of non-disjunction in this case rises steeply with the age of the mother (the chance of producing a mongol child is as high as 2% or 3% for mothers aged over 45).

(iii) *Deletion*: part of a chromosome may be missing. Homozygous deletions are usually lethal; heterozygous deletions may appear as "normal" mutants, e.g. the *Drosophila* mutant *Notch* (which produces "notches" in the wing margins) is actually a short deletion in the *X*-chromosome, and is lethal in males. Paired chromosomes, one of which has a deletion, have a characteristic appearance (fig. 13) to enable homologous portions to be aligned.

(iv) *Duplication*: here a section of chromosome is duplicated. A heterozygous duplication has a similar appearance to a deletion, but, in general, duplications are less deleterious. The mutant "gene" *Bar* of

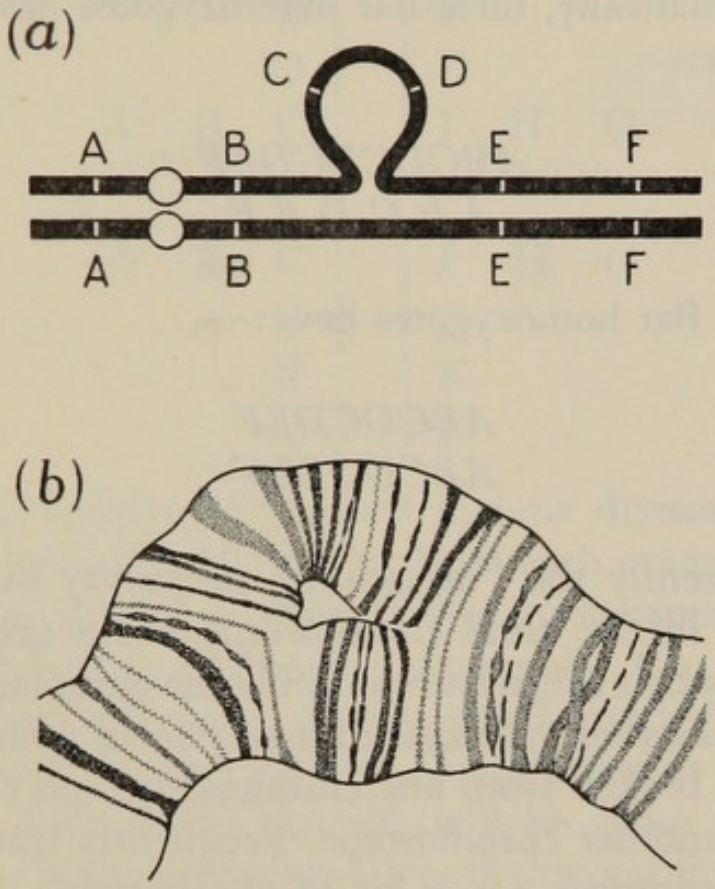


Figure 13 (a) Pairing of chromosomes, one of which has a deletion of the segment carrying C and D.

(d) Actual appearance of a pair of chromosomes in *Drosophila melanogaster*, one of which has a deficiency. Several bands which are clearly seen in the upper chromosome are missing in the lower (deficient) one.

Redrawn from GENETICS *by permission.*

Drosophila, which reduces the number of units (ocelli) in the compound eye, is, in reality, a duplication. Another feature of *Bar* is the exhibition of *position effect*: flies which are heterozygous for a normal chromosome and for one with two "Bar" duplications (ultra-bar heterozygotes) have smaller eyes than flies which are homozygous for the Bar duplication, despite the fact that both contain four

lengths of the particular section of the chromosome. Schematically, ultra-bar heterozygotes have chromosomes:—

ABCDCDCDEF
A B C D E F

while Bar homozygotes have:—

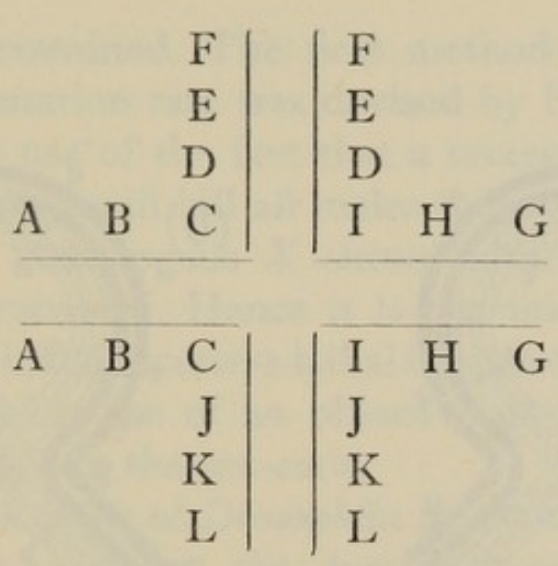
ABCDCDEF
ABCDCDEF

Apparently the "unnatural" proximity of D and C twice in the same chromosome has a greater effect than when this occurs in different chromosomes.

(v) *Translocation*: consists of a section of a chromosome being broken from one chromosome and *translocated* onto another chromosome. Frequently translocations are reciprocal, i.e. a bit of chromosome A becomes attached to chromosome B, and a bit of B to A. Organisms carrying a translocation are phenotypically normal unless a position effect is operating. They are, however, frequently *semisterile*. This is easy to see: if a reciprocal translocation takes place between two chromosomes so that

A B C D E F		A B C J K L
	become	
G H I J K L		G H I D E F

and the organism carrying this translocation is mated to a normal organism, the offspring will be heterozygous for the translocation, having a translocation in one of the chromosomes of two pairs. In order to pair at the pachytene of the first meiotic division, a *quadrivalent* will be formed:



At metaphase of the first meiotic division, the four centromeres will tend to repel each other, leading to a ring formation. Now if the chromosomes adjacent in the ring go to the same pole, the gametes so formed will have certain genes carried twice and certain not at all, and will almost certainly be inviable. The only viable gametes will be those which have either both translocated or both original chromosomes.

(vi) *Inversion.* Soon after the discovery of linkage and recombination, certain "C" factors were discovered in *Drosophila* which reduced or suppressed recombination in a certain chromosome or part of it. Cytologically it was found that such chromosomes contained an *inverted* segment which delayed or prevented the pairing of homologous chromosomes.

If a chiasma is established within the inversion (fig. 14), and if the centromere lies outside the inverted segment (*paracentric*), meiotic anaphase will contain a chromatid connecting the two centromeres ("dicentric bridge") and an acentric fragment. Both these will be lost leaving the two parental chromosome types. Similarly, if the inversion is *pericentric* (i.e. including the centromere within the inversion), all cross-over s products will contain duplications and deficiencies (although no bridges will be formed). Thus in either case crossing-over will be suppressed within the in-

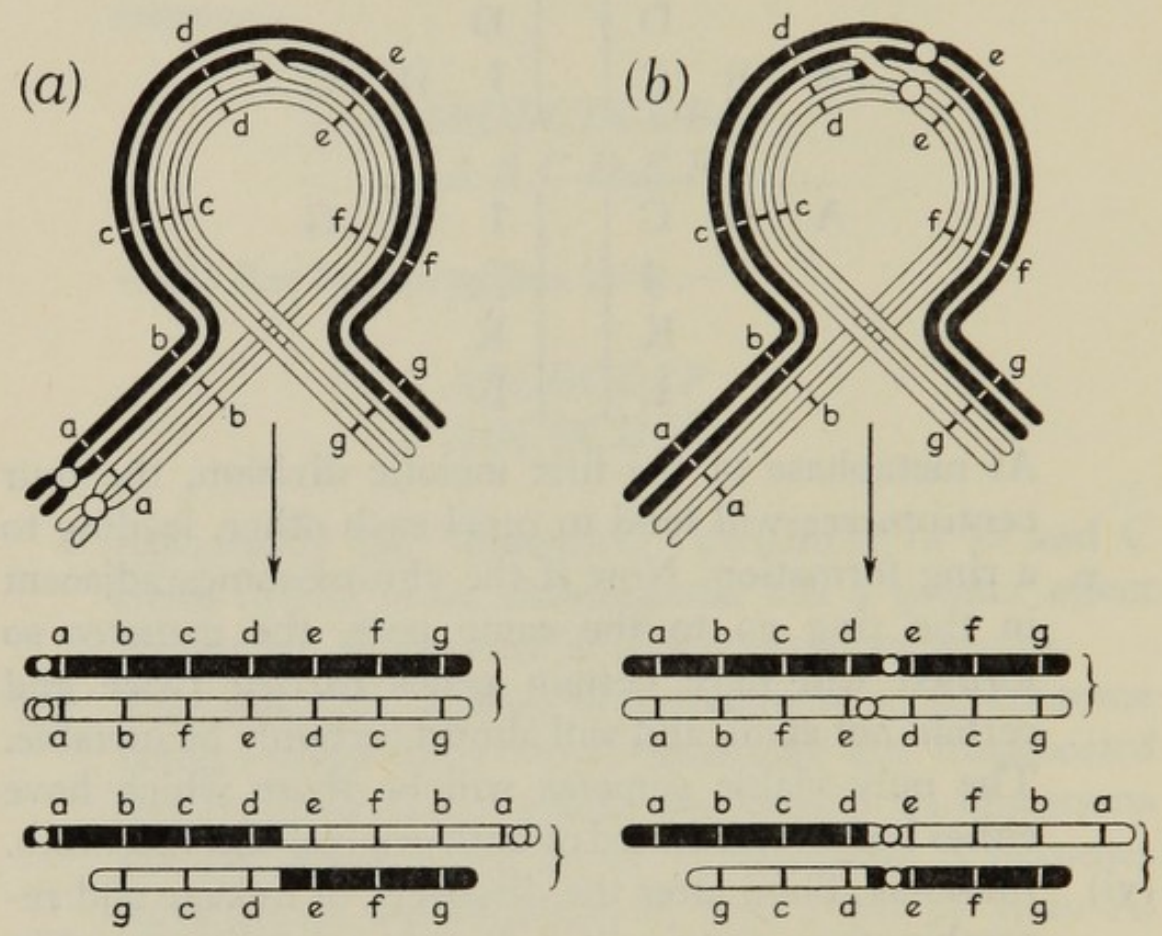


Figure 14 Effects of crossing over within (a) a paracentric inversion, (b) a pericentric one. A diagram of the appearance of the chromosomes during first meiotic division is shown above, and the resulting chromosomes below.

verted segment and the genes carried thereon will be completely linked.

7.3 The detection of mutations

A mutation may have a morphological or a physiological effect of varying degree. Clearly any study of mutation will depend very largely on the methods used to detect mutant individuals; the identification of changes in morphological characters will tend to depend on the care with which in-

dividuals are examined. The first method of objectively studying the mutation rate was devised by H. J. Muller in 1927. He made use of the fact that a recessive lethal gene which is sex-linked will kill all males that carry it, because males have no homologous *X* chromosome to counteract the lethal chromosome. Hence it is possible to count the number of sex-linked recessive lethal mutations in a group of animals by making use of an objective and easily scored character, changes in the sex-ratio.

Muller used a stock of *Drosophila* in which there was an *X* chromosome carrying: the dominant gene *Bar*, a recessive lethal and an inversion suppressing crossing-over (the ClB chromosome) (fig. 15). All males carrying the chromosome die, so mating between a ClB (heterozygous) female and a normal male give equal numbers of normal

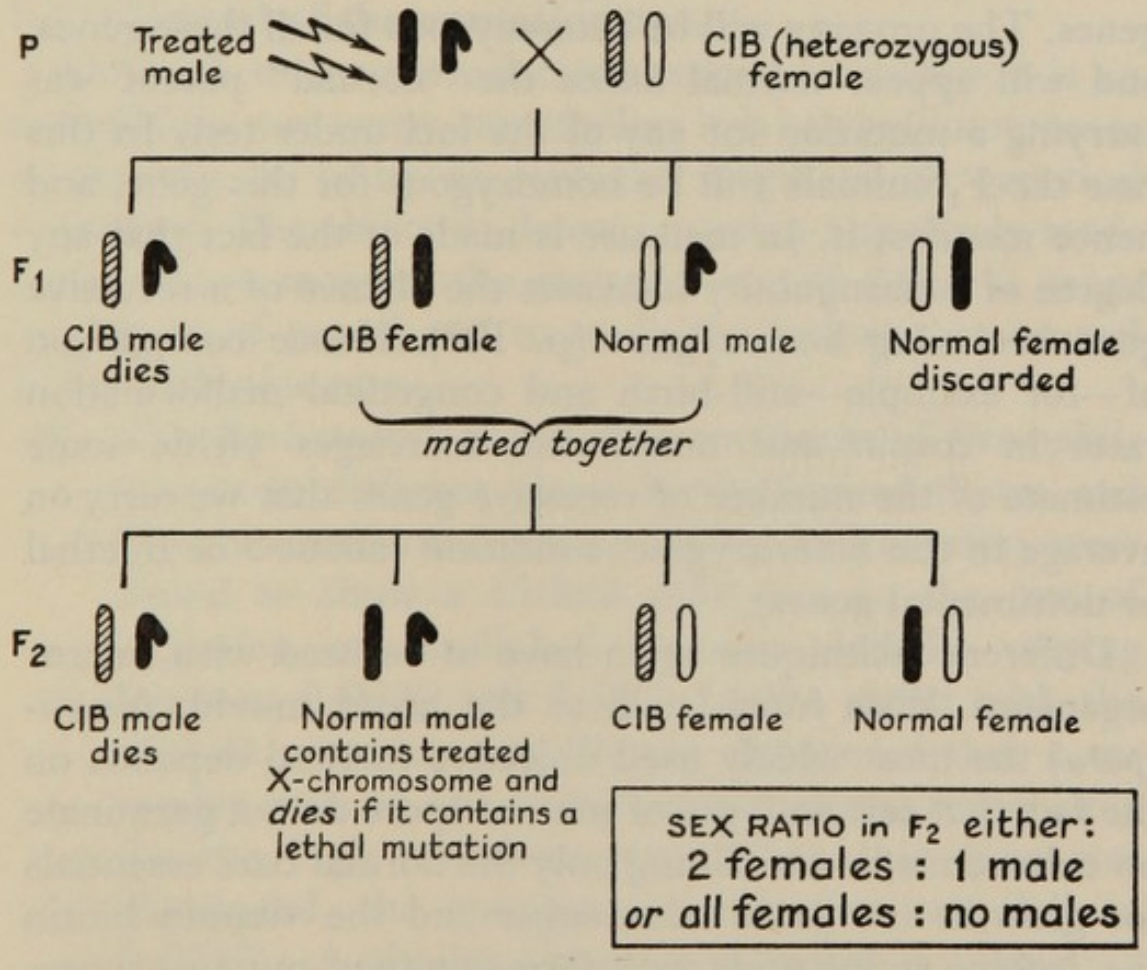


Figure 15 The ClB method for detecting lethal mutations in the *X* chromosomes of *Drosophila melanogaster*.

and Bar-eyed females, and half that number of normal males (a 2:1 sex-ratio). If the original male transmitted a sex-linked recessive lethal, this will be carried by all F_1 females, and will result in the death of all F_2 males (or a proportion of them if it is not fully lethal) arising from a Bar-eyed F_1 female. Hence it is possible to objectively determine the rate of mutation of a whole class of genes. Similar but more complicated methods are available in *Drosophila* for estimating autosomal lethal mutation and translocation rates.

In mammals (and the only mammal well studied from this point of view is the mouse), the presence of lethals can only be inferred from dead embryos when pregnant females are examined *post mortem*. The most extensive studies on mutation rate in mammals have made use of the so-called *specific locus method*. In this a "normal" animal is mated to one which is homozygous for a number of recessive genes. The progeny will be heterozygous for all these genes, and will appear normal *unless* the "normal" parent was carrying a mutation for any of the loci under test. In this case the F_1 animals will be homozygous for this gene, and hence manifest it. In man use is made of the fact that any degree of consanguinity increases the chance of a recessive gene becoming homozygous (p. 103). Hence comparison of—for example—still-birth and congenital malformation rates in cousin and non-cousin marriages yields some estimate of the number of recessive genes that we carry on average in the heterozygous condition (about 5 or 6 lethal or detrimental genes).

Different techniques again have to be used with micro-organisms. With fungi (such as the bread mould, *Neurospora*) the most widely used objective method depends on the fact that certain types of mutant spore do not germinate on culture media containing only the normal bare essentials for growth: inorganic salts, sugar and the vitamin biotin (i.e. lacking amino acids etc.). Growing (non-mutant) spores can be filtered from such a *minimal medium*, leaving only mutant spores.

A similarly elegant method for bacteria utilizes the fact that penicillin kills only growing cells. Hence all non-mutant bacteria will be removed on a minimal medium plus penicillin. Any mutants can be recovered by washing away the antibiotic and transferring the cells onto a supplemented medium.

This list could be extended a long way. Suffice it to say that the important rules in mutation research are objective methods of detecting mutants on a reasonable scale without prohibitive labour, and a sufficient understanding of the biology of the organism studied to enable extraneous and possibly mutagenic influences to be excluded (e.g. early and late hatching *Drosophila* males from the same culture have different susceptibilities to the induction of dominant lethal mutations).

7.4 Control of the mutation rate

Although under normal circumstances a mutation is an exceedingly rare event, nonetheless it is of vital importance in genetics as being at root the origin of all genetical variability. The ability to detect mutation objectively made it possible to measure the *mutation rate* of different genes (or groups of genes) and to study the factors that control and modify this rate.

(i) *Genetical control.* Seven different stocks of *Drosophila* caught in different places in the United States and kept in a uniform environment in the laboratory were found to show a 15-fold difference in the rate of mutation of sex-linked recessive lethals—varying between 0·07% and 1·0%. In the strain with the highest mutation rate, it was discovered that a recessive gene on one of the autosomes was responsible for the high mutation rate. When this gene was eliminated, the spontaneous mutation rate fell to 0·074%. A similar situation in maize is known: a gene on one chromosome in some way stimulates a high rate of mutation at a completely different locus.

Some genotypic combinations are relatively unstable —particularly some polyploids—but in no case do we understand the mechanism behind the genetical control of mutation.

(ii) *Temperature.* The rate of induction of sex-linked lethal genes in *Drosophila melanogaster* increases two or three times for a 10°C. rise in temperature. However, for several specific loci tested (particularly some "unstable" genes in both *Drosophila* and maize) this relationship does not hold. Notwithstanding, it is clear that the observed stability of the gene depends not only on its thermodynamic state, but also on its immediate environment in the cell (including the genetical environment).

(iii) *Radiation.* Soon after his invention of the ClB technique for detecting mutation, Muller discovered that *X*-rays were highly efficacious in increasing mutation rate. Mutations induced in this way seem to represent the same assortment of changes that arise spontaneously, but chromosomal aberrations arise proportionately more frequently in *X*-ray treated than in untreated cells. Mutations are also caused by ultraviolet radiation. The effect of radiation on the genetical material is considered at length in Chapter 12. All that is necessary here is to note that any amount of radiation, however small, will cause an increase in mutation rate which will, with certain reservations to be considered later, be independent of the time and intensity of the treatment.

(iv) *Chemicals.* In 1940 Auerbach discovered that mustard gas is highly mutagenic in *Drosophila.* Previous attempts at chemical mutagenesis had all been unsuccessful, and at that time the genic material was looked on as almost mystically stable, being subject to chemical modification only by the use of extremely large amounts of energy carried directly to the genes and chromosomes by penetrating radiations. In fact

the genic material is probably normally reactive. Mustards, urethane and formaldehyde all produce the same types of mutation as ionizing radiations in *Drosophila*, although the frequency of translocation and large deletions are much lower than in X-ray treated material.

(v) *Ageing Effects*. There are a number of apparently unrelated facts about mutation rates mainly concerned with ageing. The rate of sex-linked recessive mutation is higher in *Drosophila* sperm than eggs; young males produce sperm (accumulated during larval and pupal life) with a higher number of mutant allelomorphs than those produced later; sperm stored in the spermatheca of the female (and stored plant seeds) accumulate mutations. In man the rate of mutation to epiloia (a dominant condition producing mental defect and skin tumours) and retinoblastoma (cancer of the retina) increase with parental age; new mutations giving rise to short-limbed achondroplasic dwarfs—a dominantly inherited condition—are ten times more common in fathers over 40 than in very young fathers; and the risk of giving birth to a mongol (involving chromosomal non-disjunction) rises steeply with maternal age. It has been suggested that there may be mutagenic substances which accumulate in the tissues during the lifetime.

7.5 **Forward and back mutations**

Gene mutations (or *point* mutations to be more specific and to distinguish them from chromosomal mutations) are reversible, and they have a characteristic back as well as forward mutation rate. In a population this means that a deleterious mutation will come to attain an equilibrium frequency determined by back and forward mutation rates and its rate of elimination (through the lowered viability of carriers) from the population. Mutations in populations are discussed in Chapter 10.

CHAPTER 8

CHEMISTRY OF THE GENE AND MUTATION

For any further understanding of the nature of mutation, it is necessary to enquire further into the chemical and physical nature of the genic material itself. At the moment most of our knowledge about this comes from studies on fungi, bacteria and viruses, but it seems generally agreed that the genes are at least similar in higher organisms.

8.1 Chemistry of the genes and chromosomes

(i) It has been estimated that there have been over 500,000,000 different kinds of animals and plants (species) in the history of organic life. This means that there must have been at least this number of genes, i.e. the genic material must be able to exist in over 500 million alternative forms. Moreover, the genic material must be relatively stable to both external physical agents and to metabolic action, and have the ability to synthesize material both like and unlike itself. For a long time it was thought that only protein possessed sufficient specificity to fulfil these criteria.

(ii) Desoxyribose nucleic acid (DNA) is almost confined to the chromosomes. Moreover the amount of DNA per nucleus is a species characteristic and only half this amount is found in the gametes. This suggests that DNA might be the genetic material. However, other substances are also found in the nucleus, *viz.* ribose nucleic acid (RNA)—although this also occurs in the cytoplasm; some basic proteins (histones and protamines) in association with DNA; and certain small molecules (such as calcium) necessary to maintain the integrity of the chromosomes.

(iii) It is now clear that the genic material is DNA. Direct evidence for this comes from a number of sources. Perhaps the most convincing lines are:—

(a) The highest efficiency of mutagenesis by ultra-violet light is at the wavelength of 2600 Angstrom units, which is also the wavelength of peak absorption by DNA.

(b) True-breeding, capsuleless (rough), non-virulent strains of pneumococcal (bacterial) cells can be *transformed* into the encapsulated (smooth), virulent form by an extract from the latter consisting of DNA only. The "transformed" strain is genetically changed and true-breeding.

(c) Bacteriophage (i.e. virus which lives on bacterial cells) consists of an envelope of protein containing DNA. This affixes itself to the outside of bacterial cells, and the DNA is injected into the cell (p. 29). Bacteriophage particles (both DNA + protein) continue to be produced inside the cell after DNA has been injected, even after the protein envelopes are removed mechanically.

8.2 The Structure of Nucleic Acid

(i) The nucleic acids are polymers (high molecular weight compounds formed from many small, identical compounds) of nucleotides, each of which consists of a purine or pyrimidine base, a five-carbon sugar (D-2-desoxyribose in DNA; D-ribose in RNA) and a phosphate group. The purines in DNA are adenine and guanine; the pyrimidines are cytosine (5-methyl- or 5-hydroxy-methyl-cytosine in some bacteria) and thymine. Uracil replaces thymine in RNA.

(ii) The organization of DNA into crystals permits X-ray diffraction studies. These show that the poly-nucleotide chains are arranged in a helix.

(iii) There are certain restrictions in the occurrences of bases: thus the ratio of both adenine to thymine and

guanine to cytosine is always about 1:1, but adenine (or thymine) to guanine (or cytosine) varies from 0·4 to 1·9.

(iv) In 1953, Watson and Crick put forward their now famous model of the structure of DNA. They postulated two parallel polynucleotide chains so that the bases of one chain match those in the other. In order to maintain a uniform distance of the chains apart it is necessary for purines to be matched with pyrimidines: adenine with thymine, guanine with cytosine. In such a model, the desoxyribose-phosphate links would not be perpendicular to the chain; for each base pair, the whole structure rotates 36°. Perhaps the easiest way to visualize this is to think of a rope-ladder coiled round an imaginary tall column. The rope would then represent the nucleotide chains, and the rungs hydrogen bonds linking the bases together (fig. 16).

One of the essential features of this model is the two complementary chains. This implies that each DNA chain might serve as a template for the synthesis of its complementary pair, and in this way the structure of the molecule could be reduplicated exactly. Such a property is essential for any substance with the stability known to be possessed by the genes. Although the details of the replication of DNA have not been worked out (the evidence seems to show that the helix unwinds in an unexplained way, and a new complementary chain is formed alongside each of the original chains), it has been possible to synthesize DNA in the laboratory from a mixture of natural DNA (as a template) and the four bases. The DNA formed in such an experiment has the same proportions of adenine plus thymine to cytosine plus guanine as in the original template DNA, indicating that the newly synthesized DNA is a replica of the old.

It is much more difficult to obtain crystals of RNA than

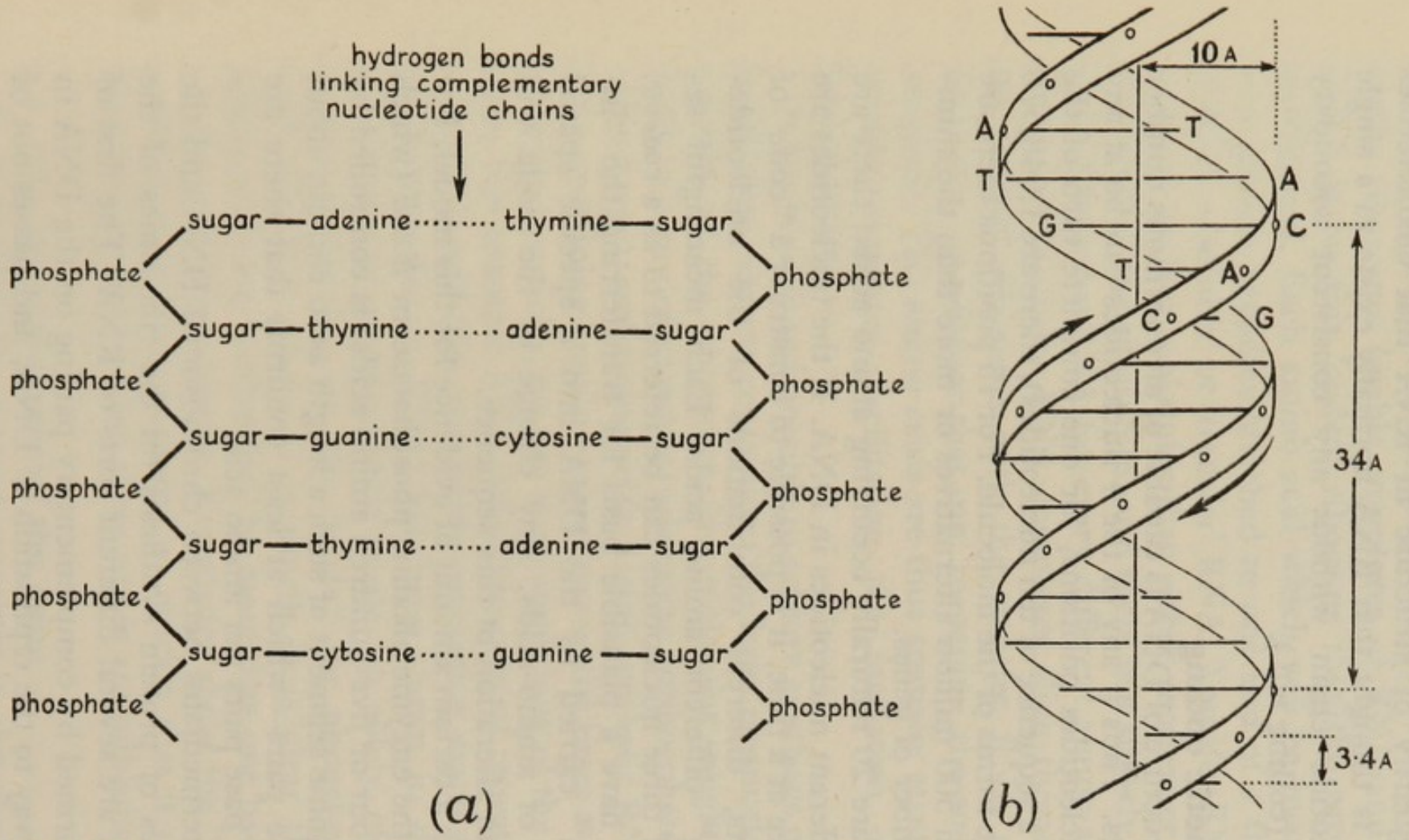


Figure 16 The structure of DNA.

(a) Chemical formula of the paired polynucleotide strands of DNA.

(b) Diagrammatic representation of the double helical structure of DNA. The two ribbons symbolize the two polynucleotide strands, and the horizontal rods indicate the position of complementary base pairs linked by hydrogen bonds. The vertical line marks the axis of the molecule.
1 Angstrom unit (A) = 1×10^{-10} metres.

Based by permission on Watson and Crick (1953) GENETICAL IMPLICATIONS OF THE STRUCTURE OF DNA. *Nature, Vol.* 171, *Page* 965.

of DNA. X-ray diffraction studies have not shown the same regularity of structure in RNA that characterizes DNA. It is thought that RNA normally exists as a single polynucleotide chain without any consistent secondary structure (coiling etc.).

8.3 **Genetic coding**

The structure of DNA is capable of an enormous number of variants. Thus if any of the 4 nucleotides can be at any of the nucleotides positions, for one complete turn of the helix (i.e. a sequence of ten nucleotides), there are 1,048,576 alternative forms of the molecule. For 15 positions there are more than 500 million alternatives or more than the minimum number of genes.

There are 20 naturally occurring amino acids; there are only 4 different nucleotides in DNA. If the nucleotides are taken three at a time, it is possible to construct a "code" of 64 triplets, different combinations of the nucleotides "meaning" different amino acids. Each meaningful sequence of three nucleotides can be referred to as a *codeon*. Thus we have a plausible basis for transferring the "information" carried by the DNA into a specific spatial sequence of amino-acids. Any change in the code will result in an alteration of this sequence.

There is a certain amount of evidence for this model. For example, the enzyme alkaline phosphatase in *E.coli* (which contains four or five hundred amino acids) is controlled by a chromosome segment of such a length as to contain about 2,000 base pairs—which at least confirms that there are not many base pairs per amino acid.

The intermediates between chromosomal DNA and the actual sites of protein synthesis on the ribosomes of the cytoplasm are several different sorts of RNA. The first of these is formed by complementary pairing on the DNA in a similar way to the replication of DNA, and passes out of the nucleus. This "messenger" RNA consists of a polynucleotide chain in which the bases are arranged in the

same (or rather the mirror-image) order to that in the DNA. In the cytoplasm the messenger RNA becomes attached to the ribosomes (stable complexes of RNA and protein) and it is on this 'coded' ribosome that the proteins are synthesized. Each amino acid which will be incorporated into protein becomes attached to one end of a third type of RNA—'soluble' or 'transfer' RNA. Transfer RNA exists in much smaller molecules than either messenger RNA or the RNA of the ribosomes, and there is a slightly different type of transfer RNA for every different amino acid. The amino acid-transfer RNA complexes align themselves on the 'coded' ribosome with the transfer RNA somehow serving as an adaptor that can 'recognize' the code on the template. The amino acids are thus spatially arranged in a specific sequence, facilitating the formation of bonds between them.

It has been found possible to achieve synthesis of protein in cell-free extracts containing: the large ribonucleoprotein particles of the ribosomes, low molecular weight transfer RNA, a series of enzymes, adenosine triphosphate (to provide energy), and amino acids. Using synthetic RNA molecules containing known proportions of the bases to code the ribosomal particles, we can learn something of the genetical code. For example RNA consisting only of repeating units of uridylic acid (the nucelotide containing uracil which replaces thymine in RNA) has been shown to direct the production of a polypeptide made up solely of phenyl-alanine molecules, i.e. the "code" for phenyl-alanine is —U—U—U— where U is uracil. It is clear that some amino acids are "coded for" by more than one base triplet, i.e. the code is not simple. Knowledge about the "genetical code" is now being gathered so quickly that it may have been broken by the time these words are published.

8.4 **The fine structure of the gene**

So far we have concerned ourselves in this chapter with the chemical nature of the genic material. We can now pro-

ceed to the way it is organised to form the genes themselves. Work in recent years on the genetics of fungi, and, even more recently, on bacteria and their viruses, have given us an understanding of the fine structure of the gene as different from the old idea of the gene being the ultimate genetic unit (of function, mutation and recombination) as is a modern chemist's picture of the atom from Dalton's original "billiard balls".

The reason micro-organisms have been so valuable in this work is the ease with which it is possible to study millions of individuals. The massive numbers involved enable events, which in absolute terms are very rare (such as recombination between "genes" so close together on a chromosome that in higher organisms they would be regarded as allelomorphic) to occur sufficiently often to be studied. The organism most intensively studied is a particular strain of bacteriophage, T4, which attacks the colon-living bacillus, *E.coli*. An area of killed, or lysed, bacteria in a culture infected with phage, forms a *plaque*, and mutant phage strains can be recognized from their production of plaques atypical in shape or size. If two recognizably different mutants are sown onto a bacterial culture, most of the progeny will resemble one or other parent, but occasionally a few individuals arise in which the genetical information from both parents has "recombined" to give a new genetical type (p. 28). The closer together that two mutants are, the more rarely they will recombine. This is exactly analogous to the behaviour of two closely linked genes in a higher organism. However, it is easy with phage to detect a single recombinant among a thousand million individuals (simply by seeding two mutants onto a bacterial strain on which neither of them will grow, but on which recombinants forming the standard type will), and to distinguish between two mutants which are as close together as one base pair in the DNA chain.

Some of the mutants studied occasionally revert (or back-mutate) to the standard type when they reproduce,

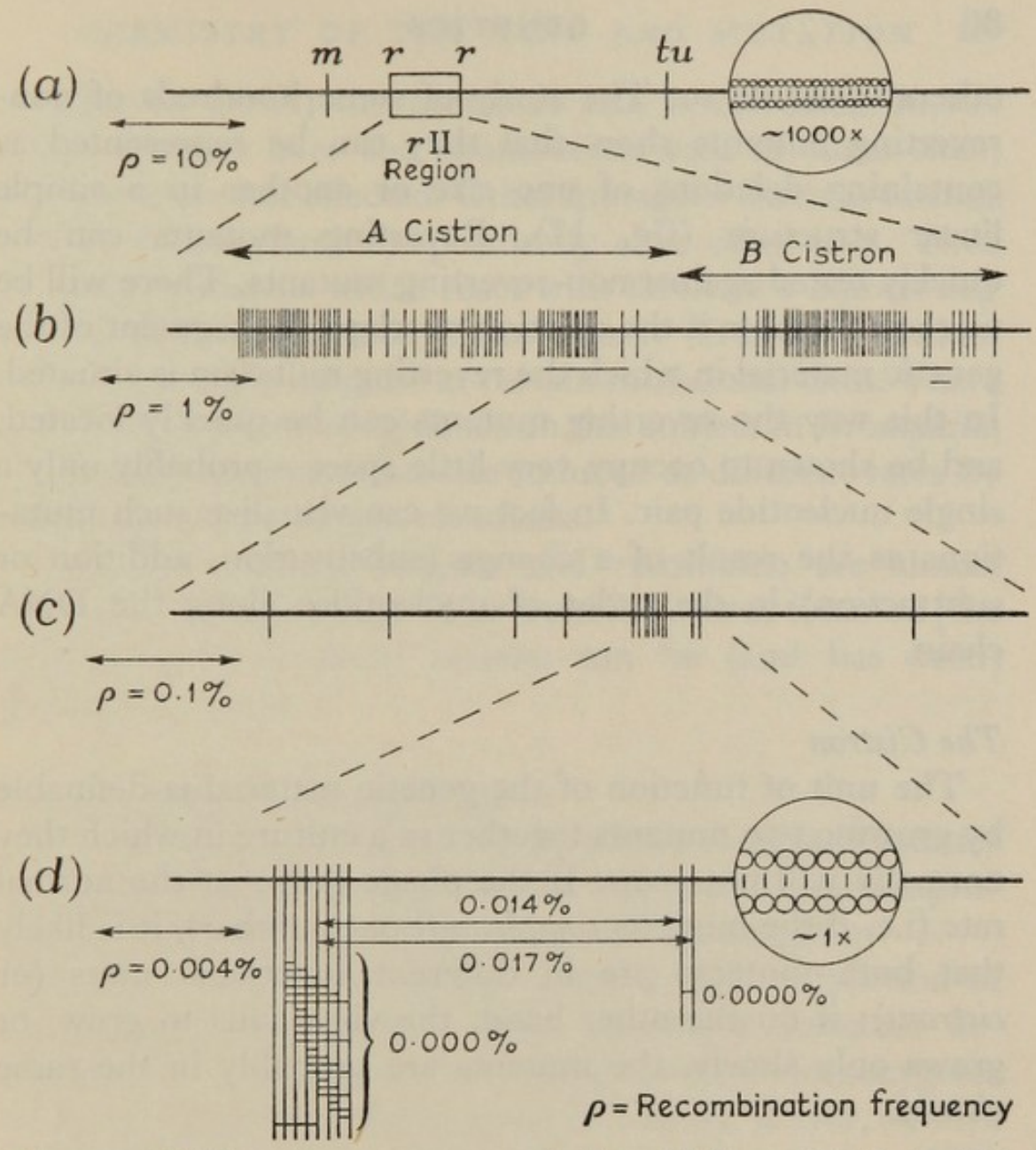


Figure 17 The fine structure of the rII "gene" of the T4 bacteriophage.

(a) The location of the rII region in the bacteriophage "chromosome" linkage map. *m*, *r* and *tu* are different "genes". The symbols mean "minute plaque", "rapid lysis" and "turbid plaque" respectively. The inset shows the estimated corresponding spacing of nucleotides (circles) in the structure of DNA.

(b) The spacing of a number of rII mutants within the two cistrons of the "gene".

(c) and (d) are further magnifications of part of the A cistron.

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others never do so. The study of some hundreds of non-reverting mutants show that they can be represented as containing deletions of one size or another in a simple linear structure (fig. 17). Reverting mutants can be quickly tested against non-reverting mutants. There will be no recombinants if the deletion overlaps the segment of the genetic material in which the reverting mutation is situated. In this way the reverting mutants can be quickly located, and be shown to occupy very little space—probably only a single nucleotide pair. In fact we can visualize such mutations as the result of a change (substitution, addition or subtraction) in the order of nucleotides along the DNA chain.

The Cistron

The unit of function of the genetic material is definable by growing two mutants together in a culture in which they normally will not grow. If the phage grows at the normal rate (i.e. if the mutants *complement* one another), it is likely that both mutants are in different functional units (or *cistrons*); if on the other hand, the virus fails to grow, or grows only slowly, the mutants are probably in the same *cistron.*

The Muton

The unit of mutation has been called the *muton.* It is almost certainly a single nucleotide. In the most intensively studied genetical region of T4, producing the rII series of mutants, more than 300 distinct mutational sites divided into two cistrons are known. The distribution of "repeat" mutations therein is far from random. Thus in a single deletion, 145 point mutations mappable at 11 sites have been found. Five of these sites are only occupied by a single mutant; one "hot spot" by 103. This suggests that neighbouring nucleotides may influence the probability of an error (i.e. a mutation) occurring. Using the chemical mutagen 5-bromouracil (which can quantitatively replace

thymine in DNA) the mutation rate is increased 10,000 times or more over the spontaneous rate at some sites; other sites are not affected. Other mutagens (such as nitrous acid or hydroxylamine) specifically alter other sites. Thus by using mutagens which react with DNA in a known way it is possible to produce, if not exactly directed mutation, at least a specific increase at certain mutational sites. There is a certain amount of evidence on this subject in *Drosophila*, where different mutations are induced at different rates by radiation and by certain chemicals.

The units which mutate and recombine are almost certainly the same; they differ from the unit of function (the cistron). Any of these entities can be (and has been) defined as a gene.

8.5 **Human haemoglobins**

An example of a series of mutations which illustrates several of the points made in the last two chapters is provided by the different types of human haemoglobin.

In certain parts of Central Africa a high proportion of the natives suffer from a mild haemolytic anaemia determined by a gene in the heterozygous state.Homozygotes for this gene are severely anaemic and rarely, if ever, survive to adulthood. The frequency of the gene is as high as 40% in some parts: the reason for an apparently disadvantageous gene being so common is that heterozygotes are much less susceptible to cerebral malaria than normal people (see p. 112). The anaemia is characterized by the fact that deoxygenated red blood corpuscles frequently assume a sickle-shaped appearance instead of the normal biconcave discs (hence "sickle cell" trait and disease for heterozygote and homozygote respectively). "Sickled" cells tend to flow less easily in the veins, and hence to be removed by phagocytes. This is probably the chief method by which a deficiency of red cells is produced. Sickle cell heterozygotes have about 60% normal haemoglobin (haemoglobin A) in their corpuscles, and 40% of an atypical haemoglobin

(haemoglobin S) characterized by a greatly (25 times) reduced solubility of the reduced form. Haemoglobin S was first detected by differing from haemoglobin A in electrophoretic mobility, i.e. its rate of movement in an electric field.

The haem portion of haemoglobin is a relatively simple iron-containing molecule; the globin portion is a protein arranged in four poly-peptide chains—two identical α-chains, and two identical β-chains. Each chain contains about 140 amino-acids. By a combination of enzymatic digestion, electrophoresis and chromatography, the sequence of amino acids in the chains has been determined. Haemoglobin S is found to differ from haemoglobin A by only a single amino acid in the β-chains. The sequence of amino-acids at one end of the β-chain in haemoglobin A is:

Valine - Histidine - Leucine - Threonine - Proline - Glutamic acid - Glutamic acid - Lysine . . .

In haemoglobin S the first glutamic acid after proline is replaced by a molecule of valine. Furthermore, glutamic acid carries a negative charge, while valine is neutral, accounting for a difference in total charge and hence the behaviour in an electric field of the globin molecule.

Another anomalous haemoglobin C, differs from the others by the substitution of the positively charged amino acid lysine at the same place in the molecule. The genetical evidence suggests that the genes controlling haemoglobins A, S and C are allelomorphic.

Over thirty abnormal haemoglobins are now known in man. In some of these the amino-acid sequences have been determined. The α and β chains are apparently controlled by different genes, so it is possible for a single person to have four different haemoglobins. We have here a very precise relationship between a mutation and an altered protein, which nevertheless produces profound biological effects.

CHAPTER 9

DEVELOPMENTAL GENETICS

9.1 The relation between gene and protein

In a few, very few, organisms (e.g. the horse round-worm, *Parascaris equorum*) the chromosomes divide unequally between the somatic cells during early development, and hence different cells have different potentialities. In the vast majority of animals and plants all cells have an identical chromosome complement. It is a major problem for geneticists and embryologists alike to know why, when two cells both have the genetical potentiality to make a given protein, one may make little else, one may make none at all.

We have seen that the "information" carried by the chromosomal DNA is transferred into a spatial and specific arrangement of amino-acids on the ribosomes. Two Frenchmen, Jacob and Monod, have proposed a model for the control of gene activity based on the induction and suppression of enzyme (i.e. protein) synthesis in bacteria, and in particular the enzyme β-galactosidase (which catalyses the hydrolysis of β-galactosides) in the colon-dwelling bacillus, *E.coli*. Normally the bacteria only produce enzyme in the presence of the substrate (galactoside), but other substances (e.g. thiomethylgalactoside) can serve to "switch on" (induce) synthesis, but not to function as a substrate, i.e. the inducing substance serves merely as a switch for turning on enzyme synthesis. A single mutation (in a different cistron to the "gene" concerned with the ability to synthesize the enzyme) causes the production of enzyme whether or not an inducer is present. In this case, the bacteria are said to be *constitutive* rather than *inducible*. Since enzyme production can be shown to occur without an inducer for a short time in a newly arising inducible strain, Jacob and Monod suggest that enzyme production

is normally (in an inducible strain) *repressed* by some extra-chromosomal repressor substance (it must reach a critical level before enzyme synthesis is stopped) which is not produced in constitutive strains. The nature of these repressor substances are not known; they do not seem to be proteins. Recent evidence suggests that they may include some substances that we know as hormones. Now, since a repressor substance can affect a whole series of enzymes (induction of β-galactosidase also involves the formation of a permease, enabling galactosides to pass through the cell membrane), Jacob and Monod argue that there must be some substance (the "operator") with which the repressor substance combines in a stereospecific way. Furthermore the operator, being a specific substance, must have its structure controlled by a gene. There is evidence that the operator locus does not produce an extra-chromosomal substance, i.e. it acts on the genes which actually produce the enzymes (the structural genes) by some mechanism transmitted along the chromosome (fig. 18).

There are several groups of phenomena which suggest the control of gene-action systems by effects on the genes themselves on the lines suggested by Jacob and Monod. For example, in one of the chromosomes of a midge (*Acricotopus lucidus*) at the end of the larval period, there are signs of swelling of the bands (chromomeres) that run across the chromosomes (to form *Balbiani rings*) and the appearance of droplets, presumably indicating synthetic activity. These signs of activity gradually spread along the chromosomes during the prepupal period i.e. we have here a visible indication of gene-action systems lying along the chromosomes. However, such cases of the successive action of genes seem at the moment to be exceptional in higher organisms (cf. p. 51) although it would not be surprising to find that they are more common than they now appear.

9.2 "Inborn errors of metabolism"

The title of this section was originally used by Garrod in

1908 in discussing the biochemical effects of gene mutation in man. Most often such effects involve the loss or change of activity of an enzyme. Here, then, we are concerned with gene effect at least one stage removed from the DNA, i.e. after the elaboration, chemical and physical, of a protein.

An example of loss of enzyme activity is provided by the recessive condition phenylketonuria in man. Homozygotes for this gene lack the enzyme phenylalanine hydroxylase which is concerned with the oxidation of phenylalanine to tyrosine in the liver. The direct consequence of this is that the concentration of phenylalanine in the blood and urine increases greatly. There is an indirect effect since tyrosine, and hence melanin, synthesis is partially blocked, and therefore phenylketonurics tend to be blue-eyed and blond. They are mentally severely retarded (although it is not known whether this is due to a poisoning of brain metabolism by phenylalanine or not). Heterozygotes for the gene are

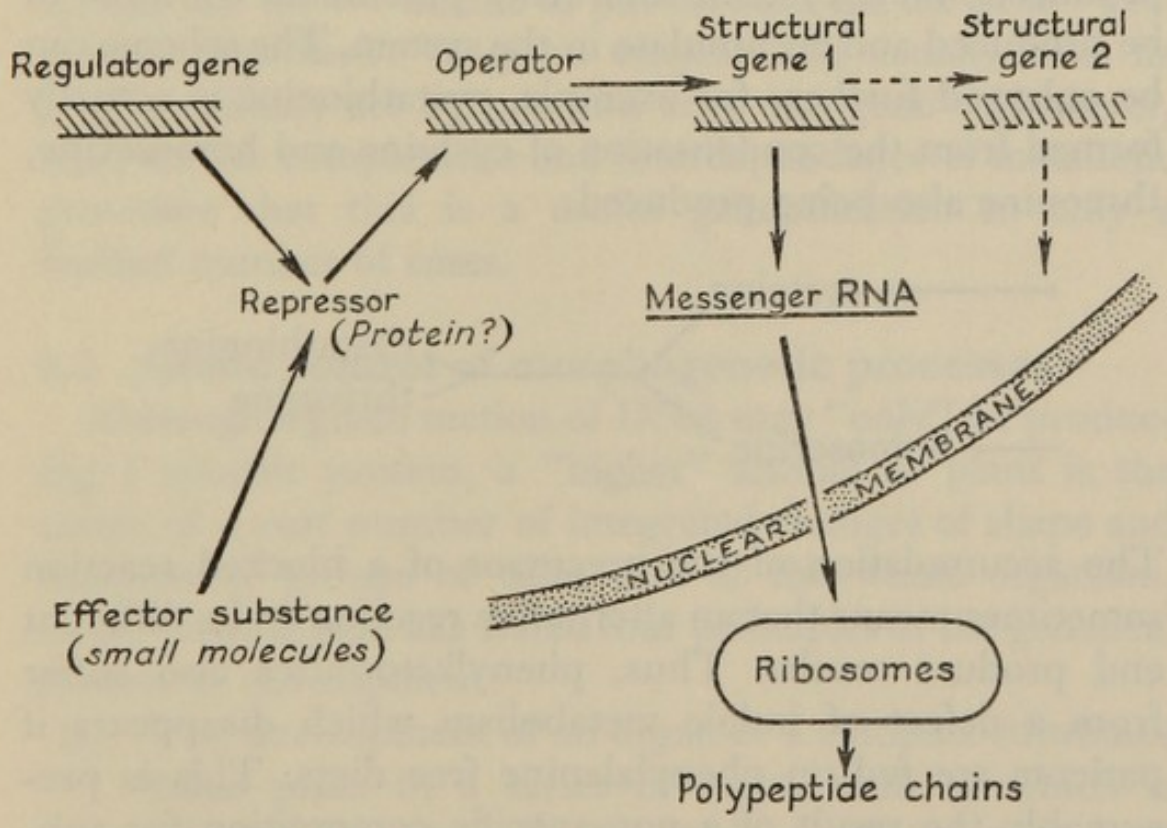
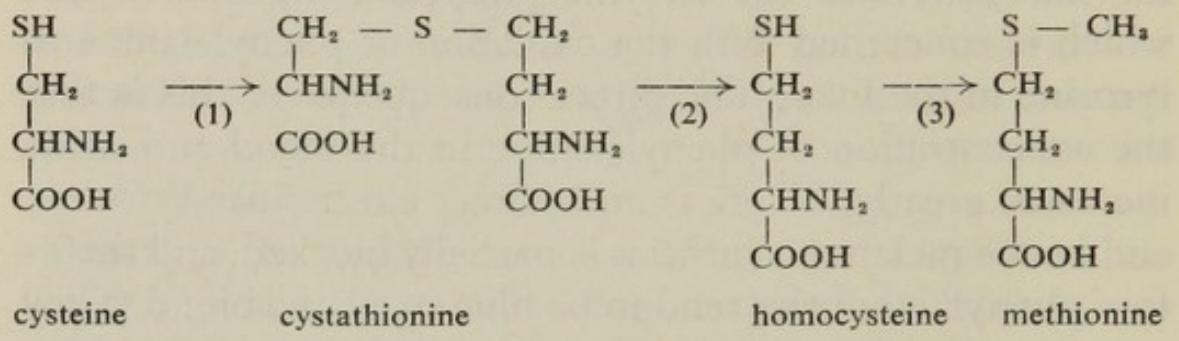


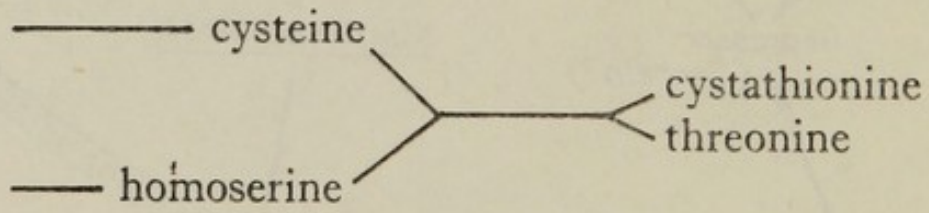
Figure 18 Jacob & Monod's repressor-operator model for the genic control of protein synthesis.

clinically normal, but their phenylalanine hydroxylase is not normal, and they cannot oxidise phenylalanine as quickly as normal homozygotes.

A normal metabolic process can be represented as a stepwise series of reactions mediated by different enzymes. Thus the conversion of cysteine to methionine in *Neurospora* involves three separate reactions:—



Each of the reactions can be blocked by a mutation which renders ineffective the relevant enzyme. If enzyme (3) mutates there are two consequences: methionine is not produced; homocysteine and other precursors continue to be produced and accumulate in the system. The scheme can be enlarged further: for example, cystathionine is actually formed from the condensation of cysteine and homoserine, threonine also being produced:



The accumulation of the precursor of a blocked reaction sometimes means that an alternative reaction and a different end product results. Thus, phenylketonurics also suffer from a defect of indole metabolism which disappears if patients are fed on phenylalanine free diets. This is presumably the result of a non-specific competition for substrate between different enzyme systems. An enzyme block may result from several different causes e.g. change in the

affinity of an enzyme for its co-enzyme, alteration in the organization of the polypeptides that constitute the molecule, loss of specificity of the enzyme for its substrate and so on. In some cases a "blocked" reaction may be shown to be not completely stopped; enzyme is present but is functioning very slowly and inefficiently. Alternatively, a changed, but still functional product may be formed—as in the case of sickle-cell haemoglobin.

Some people are sensitive to certain drugs. In several cases such sensitivities have been shown to be due to specific enzyme deficiencies. For example, an acute haemolytic anaemia follows administration of the anti-malarial drug, primaquine, to people lacking the enzyme glucose-6-phosphate dehydrogenase on their red blood corpuscles. Loss of the enzyme is caused by a sex-linked gene.

The number of enzymes which are gene controlled, and the analogy between the specificity of enzyme and gene action, led G. W. Beadle to put forward his *one-gene—one-enzyme hypothesis*: "a given enzyme will usually have its final specificity set by one and only one gene". However, such are the complexities and interdependence of metabolic processes that this is a useful generalization in only a limited number of cases.

9.3 **Genic control of morphogenetic processes**

Although a given section of DNA may "only" be producing a specific protein, a "higher" animal or plant is the result of a vast number of integrated changes of shape and function of groups of cells, and of the whole organism. C. H. Waddington has stated four principles of the genetical control of development:

(i) The development of an organ or a complex substance takes place in a series of steps, each of which is affected by genes. For example, there are over forty different genes known to affect the tail of the mouse. They affect chiefly the major components in the

growth of the tail: the primary stimulus to tail outgrowth, the relationship between nervous and other tissues, the process of segmentation into vertebrae, and the structure of the notochord.

(ii) At each step there are several genes acting, and the actual development which occurs is the resultant of a balance between the opposing gene-instigated tendencies (e.g. sex determination in insects, p. 24). Furthermore many genes are "process specific". Thus there is a gene in *Drosophila* which causes part of the antenna to develop like a leg. In this case the extra leg is affected by genes concerned with the legs and not with the antennae, even though it develops far from the normal site of leg development. Achondroplasic dwarfs in man have an abnormality involving much of the skeleton; the actual gene-conditioned upset is absence of the layer of proliferating cells which are responsible for the growth in length of the long bones, base of the skull and the pelvis.

(iii) At certain stages in the development of an organ, the developing system is in a more than usually unstable condition, and slight disturbances at such times may produce large effects on later events. Thus the four groups of genes affecting the mouse tail take effect at characteristic times during development of the animal and they have results of varying severity on the life of the animal after birth. Furthermore, irradiation of the developing animal (*in utero*) at these times can mimic the action of the genes (producing *phenocopies*). The radiosensitivity of the cells depends on their extent of differentiation and division rate. In this case, X-rays and genes are upsetting the same process in different ways at a critical stage.

(iv) An organ or tissue is formed by a sequence of changes, so that the pathways leading to different organs or tissues are distinct from each other. At certain critical times, groups of cells are *induced* by some stimulus so

that, thereafter, they are *determined* to follow a certain course of development, and it is difficult to persuade them to become something different. Furthermore, the sensitivity of a given pathway to environmental stimuli is under genetical control. A character, such as an extra vein in the wing of *Drosophila* which is normally produced only by a heat shock during development, can be made to manifest in a high proportion of flies by selection for manifestation of the character.

In some micro-organisms investigated, it has been found that the genes are not randomly distributed on the chromosome but are sequentially arranged, their relative order agreeing with the sequence of the reaction they control. For example, eight gene loci have been identified concerned with the synthesis of the amino acid histidine in *Salmonella* bacteria: four of these lie next to each other on the chromosome and are concerned with successive chemical reactions, involving a dehydrase enzyme, a transaminase, a phosphatase and a dehydrogenase.

Not much is known about the inheritance of patterns. Although genetically-determined upsets in pattern are relatively common—such as variation in Lepidopteran (butterflies and moths) wing patterns, or bristles on *Drosophila*, or polydactyly (extra fingers or toes) in mammals—they usually affect a balance which is normally maintained between competing embryological processes, and hence directly or indirectly controlled by a large number of genes.

9.4 **The unity of gene action**

Many genes produce effects on a wide variety of different organs. There is a gene in *Drosophila* which, when homozygous, inhibits wing growth, modifies the halteres, alters the shape of the spermatheca and decreases the length of life. During the development of a complex animal, any alteration produced at an early stage may have many later

repercussions, perhaps in organs quite different from that in which the original effect occurred. An obvious example occurs if a gene affects an endocrine gland. There is a recessive gene in the mouse which, when homozygous, causes the absence of acidophil cells in the anterior lobe of the pituitary gland, resulting in a failure to produce growth hormone. The mice are dwarfed and sterile. A recessively determined defect of copper metabolism in man (Wilson's disease) causes copper to be deposited in, particularly, the liver and the brain. The clinical symptoms that predominate depend on which organ is the most severely affected. A dominant gene in the mouse primarily affects the notochord, but the vertebral column and neck musculature are, secondarily abnormal, and the kidneys are also affected in a high proportion of cases *via* the inductive relationships that exist between notochord and cloaca, and cloaca and kidney forming tissue. The lowered viability of the animals is entirely due to the indirect or "pleiotropic" effect on the kidneys (which may be inadequate for normal function).

In many cases it has not been possible to trace the connection between different effects of a gene, e.g. it is not clear why a gene which causes degeneration in the inner ear of the mouse, also causes spotting and dilution of the fur pigment. However, the "principle of unity of gene action" serves as a useful working hypothesis with an underlying truth which derives from our knowledge of the fine structure and working of the gene.

9.5 **Growth rates**

The development of an animal depends, not only on the right constituents for growth being available, but available in the right place at the right time. For example, many of the gross central nervous system malformations and congenital heart defects in man can be attributed to an unpunctual fusion of various clefts and grooves, the extent of punctuality being under rather complex genetical control. Change in a growth rate frequently brings correlated change

in the relative size and shape of other organs (*allometry*), and this has certainly been of importance in evolution (we shall see (p. 134) that in some ways man resembles a foetal ape). A rather simple example of growth rate control is provided by the freshwater shrimp *Gammarus chevreuxi*. Melanin is formed in the eyes during larval life, so that the adult has black eyes. There is a red-eyed mutant in which darkening of the eyes begins later and is much slower; the eyes never become fully black. However, melanin is deposited so quickly if the mutants are raised at a temperature of 28°C that the eye does, in fact, become black. Conversely, melanin deposition is so slow, even in normal animals, at 10°C, that the eye never becomes really dark. There is another gene which causes dwarfing in *Gammarus*; carriers have the area of the eye reduced to such an extent that the gene for slow melanin production can still produce enough melanin to make the eye black at normal temperatures. There is a dominant gene in the mouse which halves the rate of cell division in the notochord at the time of maximum growth (the rate of cell division in the mutant homozygote is halved again). This is an intensification of a normal process: the tail is shortened and sometimes other organs are affected indirectly. The embryos of large and small races of rabbit are already distinguishable at 40 hours after fertilization due to a higher rate of cell division in the former.

9.6 **Genic balance**

We have already seen that a chromosomal deletion produces a genetical effect. This is understandable. It is not so clear why the addition of chromosomal material, as in duplications and trisomics, should also produce effects. For example, sex determination in insects is a result of balance between the autosomes and sex chromosomes (p. 24). Thus, if A is the haploid number of chromosomes, and X and Y are the sex chromosomes, a normal *Drosophila* male is $2A + XY$ and a normal female is $2A + 2X$. $3A + 3X$ is, as might be expected, a normal female; $2A + 2X + Y$ is

also a female but both $3A + 2X$ and $3A + 2X + Y$ are intersexes.

Chromosomal alterations differ from single gene effects in that they are not errors of instruction which lead to failure or inefficiency in particular biochemical tasks. The genes are presumably normal and efficient, but produce the wrong *dosages* of their effects—one, three or four instructions at the same locus instead of two (or one in the case of the sex chromosomes). The extra dosage of genes in a trisomic individual may perhaps be discernible in greater concentrations of the particular proteins manufactured according to their instructions; it has been suggested that some of the morphological peculiarities in mongolism in man could arise from the fact that the size of cells may be altered and be never exactly suitable for the structures they are required to build. No critical biochemical studies have been made on such dosage effects.

9.7 The time of gene action

The fact that the sensitive time for producing a phenocopy of a gene occurs very near to the time at which the development of a mutant becomes recognizable suggests that this is the stage at which the gene becomes active. This is an incorrect conclusion: all that the production of a given phenocopy at a certain stage shows is that the relevant embryological process is unstable at that time. Until we know much more about the organization of the genes it is impossible to say when a certain gene is, or is not, active. For example, it seems reasonable to assume that the genes concerned with the patterning of the wings of butterflies are inactive in the caterpillar, but they may in fact be very important in, say, modifying a character of survival importance to the larva. A developing organism is a vastly complicated integrated and interdependent feedback system: although we now know something about the actual activity of genes, we are still far from understanding how genic instructions are translated into living organisms.

CHAPTER 10

GENES IN SPACE: POPULATION GENETICS

So far we have considered only genes segregating in families. Now we must think of whole groups of individuals which can and do breed with each other with the formation of new gene combinations. Such a group of animals (or plants) is spoken of as a population, or sometimes as a *Mendelian population*. All the genes within a population may be thought of as constituting the "gene-pool" of that population, which can be churned, added to, and subtracted from by various influences acting on the members of the population. Different allelomorphs of any gene may or may not occur in any population: it is with the numbers (and hence the *frequencies*) of different allelomorphs that population genetics is principally concerned. We can calculate the frequency of a gene if we know how many individuals in a population manifest it, and whether it is dominant or recessive.

10.1 **The Hardy-Weinberg Law**

In 1908, an English mathematician and a German physician demonstrated independently from the binomial theorem that populations may have any proportions of dominant and recessive genes, but in the absence of any forces that change gene frequencies, the relative frequencies of each allelomorph tend to remain constant from generation to generation. This principle has become known as the Hardy-Weinberg law, and is the foundation of population genetics.

Its basis can be easily understood: consider any gene locus with two allelomorphs A, a such that the frequency in the parental generation of $A = p$, and that of $a = 1—p$.

Then if mating takes place at random, a gamete carrying the *A* gene will have a chance of combining with a gamete carrying either an *A* or an *a* gene in proportion to the relative frequencies of the gametes, and likewise a gamete carrying the *a* gene. Thus:

Gametes from one parent	*Frequency of gamete*	*Gamete from the other parent*	*Frequency of gamete*	*Genotype of children*	*Frequency of genotypes of children*
A	p	*A*	p	*AA*	p^2
A	p	*a*	$1-p$	*Aa*	$p(1-p)$
a	$1-p$	*A*	p	*Aa*	$p(1-p)$
a	$1-p$	*a*	$1-p$	*aa*	$(1-p)^2$

The population composition in the children's (filial) generation will be:—

p^2AA; $2p(1-p)\ Aa$; $(1-p)^2\ aa$.

Counting up the genes in the filial generation:

the frequency of $A = p^2 + \frac{1}{2}(2p(1-p))$
$= p(p + (1-p))$
$= p$

and the frequency of $a = \frac{1}{2}(2p(1-p)) + (1-p)^2$
$= (1-p)(p+(1-p))$
$= 1-p$

i.e. the gene frequencies are unchanged from the parental generation. For the mathematically allergic, the essential point is not the mathematical details but the stability of the gene frequencies.

10.2 Conditions for gene frequency stability

Four conditions must be satisfied to ensure the truth of this proposition:

1. The population is large enough for accidents of sampling to be ignored.

2. Mates are chosen at random.
3. Mutations are infrequent, and
4. Individuals of the different genotypes (*AA*, *Aa*, *aa*) have equal survival and reproductive rates.

If any of these conditions are not satisfied, it is likely that the gene frequencies will change.

10.2.1 **Genetical drift**

The Hardy-Weinberg equilibrium only holds strictly in (mathematically) ideal populations with an infinite number of breeding individuals. The smaller the population, the greater will be the probability that an allelomorph will be lost by chance. To take an extreme example: a husband and wife may have all their children of one sex—say, four boys or four girls. This quite often happens even though every ovum has an approximately equal chance of being fertilized by an *X*-bearing or a *Y*-bearing spermatozoon (p. 24); the probability of a family of four children being all of the same sex will be $(\frac{1}{2})^4 = 1$ in 16. Now if there are many families, we know that the sex ratio of all their children added together will be unity, i.e. there will be as many boys born as girls, and families of four boys only will be as common as ones of four girls only. However, if the human population was reduced to a single couple, and that couple had, by chance, four girls, then the *Y* chromosome would be lost from the human population, and the *X* chromosomes would be *fixed*. This would, of course result in the extinction of all humans, and it may be that some groups of animals and plants have become extinct in this way: by becoming so reduced in numbers that advantageous traits have been lost by chance.

It is more profitable to consider the more general situation of two populations with two equally frequent allelomorphs *A* and *a*, such that $p = 1-p = 0{\cdot}5$, one population consisting of 500,000 individuals and the other of only 50 individuals. The larger population will have arisen from a million gametes, the smaller from 100. Now, when one million genes are taken from a gene-pool containing equal

numbers of *A* and *a*, the number of *A* and *a* genes will each be 500,000$\pm$500 where 500 is the *standard error* of the sample (i.e. there are likely to be as many as 500,500 *A* genes by chance, or as few as 499,500 and likewise with *a* genes). Similarly in the smaller population the expected numbers of *A* and *a* allelomorphs in a sample of 100 gametes will be 50 $\pm$ 5. In this latter population the proportions of *A* and *a* gametes will be much more variable from generation to generation than in the larger one, and, hence, the genotypes of the offspring are likely to vary. Variations in gene frequencies in small populations due to sampling errors are known as *genetical drift* or "the Sewall Wright effect" after the geneticist who first studied them in detail. Sewall Wright showed that, if isolated small populations have at some time identical gene frequencies, these gene frequencies may, because of genetical drift, become different with time.

The smaller the population, the greater will be the importance of genetical drift; in very large populations its influence will be negligible. In general terms, the probable size of the effect (= the standard deviation of the sample of gametes that produces the new generation) for a single gene with frequency p is $\left(\frac{p(1-p)}{2N}\right)^{\frac{1}{2}}$ where N is the effective breeding population (and is hence smaller than the actual population size). The probability is that $1/2N$ of the genes that vary in the population will be lost or fixed in each generation.

An effect that is slightly different from drift, but may be included here because it results from chance, is the *founder principle*. If a small party of animals and plants succeeds in colonizing an isolated habitat such as an island, it is unlikely that all the allelomorphs represented in the original population will be present in the new population. Moreover the allelomorphs that are present in the newly founded population will be at different frequencies from those in the main population. This colonization by fortuitous groups

of individuals may have been important in the establishment of some of the strikingly distinct forms that are often found on off-shore islands.

10.2.2 **Differential migration**

The Hardy-Weinberg equilibrium depends upon random mating among individuals. It will be disturbed if (say) a proportion of a particular genotype tends to migrate away from the breeding area, or, more important, if there is immigration between two partially isolated, and hence probably genetically different, populations.

Another departure from random mating is shown by inbreeding in which there is a tendency for related individuals to mate with one another. This leads to an increase in homozygosity such that in a population containing two allelomorphs, *A* and *a*, the two homozygous genotypes *AA*

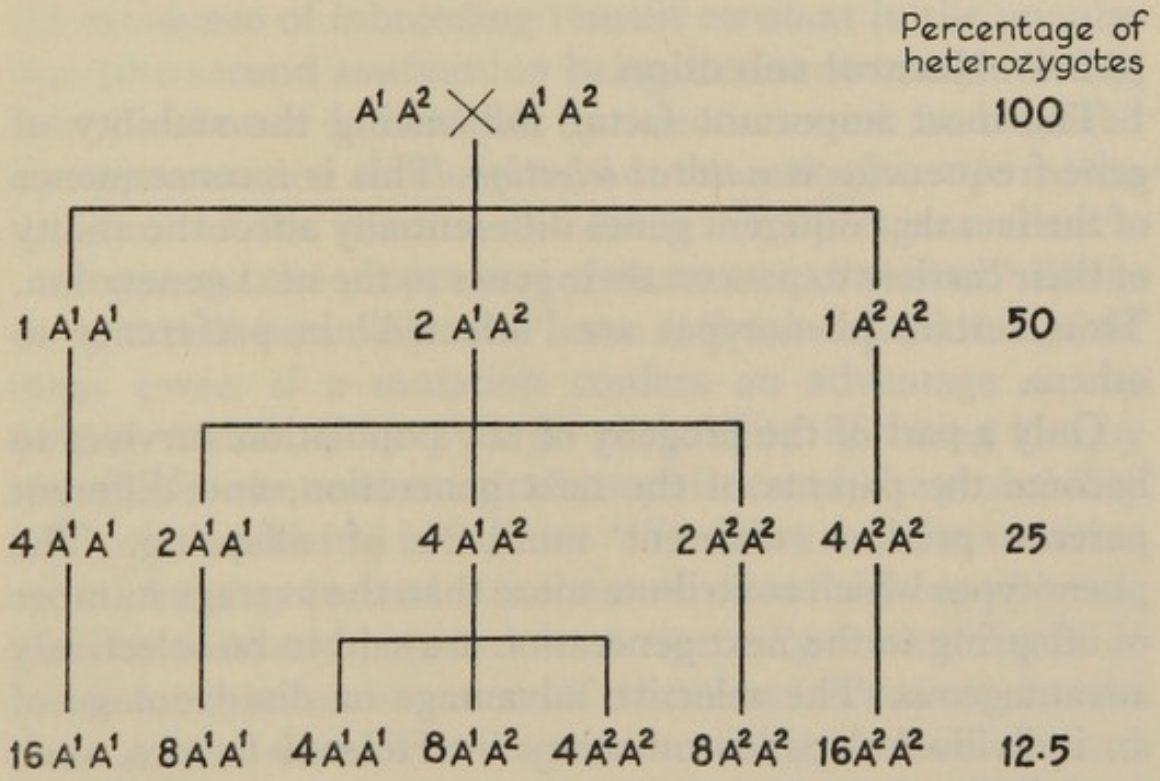


Figure 19 Diagram to show the effect of inbreeding (either from self-fertilization, or like genotypes mating together) in reducing the amount of heterozygosity in a population, although the frequencies of the two allelomorphs remain unchanged.

and *aa* will increase at the expense of the heterozygous *Aa*. However, inbreeding alone does not lead to change in gene frequencies (fig. 19).

10.2.3 **Mutation**

Although mutations are rare events, they are continually occurring and bringing about changes in gene frequency. The chance of any particular mutant gene surviving and being transmitted to future generations depends largely on chance (p. 105), but, assuming that mutations at a particular locus are recurring, it can be assumed that the fate of a mutant gene depends ultimately on how it affects the individuals that carry it. If it makes its carriers more fit to survive and reproduce in their environment, it will spread, replacing the former allelomorph; if its carriers are less fit than the carriers of the normal allelomorph, it will be eliminated.

10.2.4 **Natural selection**

The most important factor influencing the stability of gene frequencies is *natural selection*. This is a consequence of the fact that different genes differentially affect the ability of their carriers to pass on their genes to the next generation. Thus certain phenotypes are "selected" in preference to others.

Only a part of the progeny of any population survives to become the parents of the next generation, and different parents produce different numbers of offspring. The phenotypes which contribute more than the average number of offspring to the next generation are said to be selectively advantageous. The selective advantage or disadvantage of an individual depends on many interrelated factors, such as viability, fecundity, ability to choose a mate, etc. When considering the effects of selection the various causes of loss of potential parents can be lumped together. Thus, in any generation the relative frequencies of the three genotypes of an allelomorphic pair will be $p^2 : 2p(1-p) : (1-p)^2$.

If selection is acting, the frequencies in the next generation will be ap^2: $2bp(1-p)$: $c(1-p)^2$, where a, b and c are the relative selective values of the three genotypes. For example, the disease phenylketonuria in man causes gross mental deficiency. It is determined by a recessive gene in the homozygous state. Although carriers of the gene can be detected by biochemical tests, they are, to all intents, normal. The frequency of the condition in the population is 1 in 40,000. If the frequency of the phenylketonuria gene is p, then the incidence of the disease is $p^2 = 1$ in 40,000 or 25×10^{-6}, and $p = 5 \times 10^{-3}$ or 1 in 200.

Now no phenylketonurics can ever marry and have children; so the selective value of the recessive homozygous genotype (a) is 0; those of the heterozygotes and normal homozygotes (b and c) are, apparently, both the same and, by definition, equal to one. We can go one stage further and say that if the incidence of the condition and the incidence of inbreeding remain constant in the population (the second assumption being almost certainly untrue), then the loss of individuals by selection must be balanced by new mutation to the gene, i.e. the mutation rate = the incidence of the condition $= 25 \times 10^{-6}$ per generation.

In general the proportion of mutants to "normal" allelomorphs will be smaller the more active is selection against them (even if a mutation confers an advantage on its carrier, it has quite a large probability of being lost by chance: for the mathematically sophisticated, the probability of a gene surviving is $2s/1-e^{-4Ns}$ where s is the selective value of the gene, and e is the root of natural logarithms). Despite this any population carries a "genetical load" of deleterious mutants, most of them as recessives in the heterozygous state. The magnitude of this load will depend on the balance between mutation and selection. This load is surprisingly large: normal, healthy *Drosophila* flies collected from their natural habitats have genes in between a quarter and a third of each of their chromosomes that kill the flies if they become homozygous. It has been pointed

out that even in Western European man, where medical care is expected to be good, 15% of pregnancies terminate in abortion, 3% in still-births, 5% in neonatal and infant deaths, and, of the survivors to adulthood, 20% of the total remain unmarried, and 10% marry but fail to reproduce—in other words, about half of the zygotes fertilized in every generation fail to pass on their genes to the next. Much of this lethality—perhaps as much as a half—may be due to the operation of the genetical load.

10.3 **Selection v. drift**

The minimum selective advantage that will be effective in causing the spread or eradication of a gene varies inversely with the size of the effective breeding population. R. A. Fisher, who with J. B. S. Haldane and Sewall Wright laid the foundation of population genetical theory, concluded that even a selective advantage of $1/N$ was normally too small for any gene to be effectively neutral because the environmental conditions are certain to alter from time to time and the selective advantage of the gene will alter with them.

On the other hand, in small populations where N is less than, say, 100, selective advantages of an appreciable size may be ineffective. Under such conditions, chance will play a large part in the control of gene distributions, and genes may be fixed or eliminated with no relation to their selective advantages. Considerable academic argument has been waged over the question of whether any significant genetical change can be wholly fortuitous. Although this is almost certainly one of those questions to which there is no hard and fast answer, it is significant that work on populations in nature has time after time demonstrated the over-riding importance of natural selection. For example, many genetically controlled characters whose frequencies in populations were once thought to be controlled by genetical drift (such as chromosomal inversions in *Drosophila* populations (p. 126), banding patterns on the shell of the

snail *Cepaea nemoralis* (p.124) and even the distribution of the blood groups in man (p. 111)) have now been shown to be controlled largely by selection. It is clear that quite small changes in a character can have very large advantages or disadvantages to their carrier. For example, the influence of the changing environment has been shown in a marked way in forms of the Twin Spot Ladybird, *Adalia bipunctata*, which can be divided into two groups, red ones with black spots, and black ones with red spots. In the Berlin region, the black form is at a great advantage in summer and, therefore, increases in frequency, whereas the red one is at an advantage in winter.

10.4 **Inbreeding**

Marriages between close relatives has been mentioned as a factor leading to increased homozygosity in a population. In both animal and plant kingdoms there are many and various devices to promote out-crossing. The great advantage of out-breeding is that it results in increased variability through gene recombination and, hence, the possibility of new phenotypes differing in selective value. On the other hand, inbreeding results in the fixation of the genotype, which may be advantageous in existing conditions, but does not permit change if the environment changes. Self-fertilization, which is the most extreme form of inbreeding (leading to 99% homozygosity after 8 generations), is found in many flowering plants (e.g. dandelion).

The chief danger of inbreeding is that any deleterious recessives in the genotype will become homozygous and manifest themselves with a consequent fall in viability of the progeny. It is the reservoir of potentially detrimental recessive genes that provides the genetical justification for most of the marriage prohibitions found in Leviticus XVIII, and for about a third of those in the Table of Affinity in the Book of Common Prayer. On the other hand, it is often commercially important to perpetuate a particular characteristic of a domestic animal (such as a race

horse, or pedigree dog) or crop plant. This is usually most efficiently done by inbreeding and ruthlessly discarding unwanted progeny.

10.4.1 Almost all the sweet corn (maize) grown in the United States of America is in the form of hybrids between inbred, self-pollinated lines. Although self-pollinated maize has a high degree of "inbreeding depression", with short stems and low seed yield, crossing of inbred lines leads to restoration of normal vigour. The average yield from most intercrosses between two inbred lines is about as high as the crossbred parental lines from which they were isolated, but the hybrids between a few lines are exceptionally high-yielding and these are the crosses that are grown commercially. The advantage of the method is that the existing valuable genetical characters are conserved in the inbred lines, and the hybrid product is predictable and uniform. The crop yield has been increased over 40% by growing 'hybrid corn'.

10.4.2 It could be objected that, if inbreeding depression is the result of homozygosity of deleterious recessives, homozygous dominants for all growth-promoting genes ought to be found occasionally in inbred lines. That they have never been isolated is not very convincingly put down to the fact of linkage: every individual in an outbred population may contain several deleterious recessives linked in the same chromosome. To get a chromosome containing none of these recessives would require an improbable combination of crossing-over in just the right places.

10.4.3 Commercial breeding success demands selection of desirable characteristics together with inbreeding for their fixation and standardization. The theory of inbreeding was first put on a quantitative basis by Sewall Wright with his introduction of the "coefficient of inbreeding", which is the probability that the two allelomorphs at a given locus in an

individual are identical by descent. The inbreeding coefficient measures the expected increase in homozygosity of an individual's genotype due to consanguineous mating. Selection in this instance, of course, acts through the chosen pairs of parents, not individual phenotypes as is normally the case.

10.5 **Polymorphism**

E. B. Ford has defined *polymorphism* as "the occurrence together in the same habitat at the same time of two or more distinct forms of a species in such proportions that the rarest of them cannot be maintained merely by recurrent mutation". This definition excludes seasonal and geographical variations since the variants in polymorphism occur at the same time and in the same habitat. It also excludes continuous variation (such as height in man), since in continuous variation the forms grade into each other.

In the absence of selection, the number of individuals in a population which possess a gene derived from a single mutation cannot greatly exceed the number of generations since its occurrence (unless the population increases greatly in size). In the majority of species this would require a period of time immensely greater than could possibly be allowed for the establishment of polymorphism. The presence of two or more forms in a common species in anything approaching equal numbers must, inevitably, indicate that the spread of that dependent on the more recent mutation has been hastened by selection. Ford distinguishes two types of polymorphism: *transient*, in which a gene is in the process of being replaced by another allelomorph, and *balanced* where an equilibrium distribution of allelomorphs is maintained by a balance of selective forces. This latter type of (stable) polymorphism has been investigated in some detail and found in most, if not all, of the species studied from this point of view.

R. A. Fisher was the first to show mathematically that *an equilibrium will be established if the heterozygote has a higher*

selective value than both homozygotes. The frequency of the heterozygote will be determined by its fitness relative to those of the homozygotes. This state of affairs is usually the genetical basis of a balanced polymorphic system. Such a polymorphism will not be much affected by mutations of either allelomorph: its main determinant will be the environment, upon which the fitnesses of the different genotypes depend. Two types of equilibrium are possible: either the heterozygote possessing some intrinsic physiological advantage (such as fertility) over both homozygotes or one controlled by the nature of the advantage itself. The latter case is illustrated by forms of certain butterflies controlled by a dominant gene (the dominant homozygote being less fit than the heterozygote) which are palatable to birds. These come to resemble unpalatable warningly coloured species (Batesian mimicry), and are, thus, afforded a certain degree of protection against predation. However, a mimic progressively loses its advantage as its numbers increase relative to those of its model, until its conspicuous pattern actually becomes a danger when predators no longer associate the pattern with an unpleasant taste.

J. B. S. Haldane has pointed out that in many cases in nature, the polymorphic forms are heterozygotes in which the polymorphism is associated with close linkage between genes or whole chromosomes (probably involving inversions of chromosomal segments), and with the occurrence of a relatively common recessive. To the latter the polymorphic forms are completely dominant, although showing no dominance between each other. This condition has been found in such widely distinct groups as grouse locusts (*Paratettix* and *Apotettix*), snails (*Cepaea*) and fish (*Lebistes reticulatus*). In this way a complex character (such as that of the wing pattern in butterflies and moths), although determined by many genes, may effectively be controlled by a single segregating "super-gene" which functions as a switch for a whole range of characters. It should by now be increasingly clear that the genotype of an individual is not a

mere random assemblage of genes, but that it has a structure of its own, i.e. even in the formal genetical sense, an individual is more than the sum of his genes.

10.6 Polymorphism in man

It is sometimes claimed that natural selection does not operate in man. This does not seem to be true on a number of counts, although its outworking may be rather different to that in other species. The study of human polymorphisms has been particularly fruitful in the last few years.

The most well-known polymorphisms in man are those of the blood groups. Attempts to show that differences in frequency of different blood groups are purely due to chance are not convincing. Associations have been shown to exist between blood group O and duodenal ulceration (between 17% and 54% higher in O people than those of other groups), and cancer of the stomach and group A (up to 20% higher than in other groups) among others. These diseases tend to be those of middle life or later and hence cannot directly influence reproductive ability, but at least these associations show that there is a connection between the blood groups and physiology. It has been suggested that the present distribution of the blood groups may be a reflection of the diseases and plagues of the past, e.g. cholera germs are extremely susceptible to acid conditions, and one of the major mechanisms by which the body is protected against cholera is the inability of the germs to survive the acid in the stomach—but there are differences between the blood groups in the amount of stomach acid and these may indicate different susceptibilities to cholera.

One of the most striking polymorphisms in man involves a gene which causes a severe and often fatal anaemia in homozygous condition, and in the heterozygote state frequently produces a mild anaemia (p. 87). In parts of Central Africa this "sickle cell" gene has a frequency of 40% or more. The mutation rate needed to maintain this would have to be about 3000 times higher than any other

known mutation rate, unless the heterozygote has a selective advantage of about 25% over the normal homozygote. In fact, possession of the gene affords a significant degree of protection against malaria, and particularly against cerebral malaria which is the type most frequently fatal in childhood. This protection clearly outweighs the anaemia suffered by the heterozygotes.

Another inherited disease in man for which an improbably high mutation rate is demanded if there is no advantage of the heterozygote over both homozygotes is cystic fibrosis of the pancreas. Unfortunately there is no clue as yet to the possible advantage in this case.

CHAPTER 11

GENES IN TIME: EVOLUTION

WE have seen how genes can be replaced in a genotype, and how populations in nature may differ genetically. What we have, in fact, been discussing under these headings is the mechanism of evolution.

The publication of *The Origin of Species* by Charles Darwin in 1859 brought a general acknowledgement of the fact that evolution—i.e. "modification with descent"—has occurred because it suggested a causal and non-mystical mechanism of the way it could have happened. Much has been written about the influences that led to Darwin formulating his theory. Without doubt, the climacteric was the voyage that Darwin made as naturalist on the survey ship "Beagle" during a round-the-world trip from 1831 to 1836. On the outward journey Darwin read the recently published "Principles of Geology" by Charles Lyell, which introduced him to dynamic concepts in geology. Visiting different parts of South America he saw for himself evidence of change both in geographical replacements of animals and plants by similar forms, and in temporal changes in the fossils of the rocks (wherein he found many extinct and primitive mammalian species). Oceanic islands showed the divergence manifested by isolated forms. Back home, Darwin read the gloomy prognostications of Thomas Malthus, who predicted that the growth in numbers of mankind would, eventually, outstrip the supply of food. By 1842, Darwin "allowed himself the satisfaction of writing a brief abstract of his theory in pencil in thirty-five pages".

11.1 **Darwin's theory of the mechanism of evolution**

Darwin's theory of "natural selection" as it is commonly

called, is simply based on three postulates and two deductions from them.

Fact 1: All species have a great potential for increase (e.g. every cod lays about a million eggs).

Fact 2: The numbers of most species remain approximately constant.

Deduction 1: There is a struggle for existence.

Fact 3: All organisms show variation.

Deduction 2: "Survival of the fittest" (i.e. natural selection).

Darwin's own summary of his theory bears quoting: "Now can it be doubted, from the struggle each individual has to obtain subsistence, that any minute variation in structure, habits or instincts, adapting that individual better to the new conditions, would tell upon its vigour and health? In the struggle it would have a better *chance* of surviving; and those of its offspring which inherited the variation, be it ever so slight, would have a better *chance*. Yearly more are bred than can survive; the smallest gain in the balance, in the long run, must tell on which death must fall and which must survive." Evidence of the efficacy of natural selection has now been gleaned from many plant and animal groups; most of the evidence collected by Darwin and set out in his book, was gleaned from horticulturalists and animal breeders and referred only to artificial selection under conditions of domestication.

11.2 **Adaptation**

Implicit in the idea of an inherited character conferring any advantage on an individual, spreading through a population and, hence, increasing the fitness of the population to live in that particular environment, is the concept of adaptation. Thus we can speak of an organ being *adapted* to a particular environment in the way that the "telescopic" eyes of deep-sea fish are adapted to dim light, the "radar" of bats is to movement in the dark and so on. From a

genetical point of view the question is whether any evolutionary change is non-adaptive, can a gene with unfavourable or neutral effects become common in a population? Certainly, the pleiotropic action of genes which are selected for some beneficial effect may produce some non-adaptive side-effect; or a gene which has an advantageous influence in (say) the juvenile stage, may have an end-product of no adaptive significance in the adult stage. J. S. Huxley has pointed out that changes in absolute body-size, in themselves probably adaptive, may, automatically, lead to disproportionate growth in a variety of structures, such as horns and antlers in mammals and appendages in arthropods. The effects so produced may be very striking, but as they are the inevitable result of alteration in size, they can rarely have an adaptive significance.

This is really another aspect of the same problem that has already been discussed in section 10.3.5, and to which it is impossible to give a dogmatic answer. However, as E. B. Ford points out, "even if a non-adaptive character were to be established by a chance survival, it appears in the highest degree improbable that it could be maintained in a constant condition purely fortuitously".

11.3.1 **Objections to the theory of natural selection**

There are a number of objections to the theory of natural selection which were anticipated by Darwin himself. The most important derives from Darwin's lack of knowledge of particulate inheritance. He accepted the current views that inheritance was "blending", from which it follows that half the genetical variation is lost in every generation in a bisexually reproducing organism. Thus it was necessary to postulate an extremely high rate of origin of variation. In fact Darwin took over from his evolutionist predecessor Lamarck the notion that exposure to current differences of environment, accidentally formed habits, and mental or physical exertion of any kind, could produce hereditary effects. Our current understanding of particulate inherit-

ance with its automatic conservation of existing variation completely removes this difficulty.

A second class of objections relates to the difficulty of imagining functional intermediate stages in the development of a character such as the electric organ of a fish, or rather similarly, to the acquisition of organs of "extreme perfection" such as the vertebrate eye. In general, specific difficulties like these tend to diminish as comparative studies progress and advantageous (functional) intermediate stages are discovered. Moreover, as Fisher has pointed out, evolutionists could not explain the production of complex organs except by postulating natural selection, for the probability of all the necessary modifications appearing initially in one organism (except by special creation) is virtually zero. It is only their gradual accumulation as the result of natural selection, which increases sufficiently the probability of their appearing in the same individual that make it possible for highly integrated systems to be evolved.

The last group of objections is the most important, and give rise to the most difficulty in people's minds, because many of the popular histories of biology were written in the 1920's and 1930's, before the solution was realized. In the first decades of this century there was a difference of understanding of evolutionary processes between the early geneticists, and the palaeontologists who alone directly study the course of evolution in the fossils. The fossil record, incomplete though it is, shows a picture of continual, gradual change in many forms over many generations. This led to palaeontologists putting forward "orthogenetic" theories of evolution, implying some inherent characteristics of the organisms causing them to have a tendency to evolve continuously in certain directions. On the other hand, the mutations studied in the laboratory seemed to have little connection with the type of change observed in the fossils. Virtually all mutational changes are disadvantageous and the enormous preponderance are recessive (200 recessives to 13 dominants in *Drosophila*), in sharp

contrast to the normal dominant factors found in nature. As a consequence some geneticists put forward mutationist (or saltationist) theories of evolution, suggesting that new species (and higher categories) of organisms arise by sudden, single mutations (p. 66). This paradox was largely resolved by R. A. Fisher with his theory of the "evolution of dominance".

Fisher postulated:—

1. Mutations are recurrent, and all mutations occurring will have done so many times previously in the history of the race.
2. When a gene is rare, the heterozygote will be very much commoner than the homozygote.
3. If the original mutation was advantageous (even as little as 1% or less over the existing gene), selection will tend towards the expression of the gene in the heterozygote, i.e. towards dominance, or vice versa in the case of an originally disadvantageous mutation.

This means that any detrimental condition will be expected to be determined by a recessive gene, and any such conditions that are not so inherited will presumably represent rare new mutations, or those whose advantage has recently changed as the result of change in the environment. Furthermore, it would be expected that evolution would proceed by the accumulation of small steps as the expression of the genotype is modified by the accumulation of modifying genes with small effect, i.e. as seen in fossils. The dominance of genes will, therefore, be the result of a number of genes acting together; once more we have the internal structure of the gene-complex being important.

Historically, Fisher's theory of the evolution of dominance broke the apparent deadlock between the results of genetics and those of palaeontology and morphology. Its acceptance (if not its universal applicability: there are other theories of dominance) was made more sure by experimental

testing, and removed one of the chief difficulties in the way of a genetical theory of evolution.

11.3.2 **The modification of dominance**

Examples of modification of dominance by altering the genetical background of a gene have been recorded in a number of cases. E. B. Ford selected for greater and less expression the heterozygotes of the normally semi-dominant yellow variant of the currant moth, *Abraxas grossulariata*. In a very few generations he achieved complete dominance and complete recessivity. By crossing both his selected lines back to the original stock, he immediately recovered the original semi-dominant condition of the gene, i.e. the gene itself was not affected; modification of the dominance was achieved by other genes.

The lesser yellow underwing moth, *Triphaena comes* has a dark coloured variant *curtisii* in the north of Scotland, which occurs as a dominant alongside the typical pale form. Ford crossed heterozygous *curtisii* moths from the two extremes of its range in Orkney and in Barra (100 miles away in the Outer Hebrides), and in the offspring found that the normal, virtually complete dominance of the gene disappeared. He obtained all intermediates between the pale homozygote and dark coloured *curtisii*. In genetical language, the experiment demonstrated that the normal dominance of the gene in the two areas resulted from the accumulation of different modifiers and that, when the modifying system was broken down by crossing, dominance disappeared, i.e. there is clear evidence of the evolution of dominance by the accumulation of different modifying genes in two relatively isolated populations.

In recent years, black (*melanic*) mutant forms have replaced the cryptically coloured form in industrial areas in many tree and rock sitting species of moths. H. B. D. Kettlewell has found that whereas the earlier (presumably heterozygous) melanic mutants of the peppered moth, *Biston betularia* that occurred 100 years ago (and are

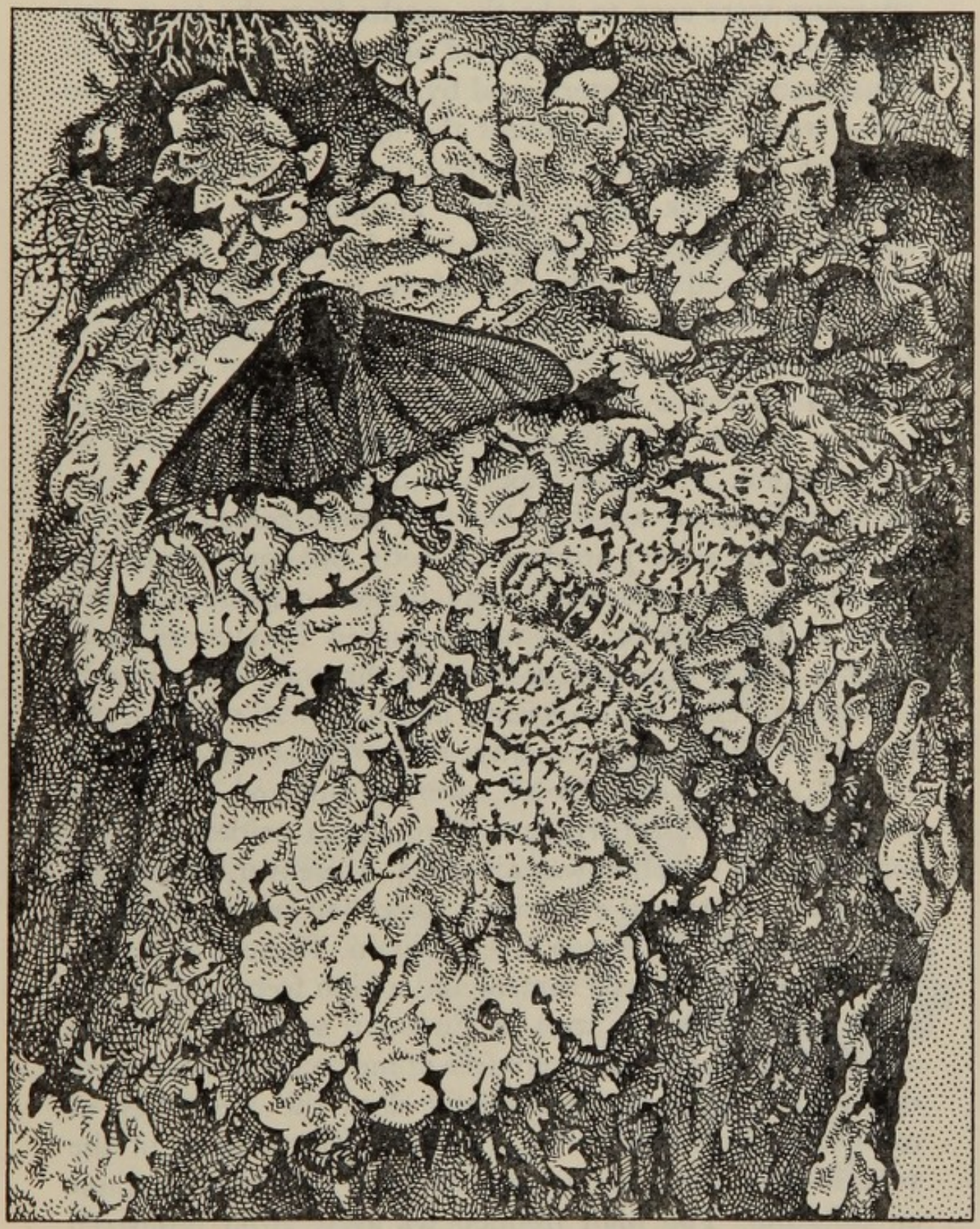
treasured collectors' specimens) showed a number of markings reminiscent of the typical form, modern heterozygotes caught in the wild are almost completely black and are indistinguishable from the homozygote, i.e. a change has taken place to complete dominance in nature.

11.4 Experimental evidence of natural selection

Undoubtedly, the most spectacular example of evolution that has been witnessed is that of industrial melanism, the spread of melanic forms in industrial areas of many moths referred to above. Evidence of selective values as high as 30% to 50% have been recorded.

Melanic forms are normally rare in most places. Industrialization produced air pollution which resulted in a significant change of environment for many moths living in the widespread polluted areas: instead of being virtually hidden by day on lichen-covered trees and rocks, the moths became extremely conspicuous on the smooth, soot-covered surfaces. In the middle of the nineteenth century, black forms of a number of species began to be caught in the neighbourhood of industrial towns. This process has continued to the present day, and many species are now dimorphic (exist in two distinct forms), up to 99% of the population consisting of the melanic form in polluted areas. These industrial melanics are, with only one or two exceptions, determined by a dominant gene. Kettlewell has studied the maintenance of the melanic form of the peppered moth. He released individuals of both the typical and melanic (*carbonaria*) forms on to their normal resting places, tree trunks, outside Birmingham, where the normal frequency of the typical form is only 10%. To the human eye, over 97% of the black form appeared inconspicuous, while 89% of the typical form were judged to be conspicuous (fig. 20). Direct observation on the released insects showed that by late afternoon on the day of the release, 54% of the light form had disappeared compared with only 37% of the *carbonaria*. Furthermore, both robins and hedge

Figure 20 Black and light forms of the peppered moth on an oak trunk in an industrial area. The normal protective colouring of the latter is clearly no longer effective.



Black and light forms of the same species of moth resting on a lichened tree trunk; the black form is now the more conspicuous.
Redrawn from photographs with permission from H. B. D. Kettlewell.

sparrows were seen to take the moths from the trees, and this they did, on the majority of occasions, in the order of conspicuousness as determined by the human observers. In other words the birds *selected* the light moths. Kettlewell went on to release moths marked on the underside of the wing with quick-drying paint. Trapping the moths on successive nights, he recaptured 27·5% of the *carbonaria* that he released and only 13% of the typicals, thus clearly showing differential mortality between the two forms. He concluded that these experiments showed that birds are acting as selective agents, and that the melanic *carbonaria* is at a cryptic advantage in an industrial area such as Birmingham. The same experiments carried out in an unpolluted lichened wood in Dorset (where *carbonaria* does not normally occur) produced exactly the converse of the results: all the *carbonaria* were judged conspicuous and none of the typicals; redstarts, spotted flycatchers, nuthatches, yellowhammers, robins and thrushes were directly observed to take 164 *carbonaria* moths and 26 typicals, the forms being present in equality; and twice as many typicals (12·3%) to *carbonaria* (6·3%) were recaptured in a mark-release-recapture-experiment. Thus direct evidence of intense natural selection was obtained. Moreover, Kettlewell found circumstantial evidence of selection in the distribution of melanic forms over Great Britain. There is a correlation between industrial centres and a high frequency of the black form; only the west of England, south west Wales and the north of Scotland are free of melanics; and nowhere down the east coast of England does the frequency of *carbonaria* drop below 75% (fig. 21). Examination of the vegetation in these last regions shows a significant amount of pollution. The high frequencies away from industrial areas are the indirect result of pollution being carried over long distances by the prevailing south-westerly wind, so altering the environment of the moth as to place *carbonaria* at a selective advantage.

It has been stated that almost all industrial melanics are

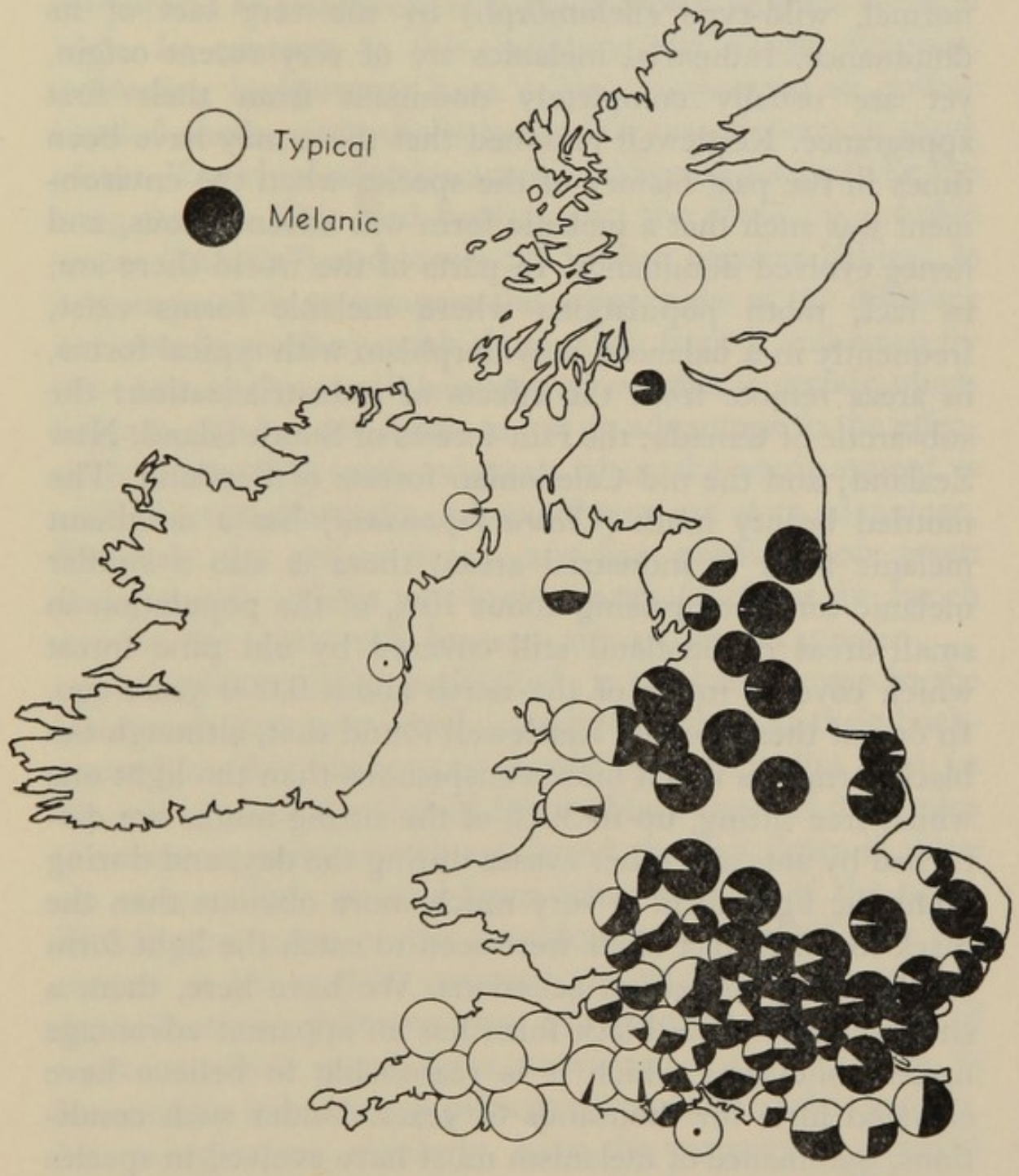


Figure 21 Proportions of black and light forms of the peppered moth in samples caught at different places in the British Isles.

Work of H. B. D. Kettlewell.

determined by a dominant gene, yet if Fisher's theory is correct, a dominant gene would be expected to have a selective advantage over its allelomorphs (including the normal, wild-type allelomorph) by the very fact of its dominance. Industrial melanics are of very recent origin, yet are usually completely dominant from their first appearance. Kettlewell reasoned that there may have been times in the past history of the species when the environment was such that a melanic form was advantageous, and hence evolved dominance. In parts of the world there are, in fact, moth populations where melanic forms exist, frequently in a balanced polymorphism with typical forms, in areas remote from the effects of industrialization: the sub-arctic of Canada; the rain-forests of South Island, New Zealand; and the old Caledonian forests of Scotland. The mottled beauty moth (*Cleora repandata*) has a dominant melanic form in industrial areas; there is also a similar melanic form comprising about 10% of the population in small areas of Scotland still covered by old pine forest which covered much of the north about 6,000 years ago. In one of these woods, Kettlewell found that, although the black form was much more conspicuous than the light one whilst tree sitting, up to 50% of the sitting moths are disturbed by ants and other causes during the day, and during flight the light form is very much more obvious than the black form. In fact birds were seen to catch the light form on the wing on several occasions. We have here, then, a situation where the black form has an apparent advantage under conditions which it is reasonable to believe have changed little for thousands of years. Under such conditions, dominance of melanism must have evolved in species which are now producing industrial melanics.

Natural selection in operation has been studied in other types of animals besides moths. For example, populations of the snail *Cepaea nemoralis* show different degrees of shell banding pattern on a background colour of yellow, pink or brown. There is found to be a strong correlation between

the frequency of the colour and banding patterns, and the background on which the snails are living. Thus in woods which tend to have a uniform carpet of brown leaves, the proportion of effectively unbanded brown or pink shells is high. In contrast to this, habitats with rough herbiage (including hedgerows) have a high proportion of yellow banded shells, such shells being less conspicuous in these places. The chief selective agent in this case seems to be the song thrush. This bird breaks open the shells on suitable stones ("anvils") and leaves the broken remains behind. It is thus possible to compare the proportions of the different varieties in a colony, with those taken from it and eaten by thrushes. In this way it has been shown that in certain rough habitats, the banded forms are at an advantage to the effectively unbanded ones, whereas when the environment is uniform, the effectively unbanded ones are at an advantage. Similarly the yellow forms are less predated on green backgrounds, whilst on brown ones (such as in beech woods) the pink and browns are at an advantage.

Examples could be multiplied: it has been shown in the laboratory that mice which match the colour of their background, are less likely to be caught by owls in dim light. In the mid-west of the United States, black races of deer-mice (*Peromyscus maniculatus*) are found on lava flows if these are more or less isolated from other habitats of the mice. Within two years of the introduction of D.D.T. for the control of house flies, resistant strains had developed independently in different parts of the world. The growth of resistant rabbit populations, survivors of myxomatosis, is becomingly increasingly plain in many parts of the country. Micro-organisms, similarly, have the capacity to develop strains resistant to antibiotics and other drugs. This resistance results from the selection of a few resistant mutations or gene combinations, exactly as in the higher organisms.

Particularly impressive in this experimental work has been the extraordinary sensitivity of the selective response

to slight changes in the environment. Dobzhansky has studied the frequencies of different inversions (p. 71) in the easily examined salivary gland chromosomes of *Drosophila pseudoobscura*. The inversions can be readily recognized from the patterns of bands along the chromosomes. Three of the inversions studied in the third chromosome are called Standard (*ST*), Arrowhead (*AR*) and Chiricahua (*CH*). Dobzhansky made collections from a wild population. He found that the frequency of *ST* was high in the spring, dropped steadily until June and then rose gradually to a high level in October. *CH* was at a low frequency in March, rose steadily in frequency until June, and then fell steadily until October. The frequency of *AR* also altered to some extent but not so markedly as did the other two arrangements. These changes indicate that *ST*/*ST* is at a disadvantage compared with *CH*/*CH* from March to June, but at an advantage from June to October, there being apparently little change in the frequencies of the three types during the winter. By keeping artificial colonies of the flies, it was shown that at a temperature of about 25°C, *ST* will reach a stable equilibrium with a frequency of approximately 70% if it is in a cage with *CH*. At 15°C the forms remain at the frequencies in which they were introduced, i.e. at this temperature there is little or no selection operating on the effects produced by these inversions.

The reason for the seasonal changes seems to be selection resulting from larval crowding. It is found that when the larvae are crowded in a population cage, as they probably are in the wild in summer (although there is still much mystery about the natural ecology of *Drosophila*) the *ST* homozygote was at an advantage to the *CH* homozygote; when the larvae are not crowded, the *CH* homozygote was at an advantage to the *ST* one, so that instead of a stable equilibrium of 30% *CH*, 70% *ST*, the positions were reversed with 70% *CH*, 30% *ST*.

Selection may be *directional* when one allelomorph replaces another (e.g. industrial melanism), *disruptive*, i.e.

towards two or more different phenotypes as in the evolution of a polymorphism, or *stabilizing*, maintaining the average expression of the phenotype by the elimination of variability. This last type of selection is not very obvious despite being with us the whole time. It can be very strong in a rigorous environment. For example the wings of sparrows killed during a storm were found to be markedly shorter or longer than the average; duck eggs which fail to hatch have almost the same average size, but are far more variable than eggs which do hatch; the same principle holds for birth-weight and survival of human babies.

11.5 Clines and ecological rules

A species inhabiting a large area is likely to experience considerable variation in its environment. If out-breeding producing gene flow between different parts of the range is not too much, local adaptation is likely to take place, so that there may be continuous variation in species characters over part or all the range. Such a distribution is a cline. Part of the clinal variation will be purely environmentally caused, but much is certainly genetical. Many plants (e.g. *Achillea lanulosa*, a relative of milfoil) decrease in size with increasing altitude, yet the dwarf forms found near the tops of hills grow little bigger when transplanted to the deep soil and less extreme weather of the lowlands. Ecologists have long recognized the existence of clines in a series of empirical rules applicable to sub-specific variation, particularly in terrestrial vertebrates:

1. *Bergman's rule*—related forms are smaller in the warmer regions, larger in the colder. This is true of altitudinal changes of temperature as well as those due to latitude. The rule appears to be adaptive, since loss of heat from a larger body will be relatively less than from a smaller, and this will be of value in a cold climate.
2. *Allen's rule*—tails, ears, beaks and other projecting parts of the body tend to be shorter in a cool environ-

ment. Its results will be adaptive, since reduction of surface area will reduce heat loss.

3. *Glober's rule*—dark colour due to melanin pigmentation is more strongly developed in warm and humid environments.
4. In birds of colder climates the number of eggs in a clutch is larger, the digestive and absorptive parts of the alimentary canal are larger, wings are longer, and migratory habits better developed than in birds living in warmer areas.

A cline exists in the distribution of the melanic form *edda* of the autumnal rustic moth (*Amathes glareosa*) in the Shetland Isles north of Great Britain. The proportion of *edda* decreases steadily from 97% in the north of the islands to 3% in the south, a bare 50 miles away. This cline in colour forms is complicated by the fact that the population in the north has a different, less excitable behaviour pattern than normal. The cline seems to be partly determined by predation (particularly from large flocks of hungry, southward migrating birds) and partly, probably, to different tolerances of population density (cf. chromosomal polymorphism of *Drosophila pseudoobscura*); the vegetation in the north is apparently able tosupport a much more dense population than in the south.

11.6 **Isolation**

If two populations are in some way separated so that breeding between the two is very slight, or non-existent, each will tend to adapt to its local environment in different ways (q.v. *Triphaena comes* in northern Scotland, p. 118). The more inter-breeding there is, the greater the flow of genes between the two populations and the less the chance of any genetical divergence (whether through local adaptation due to natural selection or genetical drift due to small population sizes) taking place. Isolation may be physical, with the interposition of a barrier, or merely of space between two populations; ecological or behavioural, e.g. many

different duck species can mate and lay fertile eggs in captivity, but this rarely happens in the wild where each species maintains its own preferences; or genetical where two forms are intersterile. Except in the case of polyploids, which are genetically isolated from the parents as soon as they arise, genetical isolation seems to occur only when a certain amount of genetical divergence has already taken place between two forms, at which time it becomes selectively advantageous since hybrids have a lowered viability (adaptive value).

Animals and plants inhabiting oceanic islands provide instructive examples of isolation, since contact with other populations is slight, e.g. the house mice on one of the Faroes Islands are the biggest in the world, and show other differences from most mice. They have probably been cut off from breeding with their relatives for 300 years.

On the voyage of the "Beagle", Darwin was most impressed by the uniqueness of the flora and fauna of the Galapagos Islands, which lie in mid-Pacific, 600 miles west of South America and about 3,000 miles east of Polynesia. In particular amid a paucity of land birds, Darwin found a group of 13 species of finch, closely resembling each other in plumage, calls, nests, eggs and display yet differing in their beaks, which are adapted to different diets: thus there are 6 species of ground finches, eating different sizes of seeds and living in the arid coastal regions, 6 of tree finches (three eating insects in the forest, one in mangrove swamps, one which carries a twig and pokes insects out of the bark of trees and one vegetarian with a parrot-like beak) and a warbler-like finch feeding on insects in bushes. The most likely explanation for the origin of these birds is that they are all descended from a small group of birds which managed to establish themselves on the Galapagos archipelago—perhaps the first land birds to arrive there. With a number of islands, each with a wide variety of ecological "niches", separated populations of birds could become established and differentiated. It is instructive that there is only a single related

finch species on Cocos Island several hundred miles to the north east. This bird lives on insects in tropical forest. It seems possible that no differentiation has taken place on Cocos because, unlike the Galapagos islands, it was impossible for the birds to scatter and form isolated, non-inter-breeding groups.

11.7 Species

We have already used the term *species* a number of times without attempting to define it. The biological species has never been adequately defined despite many attempts. Ever since the days of Linnaeus, the working definition has been a morphological one based on a few "type" museum specimens. Although for many purposes this is the only practical one, it is very difficult to include the facts of variation therein. For example, the lesser blackback gull (*Larus fuscus*) and the herring gull (*L. argentatus*) are morphologically and ecologically distinct in Great Britain, but are connected by a ring of inter-breeding forms around the polar regions. Moreover the formalised "type" of the old-fashioned taxonomist has no reality in nature. Mention may be made of so-called "sibling species" such as *Drosophila pseudoobscura* and *D. persimilis* which are almost morphologically indistinguishable, yet differ in geographical and habitat preferences; show physiological differences; and are sufficiently reproductively isolated for no hybrids to be found in nature. Perhaps the best definition that can be attempted is that "a species is a population or group of populations which are capable of exchanging genes with each other in nature if they come into contact". Although sterility when crossed with other species is often included in the definition, this is not a fair criterion. It is better to say that, in their natural life, species do not *normally and successfully* interbreed. The differences that tend to prevent interbreeding between animals are not solely, or even mainly, the genetical differences that are the cause of sterility in a cross. However, since biological isolation tends

to be associated with morphological differentiation, in practice the species of the systematist and the biologist are usually synonymous.

The genetical differences between species have only been worked out in a small number of cases. Every type of chromosomal re-arrangement is found between *Drosophila* species, and in some cases the differences between species are so great that comparison is impossible. Chromosomal differences, particularly translocations, lead to failure of meiotic pairing, and, hence, hybrid sterility. Clearly also, gene differences play as great, if not a greater, part: in *Drosophila* species it is sometimes possible to find homologous gene series in which different allelomorphs are represented in different species. Hybrid sterility cannot always be ascribed to difficulties in meiotic pairing. For example, in the testes of male mules (sterile progeny of horse and donkey), degeneration of the prospective gametes begins before the stage at which the meiotic pairing of chromosomes would normally take place. In the hybrids between some strains of *Drosophila pseudoobscura* and *D. persimilis*, the chromosomes seem to pair normally but degenerative changes still occur. Attempts have been made in the past to suggest that the differences between species are qualitatively different from those which have been studied between races and populations. There is no real evidence for this (except in the probably comparatively few species that have arisen as a result of polyploidy): species are undoubtedly produced as a result of selection (and possible chance effects, particularly the 'founder principle') acting on mutations and recombinations under conditions of isolation.

A further point with regard to species is that properly they ought to be thought of four-dimensionally, because as well as having a spatial existence, they also have a temporal one extending back through generations and probably through changes in environment. This aspect is particularly important when we consider palaeontological species.

11.8 Genetics and the fossil record

We have seen how in the earlier years of this century there seemed to be a difference between the findings of geneticists and palaeontologists with regard to evolution and how this difference was resolved. As our understanding of populations in nature increases, we find that the gradual change that is found in the fossil record accords with the genetical changes that become established between populations and the species. It is sometimes possible to trace a changing fauna through long periods of time in the rocks. Under such conditions the assemblage of forms indicates something of the conditions of life of the organisms concerned. For example, studies of the origin of the coiled lamellibranch *Gryphaea* from oysters of the genus *Ostrea* showed that evolution of forms to which the name *Gryphaea* is given occurred independently several times in the strata studied. (fig. 22). Numerous characteristics altered in the course of the evolution: the shape of the shell, its angle of coil, its breadth/length ratio, the area of attachment, and so on. In general, each of these characters showed a definite trend during evolution, but their changes were largely independent in speed and amount. There can be no doubt that the changes of form are continuous and gradual: there is a complete absence of large sudden "jumps" or saltations. Moreover, the variability of a later population is usually not entirely outside the range of that of an earlier population, suggesting that the change between forms is largely due to directional selection (p. 126). Palaeontology shows us *micro-evolution* as a process of gradual change in

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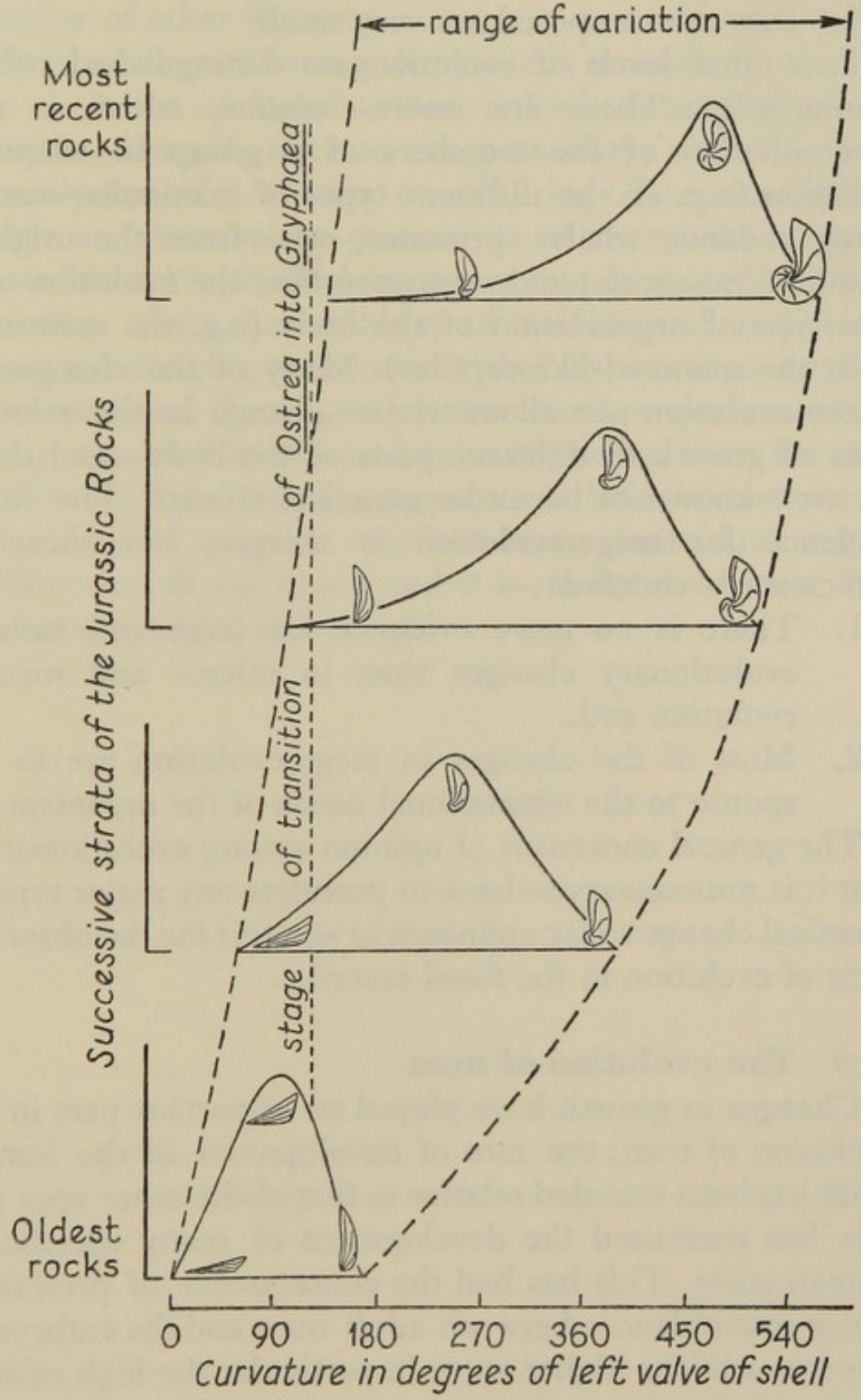
Figure 22 Evolution in fossil oysters as shown by one particular character. Individuals in each sample vary in the amount of in-curving of the shell, but the average in-curving increases in later samples. Note the arbitrary distinction between *Ostrea* and *Gryphaea*. *Based by permission of Professor T. Neville George on a figure in his book* EVOLUTION IN OUTLINE, *published by C. A. Watts & Co.*


range of variation
Most recent rocks
Successive strata of the Jurassic Rocks
Oldest rocks
of Ostrea into Gryphaea
of transition
stage
0
90
180
270
360
450
540
Curvature in degrees of left valve of shell

interbreeding populations. These changes may accumulate to form large differences of structure though the steps of which they are composed are very small.

Two other levels of evolution are distinguished palaeontologically. These are *macro-evolution*, which is the differentiation of the members of a group in adaptive radiation (e.g. all the different types of mammals—carnivores, rodents, whales, primates, etc.—from the original primitive mammals) and *mega-evolution*, the evolution of a new type of organization of the body (e.g. the mammals from the mammal-like reptiles). Many of the changes of macro-evolution are allometric——change in the relative rates of growth of different parts of the body—and these are well known to be under genetical control. The fossil evidence for mega-evolution is meagre, but there is sufficient to conclude:—

1. There is no more evidence for large and sudden evolutionary changes than in micro- and macro-evolution and
2. Most of the changes in mega-evolution are in response to the adaptational needs of the organism.

The general consensus of opinion among evolutionists is that it is unnecessary to have to postulate any major type of genetical change so far unknown to account for the observed facts of evolution in the fossil record.

11.9 **The evolution of man**

Changes in growth have played an important part in the evolution of man: the rate of development of the human body has been retarded relative to that of the other apes and this has permitted the development of many specifically human traits. This has had the consequence of producing many resemblances between adult man and the embryonic structures of the higher apes: in particular the high relative brain weight, the position of the foramen magnum at the base of the skull, the delayed ossification of the bones of the skull (allowing the head to increase in size), the dentition

(in apes the milk teeth are cut directly after birth), the hairlessness of the body, the light colour of the skin and a number of other features.

It is worth mentioning that there is no evidence at all for the evolution of moral values, indeed, rather the reverse. Darwin, himself, rejected the possibility, since "it is extremely doubtful whether the offspring of the more sympathetic and benevolent parents, or of those who were the most faithful to their comrades, would be reared in greater numbers than the children of selfish and treacherous parents belonging to the same tribe". Nor is there anything to recommend the suggestion that moral purpose was somehow embedded in the evolutionary process from the start; this is little better than mysticism. Science has not accounted for morality, truth, beauty, individual responsibility or self-awareness and it is doubtful whether, from its nature, it can ever do so.

CHAPTER 12

RADIATION GENETICS

In 1921 Mavor discovered that X-rays could produce genetical changes both by increasing the amount of crossing-over and the incidence of chromosomal non-disjunction at cell division (p. 68); in 1927 H. J. Muller, using techniques already described for objectively estimating the number of sex-linked mutations in *Drosophila*, discovered that the mutation rate itself is greatly increased by X-irradiation. This discovery (for which Muller received a Nobel prize) has produced results in the accumulation of new mutants of potential economic value (especially to horticulturalists), as a genetical tool for the elucidation of the nature of mutation and, more recently, in public disquiet following the development of atomic weapons.

12.1 **Ionizing radiation**

X-rays were discovered by Röentgen in 1895. Soon afterwards, it was realized that there exists a certain amount of natural radioactivity. Compounds of certain heavy elements in the earth's crust, such as uranium and radium, spontaneously emit rays which have similar properties to X-rays, although of different penetrating power. Some years after this, rays were identified which reached the earth from outer space and these were named "cosmic rays".

The most common types of penetrating radiation are:—

α *particles*: these are the nuclei of helium atoms and are swiftly moving particles of high energy, carrying a positive electrical charge. They have little power of penetration (only penetrating into soft tissue for fractions of a millimetre) and external irradiation of the body by them is consequently of little significance.

β *particles*: these are small, fast moving, energy-carrying

particles with a negative electrical charge (electrons). The amount of energy they carry—and hence their penetrative ability—can vary considerably.

γ-rays: these are electromagnetic radiations of high energy emitted by atomic nuclei. Compared to α and β particles they have greater penetrating powers, and the more energetic γ-rays can traverse the whole body, liberating high-energy electrons in the tissues.

X-rays: these are also wave-propagated radiations but they are usually produced artificially by electrical machines. In general the more penetrating X-rays produced at such high voltages as several million volts have an energy and penetrating power corresponding to γ-rays.

Neutrons: these are normal constituents of atomic nuclei, but they may be liberated with considerable energy. They carry no electrical charge and act chiefly by collision with the hydrogen of the tissue molecules producing 'recoil hydrogen nuclei' (protons) somewhat resembling α-particles in their action. When slowed down in the tissues they may enter the nuclei of atoms, particularly nitrogen, building up unstable compounds which often disintegrate with the production of artificial radioactivity.

These types of radiation differ not only in their penetrating powers, but also in the number of electrically charged atoms and molecules (ions) which they leave in their tracks as they pass through the tissues. Neutrons in particular cause dense ionizations and are said to have a high *linear energy transfer* (LET) thereby differing from the low LET X- and γ-rays. The biological effects of radiation are related to the dose or quantity of radiation received. The unit of radiation is the *röentgen* (*r*), which is defined in terms of the ionization produced by X or γ irradiation in air under specific conditions. The unit normally used in biological work is the *rad* which is a measure of absorbed energy (1 rad = energy absorption of 100 ergs by a gram of irradiated material at the point of interest). One röentgen in air is almost exactly equivalent to one rad in biological tissue.

12.2 Quantitative aspects of radiation mutagenesis

Mutations that are induced by radiation in *Drosophila* seem to represent a similar assortment of changes to those that arise spontaneously e.g. white eyes, yellow body, cut wings, etc., but when the chromosomes are examined, it appears that chromosomal alterations arise proportionately more frequently in X-ray treated than in untreated material. Higher doses of radiation produce more changes of the same sort, not qualitatively different, bigger ones.

Because of the existence of critical objective methods for their detection, the induction of sex-linked lethal mutations in *Drosophila* has been a favourite subject for investigation. It is found that when adult male flies are irradiated and then mated straight away, the rate of induction of mutations is directly proportional to the dose of radiation (i.e. the the number of rads) received, whether this dose is given in a short time, or spread over hours and weeks, or divided into a number of smaller doses (fractionated). The range of radiation intensity studied extends from 0·002r/min to 2000r/min. Over this range, differing by a factor of 1,000,000, no difference has been observed in the efficiency with which radiations induce mutations in *Drosophila* spermatozoa.

Furthermore, and it is this fact which causes people concern, there does not seem to be any *threshold* below which radiation has no mutagenic effect. Results have now been reported showing that the mutation frequency in *Drosophila* is linearly proportional to the dose of radiation received from 5,000r down to 5r (which is less than the average amount of radiation received per person during a lifetime in Britain). If the dose-mutation frequency relationship is extrapolated back to zero dose (fig. 23), the line will cut the mutation frequency ordinate at a point close to the spontaneous frequency, i.e. any amount of radiation, however small, will result in an increase in the frequency of mutations.

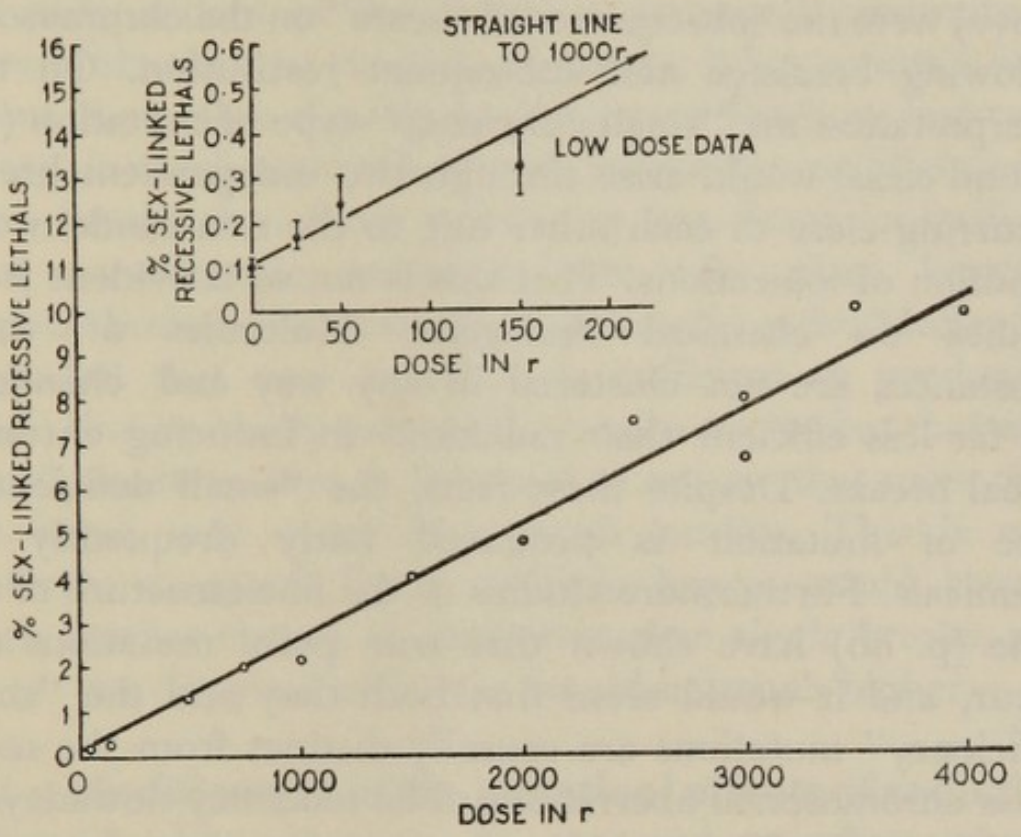


Figure 23 The relationship between radiation dose and the frequency of sex-linked recessive lethal genes induced in *Drosophila* spermatozoa. *Based by permission on a figure in* GENETIC EFFECTS OF RADIATIONS *by Purdom, published by Newnes.*

12.3 Radiation induced mutations

Recessive lethal mutations in *Drosophila* can be divided into three groups on the basis of the appearance of the chromosomes in the carriers:—

a. those unaccompanied by any detectable change in the chromosomes.

b. those detectable as small deficiencies of the chromosomes.

c. those associated with gross structural changes such as inversions, translocations and large deletions. This group increases more than the first two after high radiation doses.

It used to be thought that all mutations were really chromosomal, and that true point mutations (the first class

above) were the consequence of "scars" on the chromosome following breakage and subsequent restitution. On this interpretation the "small deficiency" type of mutation (the second class) would arise through two independent breaks occurring close to each other due to the non-random distribution of ionizations. That this is not so is evident from studies on chemical mutagens. Molecules of these substances are not clustered in any way and chemicals are far less efficient than radiations in inducing chromosomal breaks. Despite these facts, the "small deficiency" type of mutation is produced fairly frequently by chemicals. Furthermore studies of the fine structure of the gene (p. 86) have shown that true point mutations can occur, and it would seem that both they and the "small deficiency" mutations are causally distinct from the more gross chromosomal aberrations. The tendency nowadays is to think of radiation induced gene mutations as radiochemical events following the production of highly reactive chemical radicals (particularly H^+ and OH^-) in the close neighbourhood of the chromosome.

In the case of chromosomal mutations, examination of irradiated plant cells shows that the frequency with which chromosome breaks arise is linearly related to radiation dose. However, the higher the dose, the more likely it is that there will be several chromosome breaks in one cell and hence translocations, inversions, etc., will arise increasingly more frequently. In *Drosophila* sperm, chromosomal aberrations arise at a frequency proportional to a 3/2 power of the radiation dose. Now the physical effect of the passage of a radiation particle through any material is a track of ionizations which ends when the particle finally expends its energy. The production of ionizations along the track, and in the terminal clusters of the tail, is directly proportional to dose and independent of the intensity of irradiation. Hence the production of a chromosome break (and a point mutation) has been interpreted as determined by one ionization or ionization cluster,

and independent of the spatial or temporal proximity of other ionizations or clusters. However, it has recently been shown that more densely ionizing rays (such as fast neutrons) are much more effective in the production of chromosome breaks than those producing less dense ionizations. Now considerable restitution can take place between recently broken chromosome or chromatid ends: Muller has suggested that one ionization is sufficient to produce a break, that normally most of the breaks rejoin, but that with densely ionizing rays, it is logical to assume that more than one break may occur in a small locality. This is now generally accepted. Such multiple breaks would have a much smaller chance of restitution than single breaks, and hence, the net yield of breaks would be much higher.

12.4 **Modification of the genetical effects of radiation**

Considerable advances in our understanding of the genetical effects of radiation have come in the last few years with the realization that there are various factors which can modify the extent of genetical radiation damage. These underline the point already made in Chapter 7, that mutation is to a large extent dependent on cell metabolism. For example, lack of oxygen before and during radiation protects against genetical damage (both point and chromosomal changes). Thus, only about a third as many aberrations are observed following X-irradiation of bean root-tips in nitrogen rather than in air. It seems that the presence of oxygen in some way increases the number of breaks, possibly by facilitating the production of free peroxide radicals. Certain chemicals can modify radio-sensitivity. Thus, treatment before irradiation with cyanides or azides increases the frequency of mutations (possibly due to the inhibition of certain enzyme systems which destroy peroxides), while the alkaloid colchicine (which inhibits chromosomal movement) greatly reduces the frequency of chromatid aberrations.

In general, chromosomes show markedly different radio-

sensitivities at different stages of the division cycle, the differences being apparently related to differential rejoining at different stages, to the time of chromosome duplication, to the degree of condensation of the chromosomes, and probably also to oxygen concentration. Thus high doses of radiation (of the order of 1000*r*) given to immature germ cells (spermatogonia and oogonia) have a lower mutagenic effect than expected on the assumption of linearity, probably due to the survival of only the less damaged cells.

Another recently discovered modifying factor is the dose-rate effect: although the amount of genetical damage in mature gametes is independent of the rate of delivery of the radiation (*v.s.*), this is not true of irradiation of other gametogenic stages (at least in the mouse). 300—600*r* delivered at the rate of 90*r*/week to mouse spermatogonia produce only $\frac{1}{4}$ the number of mutations as when the same dose is given at 90*r*/minute, and this effect is even more pronounced for oocytes. This decrease in the yield of mutations is obviously important when assessing the dangers from chronic background radiation. The dose-rate effect is thought to be due to an intracellular radiation sensitive repair process which can survive a low rate of radiation delivery, but is destroyed at higher dose rates.

It appears that there is a definite time between the absorption of radiation energy with the establishment of a molecular lesion, and the fixation of this lesion as a self-replicating change. Repair processes under metabolic control take place in this interval and it is these processes that are modifiable by external factors. As we get to know more about these events, we shall learn more about mutation itself, and about protecting ourselves from radiation damage.

12.5 **Ultra-violet radiation and mutation**

Ultra-violet irradiation is mutagenic but in a different way from ionizing radiation, tending to produce proportionately fewer chromosomal mutations. The highest mutagenic efficiency of ultra-violet (u.v.) light is at the wave-

length which corresponds to its maximum absorption by DNA. At this wave-length of 2600 Ångstroms the capacity of u.v. irradiated DNA *in vitro* to act as a template for the synthesis of more DNA is greatly reduced (p. 80), and also at this wave-length the hydrogen bonds between the DNA chains tend to be changed to chemical linkages (which would block replication of the chains). U.v. inactivated DNA can be reactivated by light: there is an enzyme which functions in blue light to break the cross links between the DNA strands. It is thought that reactivation (only found after u.v. irradiation) is associated with the fact that ionizing radiation affects mainly the DNA 'backbone', u.v. chiefly the bases.

12.6 **Effect of radiation on a population**

Any population of living organisms in nature contains a number of deleterious genes: on the average we (the human species) all carry four or five recessive deleterious genes in the heterozygous form. If individuals are exposed to a higher level of radiation, more mutations will occur and the number of abortions, still-births and deformed children might be expected to increase. This raises two practical problems: how much would be the increase in abnormality resulting from a rise in radiation, and, assuming that much radiation is beneficial (as in diagnostic radiology, nuclear power and so on), what is the permissible (compromise) dose of radiation for humans?

On the simplest, "classical" view of population structure, there is a 'normal' gene at each locus, and in addition a series of 'abnormal' allelomorphs which have arisen by mutation and have not yet been eliminated by selection. The extent to which these 'abnormal' genes will result in death or infertility of their carriers ('genetical death') will be in direct proportion to their incidence—and hence their mutation rate—in the population. These genes represent 'the genetical load' of the population that carries them. However, we have seen that many genes are more advan-

tageous when heterozygous than homozygous, or are 'overdominant', resulting in genetical polymorphisms. In this way at least two forms of the gene are maintained in the population (e.g. the genes producing normal and sickle cell haemoglobin). The alternative to the classical hypothesis of population structure, the "balance" hypothesis, states that the best type is not a homozygous individual, but one who is heterozygous. Since heterozygous individuals do not breed true, a consequence of maintaining this best adapted type is a considerable genetical diversity within the population. The effects of a rise in mutation rates on such a system would not increase the ill-effects from deleterious recessive genes proportionately. The most important task facing population geneticists today is to determine the relative frequency and role of these two systems. All that can be said at the moment is that balanced polymorphisms have been found in all species which have been investigated from this point of view.

Direct investigations of this problem have led to apparently conflicting results. One relevant experiment may be described here. A population of *Drosophila* was rendered free of recessive lethals in the second chromosome and divided into three: the first received 2000*r*/generation of γ rays for 126 generations; the second was given an acute dose of radiation (7000*r* to males, and 1000*r* to females) at first and none thereafter; and a third, control, population was given no radiation. The incidence of lethals in the second chromosome was determined every generation. The frequency in the controls increased from 0 to around 25% to 30% in 80 generations; the continually irradiated population reached equilibrium when about 80% of the second chromosomes contained lethals; the initially irradiated population showed a frequency of about 20% of lethals which dropped slightly (probably due to the rapid elimination of partially dominant mutations), and then rose to about the same value as the control population (fig. 24). But, and this is the important fact, the average fitness of the con-

tinually irradiated population was only 2% below that of the control, i.e. the accumulation of mutants is not necessarily harmful in itself, and, conversely, a uniform phenotype may conceal many genotypes.

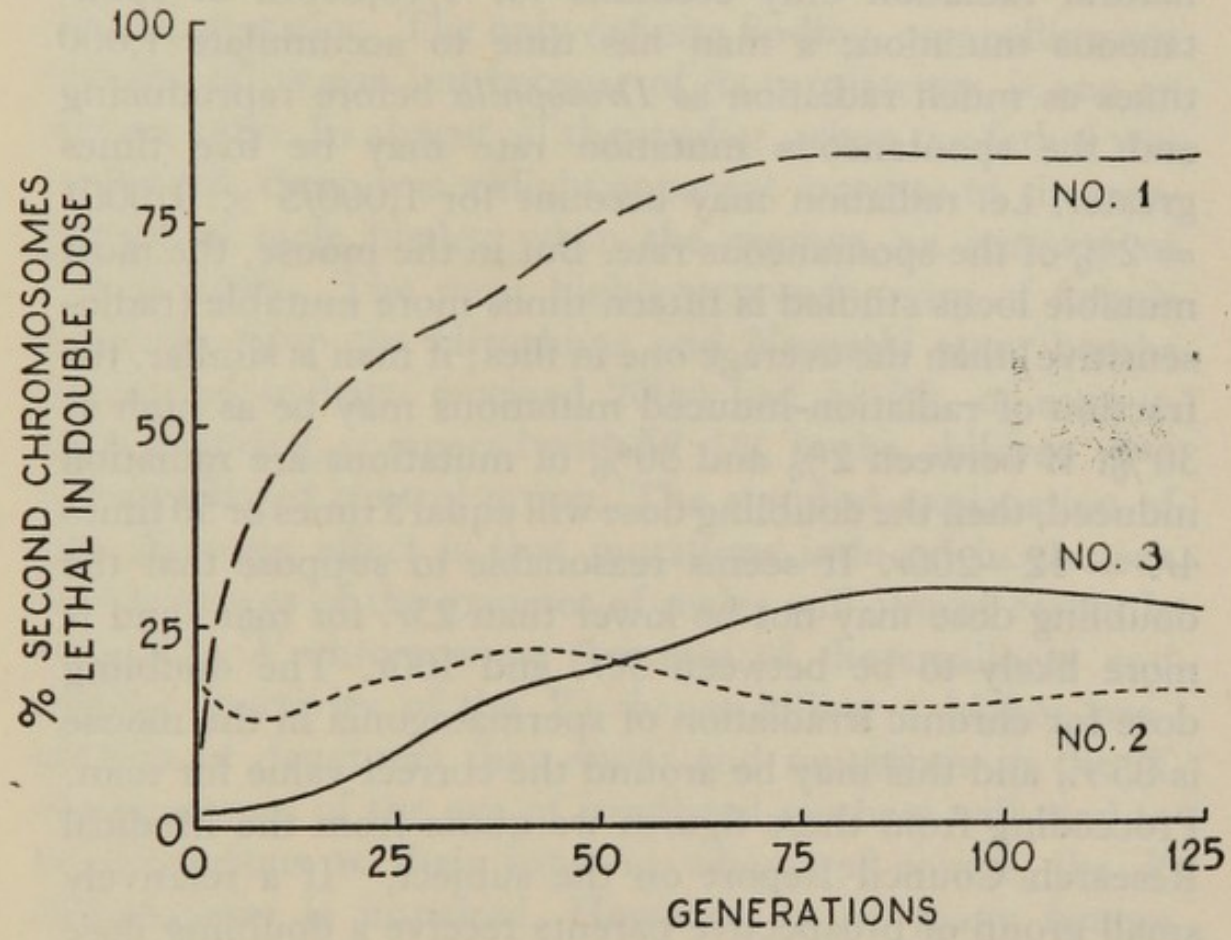


Figure 24 Accumulation of recessive lethal genes in the second chromosome of three laboratory *Drosophila* populations: no. 1 exposed to gamma rays from radium continuously for 126 generations; no. 2 exposed to a high initial dose of gamma rays and none thereafter; and no. 3 not subjected to any radiation. *Work of B. Wallace.*

12.7 Genetically permissible radiation doses

A practical guide for permissible radiation exposure has been based (by the International Commission on Radiological Protection) on the amount of radiation necessary to double the number of mutations occurring spontaneously in any generation. On the most pessimistic assumptions,

if all mutations are radiation induced, then the "doubling dose" will equal the amount of radiation received up to the average age of reproducing. The total received in 30 years in Great Britain is about 4*r*. However, in *Drosophila*, natural radiation only accounts for 1/10,000th of spontaneous mutation; a man has time to accumulate 1,000 times as much radiation as *Drosophila* before reproducing and the spontaneous mutation rate may be five times greater, i.e. radiation may account for $1{,}000/5 \times 0{\cdot}0001 = 2\%$ of the spontaneous rate. But in the mouse, the most mutable locus studied is fifteen times more mutable (radiosensitive) than the average one in flies; if man is similar, the fraction of radiation-induced mutations may be as high as 30%. If between 2% and 30% of mutations are radiation induced, then the doubling dose will equal 3 times or 50 times 4*r*. = 12—200*r*. It seems reasonable to suppose that the doubling dose may not be lower than 25*r*. for man, and is more likely to be between 30*r*. and 100*r*. The doubling dose for chronic irradiation of spermatogonia in the mouse is 85 *r*., and this may be around the correct value for man. Proceeding from these figures we quote from the Medical Research Council Report on the subject, "If a relatively small group of prospective parents receive a doubling dose of radiation no noticeable effects will be produced either on their immediate offspring or upon their descendants. For levels of radiation up to the doubling dose and even some way beyond, the genetic effects of radiation are only appreciable when reckoned over the population as a whole, and need cause no alarm to the individual on his own account".

In fact, the doubling dose concept is a gross oversimplification: mutational response to radiation depends on dose-rate, fractionation of dose, stage of gametogenesis, etc., but it remains a useful rule of thumb estimate for radiation hazard.

Studies on man have yielded no direct information about his genetical susceptibility to radiation, except that he is

not abnormally radio-sensitive. The surveys carried out on the children of irradiated human populations (of which the most extensive has been that on the survivors of the Japanese atomic bomb explosions) show no significant evidence of any increase in inherited diseases attributable to increased mutation. The only definite finding, compelling not because of its size but because of its consistency, is one on the sex ratio. In almost all the studies, when the father was irradiated, there was a slight apparent increase in the proportion of male births; when the mother, an increase of female births. The most highly exposed group of female survivors from the Hiroshima and Nagasaki atom bombs (estimated to have received 200*r*) had 51·2% of sons in their offspring, compared with 52·1% in the children of a non-irradiated control group. The simplest explanation of this sex-ratio effect is that mutations induced in the sex chromosomes of the gametes of males will almost certainly be in the *X* chromosome (because of the smallness and relative inactivity of the *Y*), hence killing a higher proportion of daughters than sons; and mutations in the *X* chromosomes of the ova of irradiated mothers will tend to be deleterious to their sons, in whom, of course, the *X* chromosome is unpaired. However, as so many factors (such as paternal age, number in the family and so on) are known to influence sex ratio these results can only be taken as being suggestive of a radiation effect.

12.8 **Somatic mutation**

Mention should be made of the effect of radiation in causing genetical changes in cells other than the germ cells (somatic cells). For example, there is some evidence that radiation decreases the life span of those who receive it. One of the current theories of the reason why ageing occurs is that it is a consequence of the accumulation by the body of somatic mutations—which would, of course, be caused by radiation. However, the most important radiation-induced somatic change of which we are aware is the pro-

duction of leukaemia. Before the dangers of radiation were fully realized many experimenters allowed themselves to be subjected to unnecessarily high doses of radiation and some developed leukaemia and other forms of cancer. Although the mode of production of cancer is still obscure, in at least one of the forms of leukaemia (the chronic myeloid type), chromosomal changes seem to play a causative role. It is a continual medical problem to balance the deleterious effects of X-rays with their beneficial ones (destroying cancer cells and in diagnostic radiology).

CHAPTER 13

ANALYSIS OF DATA

IT is beyond the scope of this book to describe the planning of experiments and evaluation of data. Any good statistics textbook describes standard techniques applicable to genetical experiments. For example, the distinguishing of the relative importance of various genetical and environmental factors frequently requires the employment of an *analysis of variance*; continuous traits are described in terms of their *mean* and *variance*, and methods exist for comparing these parameters.

Segregation and contingency

In practice, two of the most commonly occurring statistical problems in genetics concern the comparison between numbers experimentally observed and those expected on some hypothesis. The first of these is the problem of testing segregation ratios. For example, in crosses between *Drosophila melanogaster* flies heterozygous for the recessive gene vestigial-wing (*vg*), 1595 normal and 514 vestigial (*vg*/*vg*) flies were counted. The question is: do these numbers agree with the expected 3:1 ratio, or, more generally, do observed numbers *a*:*b* agree with an expected ratio *r*:1? The usual procedure to test this is to calculate a value called χ^2 (Greek capital letter *chi*-squared), which is a measure of the discrepancy between observed and expected, as follows:—

$$\chi^2 = \frac{(a-br)^2}{r(a+b)} = \frac{(1595 - (3 \times 514))^2}{3 \times (1595 + 514)} = 0{\cdot}44$$

This value is then compared with the significance points "χ^2 with one degree of freedom" given in almost all collections of statistical tables. These show, for example, a

significance point 6·64 corresponding to a *probability* of 0·01, or 1 in 100; the meaning of this is that if the segregation ratio 3:1 holds exactly, only in one sample in 100 will a value of χ^2 greater than 6·64 be observed. If such a large value of χ^2 is observed, it is usually taken to imply considerable doubt on the hypothesis—since it would be very unlikely to occur if the 3:1 ratio actually held. In this case the sample is technically said to "differ significantly from a 3:1 ratio at a level of 1%" (the same value 6·64 will hold for any r:1 ratio). $\chi^2 = 0{\cdot}44$ as calculated in our example is not significant by this test even at the 5% (0·05) level, the weakest one usually taken as significant, i.e. there is no evidence of departure from expectation.

The second problem occurs in finding out whether two characters show any appreciable association (i.e. whether the presence of one is *contingent* upon the presence of the other). For example, it might be important to know if fair people are more likely than dark people to have blue eyes, and if dark haired people have a greater chance of having dark eyes than fair people. A count of blue and brown-eyed people according to their hair colour can be arranged as follows:

		HAIR COLOUR		
		Blond	Brown and Black	Total
EYE COLOUR	*Blue*	158	28	186
	Brown	38	45	83
	Total	196	73	269

This is a 2 × 2 table (i.e. it has two columns and two rows) and, substituting letters for numbers, it can be written in a general form:

	First Classification		
Second Classification	a c	b d	a + b c + d
	a + c	b + d	a + b + c + d

To test whether the first classification is contingent upon, or associated with the second one, a χ^2 can be calculated by:

$$\chi^2 = \frac{(a + b + c + d)(ad - bc)^2}{(a + b)(c + d)(a + c)(b + d)}$$

The χ^2 calculated from a contingency table has a number of *degrees of freedom* of one less than the number of columns times one less than the number of rows of the table. Returning to the numerical example:

$$= \frac{269((158 \times 45) - (38 \times 28))^2}{186 \times 83 \times 196 \times 73}$$
$$= 54{\cdot}9$$

Looking up this χ^2 value (with $(2 - 1) \times (2 - 1) = 1$ degrees of freedom) we find that it is highly significant (with a probability of occurrence of less than 1 in 1,000), i.e. the observed data give evidence of a lack of independence between hair and eye colour.

Strictly speaking χ^2 procedures are only approximate, and these examples illustrate fully neither their potentialities nor pitfalls. Anyone concerned with or interested in these problems is referred to the "suggestions for further reading."

SUGGESTIONS FOR FURTHER READING

This list is not exhaustive: it is meant to be a general guide to the reader interested in more detailed information.

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Falconer, D. S. (1960), *Introduction to Quantitative Genetics*, Oliver & Boyd. Pp. 365

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Moroney, M. J. (1953), *Facts and Figures*, 2nd edition, Pelican. Pp. 472

GLOSSARY

THIS is a list of terms commonly used in genetics. For a more complete list, reference should be made to a dictionary of biology (such as *The Penguin Dictionary of Biology* edited by Abercrombie, M., Hickman, C. J. & Johnson, M.L.) or to R. L. Knight's *Dictionary of Genetics* (published by the Chronica Botanica Company of Waltham, Mass., U.S.A.).

ACENTRIC: Fragment of a chromosome which lacks a centromere.

ALLELOMORPH (or ALLELE): One of a pair, or series, of genes situated at the same locus on homologous chromosomes and producing different effects on the same character.

AUTOSOME: Any chromosome which is not a sex chromosome (*q.v.*)

BACK-CROSS: A cross between a hybrid and one of its parents, or (commonly) between an individual heterozygous at a particular locus, and one homozygous for the recessive allelomorph at that locus.

BIVALENT: Two homologous chromosomes paired during meiosis.

CENTROMERE: A non-staining localized region by which each chromosome is attached to the spindle at the metaphase of cell division.

CHIASMA: A visible point of interchange between chromatids of homologous chromosomes during the prophase of meiosis; an outward sign that genetical recombination has taken place.

CHROMATID: One of the two strands which result from the duplication of a chromosome during the prophase of nuclear division.

CHROMOSOME: A thread-like body in the nucleus of cells which can be seen (with appropriate techniques) at cell division. Chromosomes carry the genes.

CISTRON: A section of a chromosome containing a number of sites (probably nucleotide pairs), mutation at any one of which affects the same character; the unit of "gene" function.

CODEON: A sequence of three bases along a DNA chain which "spell" or represent the "code" of a single amino acid.

CROSSING-OVER: Failure of linkage (*q.v.*) between genes due to the exchange of parts between homologous chromosomes during the prophase of meiosis.

DEFICIENCY (or DELETION): The loss of part of a chromosome.

DIPLOID: Having a chromosome number twice the haploid number (*q.v.*) so that the chromosomes are in pairs, the members of which are homologous.

DNA (*Desoxyribonucleic acid*): The nucleic acid found mainly in the chromosomes, constituting the primary substance of the gene.

DOMINANT: A gene which produces the same effect when it is present in single dose (heterozygous, *q.v.*) as it does when present in double dose (homozygous, *q.v.*). The allelomorph which does not manifest in the heterozygote is said to be *recessive* to the other allelomorph.

EPISTASIS: Interaction between two non-allelomorphic genes such that one gene (the *epistatic* one) suppresses the expression of the other (*hypostatic*) one.

EUCHROMATIC: Those parts of the chromosomes which usually stain less deeply than the heterochromatic regions (*q.v.*) and which contain most of the genes.

EXPRESSIVITY: The degree to which the effect of a gene is *expressed* in the phenotype.

F_1 (*First filial generation*): The offspring resulting from crossing members of the parental (P) generation.

F_2 (*Second filial generation*): The offspring resulting from

crossing the members of the F_1 generation amongst themselves (*inter-crossing*).

GAMETE: Reproductive cell whose nucleus fuses with that of another gamete to form a zygote (*q.v.*). The process of gamete formation (*gametogenesis*) normally involves meiosis.

GENE: The unit of inheritance, which occupies a fixed chromosomal locus and is transmitted in the gametes. It is recognized by its effect on the transmission or development of an inherited character.

GENOTYPE: The genetic constitution (the particular set of allelomorphs present in each cell of an organism), in contrast with the characteristics manifested by the organism (its phenotype).

HAPLOID: Having a single set of unpaired chromosomes in the nucleus. Characteristic of gametes, most fungi, etc.

HEMIZYGOUS: Of a gene which is present in the unpaired state, as in a haploid organism or on an unpaired sex chromosome, such as the *X*-chromosome of a man.

HERITABILITY: The ratio of the hereditary (genotypic) variance of a character to the total observed (phenotypic) variance, or (loosely) the extent to which a given trait is determined by inheritance.

HETEROCHROMATIC: Those parts of the chromosomes which can be stained deeply and apparently contain few or no genes (*cf.* euchromatic).

HETEROZYGOUS: Having two different allelomorphs (*q.v.*) at the two corresponding loci in a pair of homologous chromosomes (*cf.* homozygous).

HOMOLOGOUS CHROMOSOMES: Chromosomes which pair at meiotic prophase. They carry allelomorphs of the same genes. With a few exceptions (e.g. sex chromosomes in the hemizygous sex), all the chromosomes of an individual can be arranged in homologous pairs, one member of each being derived from each parent.

HOMOZYGOUS: Having identical allelomorphs (*q.v.*) at the

two corresponding loci of a pair of homologous chromosomes (*cf.* heterozygous).

HYBRID: The progeny of any pair of genetically different parents.

INVERSION: Reversal of a part of a chromosome resulting from two breaks in the same chromosome and rotation of the segment between them through 180° so that the genes within that part lie in inverse order. May be *paracentric* (where both breaks are on the same side of the centromere) or *pericentric* (where the two breaks are on opposite sides of the centromere).

LINKAGE: The occurrence together of two or more genes on the same chromosome so that they are transmitted together from generation to generation, unless they are separated by crossing-over (*q.v.*).

LOCUS: A particular position on a particular chromosome which always carries one of a particular series of allelomorphic genes. Homologous chromosomes contain virtually identical sets of loci.

MEIOSIS: Two successive cell divisions involving the reduction of the number of chromosomes from the diploid ($2n$) to the haploid (n) number. Meiosis occurs at some time during the life cycle of all sexually reproducing organisms, usually during gamete formation.

MENDEL'S LAWS: First law of segregation, second law of independent assortment (see Chapter 2).

MITOSIS: The usual process by which cell nuclei divide into two with the formation of daughter nuclei having an identical chromosomal complement to that of the original nucleus.

MUTAGEN: Any agent, chemical or physical, which may cause a mutation.

MUTATION: An inherited and relatively permanent change in a gene or chromosome set.

MUTON: The smallest element which can mutate. Probably is a single nucleotide pair.

NON-DISJUNCTION: The failure of the members of a

chromosome pair to separate at meiosis (rarely at mitosis) resulting in both members being included in the same daughter nucleus.

PENETRANCE: The proportion of individuals in which a gene produces any effect at all (*cf.* expressivity).

PHENOCOPY: An environmentally induced modification of an organism resembling a phenotype produced by a genetical mutation.

PHENOTYPE: The appearance of an organism as contrasted with the genes possessed by it (genotype, *q.v.*). Organisms may have the same genotype but different phenotypes (owing to environmentally produced variation), or the same phenotype but different genotypes (e.g. the homozygous and heterozygous states of a dominant gene).

POLYMORPHISM: "The occurrence together in the same habitat of two or more forms of a species in such proportions that the rarest of them cannot be maintained by recurrent mutation".

POLYPLOID: An organism whose nuclei contain three or more times the haploid number of chromosomes (thus *triploid*, *tetraploid*, etc.). Distinguish from a *polysomic* in which particular chromosomes are present three or more times (thus *trisomic*, etc.).

POSITION EFFECT: The influence on the characters affected by a particular gene by a change in its position in the chromosomes relative to other genes (e.g. by translocation).

RECESSIVE: A gene which has no effect on the phenotype of an individual unless homozygous (converse of dominant, *q.v.*).

RECOMBINATION: The re-arrangement of linked genes due to crossing-over between homologous chromosomes usually during meiosis (the mechanism of recombination in bacteria and viruses seems to be due to copy-choice during DNA replication).

RNA (*Ribonucleic acid*): The nucleic acid formed mainly

in the cytoplasm; responsible for translating the "code" of DNA into action.

SEGREGATION: The separation into different gametes, and thence into different offspring, of the two members of any pair of allelomorphs possessed by an individual.

SEX CHROMOSOME: Chromosomes concerned with the determination of sex, so that there is a homologous pair in the nuclei of one sex, but a dissimilar pair (or only one sex chromosome) in the nuclei of the other. They are usually designated as *X* or *Y*.

SPECIES: A group of actually or potentially inter-breeding individuals, which is reproductively isolated from other groups. It represents the basic unit of classification commonly used.

TRANSLOCATION: Transfer of a part of a chromosome into (usually) a non-homologous chromosome.

ZYGOTE: The fertilized ovum, before it undergoes any further differentiation.

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London EC4