The science of heredity / [John Stanley Durrant Bacon].

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THE SCIENCE OF HEREDITY

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Dr. Bacon was born in 1917, and was educated at secondary schools in Sherborne and Croydon, and at Trinity Hall, Cambridge, where he became interested in the chemical approach to biological problems. His research has included work on nutrition, on tuberculin, and particularly on the structure and metabolism of carbohydrates. He is at present Lecturer in Biochemistry at Sheffield University. His publications include *The Chemistry of Life*, also published in the Thinker's Library.

THE SCIENCE OF HEREDITY

BY

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PREFACE

In writing about a subject in which I have had no specialized training or research experience I have received much help from a number of monographs and text-books, in particular from Sturtevant and Beadle's *Introduction to Genetics*, in which will be found references to many other publications on the subject. I have also received, and, I hope, profited by, the criticism of friends working in the field of genetics; in this way the book has been purged of at least some errors of fact, although the manner of exposition and the opinions expressed remain my own responsibility.

The greater part of the manuscript was written and revised before public interest in T. D. Lysenko's theories was renewed in the summer of 1948, but some slight alterations have been made following the appearance of an account in English of the discussion in Moscow that provoked it, and a short section summarizing his views has been inserted in Chapter XI. It does not seem possible at this stage to assess the extent to which the description of the process of heredity given here will have to be modified in the future as a result of Lysenko's criticism of the " orthodox " view.

I am very grateful to Mr. J. L. Fyfe for his constructive comments, particularly on the section dealing with

plant-breeding; to my wife for her help and encouragement; and to the publishers, for their patience and friendly co-operation.

J. S. D. B.

Sheffield, 1949.

INTRODUCTION

THAT the offspring of rabbits were rabbits, of monkeys, monkeys, of men, men, and so on, was taken for granted until comparatively recent times. It is true that where their powers of observation failed, our ancestors indulged their imagination, and saw geese as the offspring of barnacles, or permitted the union of the most diverse species in their mythology.

Charles Darwin and his forerunners directed attention to the variability of species and postulated an evolutionary scheme in which, to the general horror, the offspring of worms were insects, of reptiles, birds, and of monkeys, men. More exactly, they pictured each species as a transitional stage in the formation of one or more new species; one frame in a cinematograph film of biological history, The offspring of rabbits, they said, are rabbits, but not quite the same rabbits, and in the course of evolution this discrepancy may accumulate, so that the rabbits of today differ considerably from the rabbits of a hundred thousand years ago.

This seemed all the more probable, since in much less than a tenth of that time man had produced breeds of domestic animals which contrasted strikingly with the wild species originally brought into domestication.

Man's experience as a breeder of domestic animals had given him the impression that the link between generation and generation was not so rigid that each

offspring was an exact copy of its parents, nor was it so flexible that it could be manipulated at will. Parents and offspring were linked by something having both qualities, so that although animals could be bred for desirable qualities, much time and effort was required for the achievement.

The link between generations is what we call " heredity." Since Darwin's day we have begun to study it scientifically, and the name of " genetics " has been given to the branch of science concerned. It is the aim of this book to set out as simply as possible the first achievements of genetics, so that the general reader can grasp both its difficulties and its great significance for an understanding of our species, and of our place in nature.

The story begins nearly a hundred years ago, but for reasons which will be explained later the bulk of the scientific research was done in the second half of this period. In the first fifty years, however, one great obstacle was surmounted. This was the problem of the relation of the two parents to their offspring. The connection between mother and child is, of course, a very obvious physical one, and the maternity of a child is rarely in doubt. To primitive men, particularly those who did not lead a pastoral life, the relation between the sexual act and childbirth was probably not so obvious, and fatherhood consequently of little significance. Later, the reverse idea was held: that the female provided nothing but nourishment for a seed that came from the father, and motherhood was at a discount. The proof that each sex makes a contribution to the offspring, and that the latter begins its existence as a minute but nevertheless unique speck

of living matter, was not obtained until the last decades of the nineteenth century. What was considered probable from general observation became established as one of the fundamental facts of the new science.

Another discovery of the same period, the invention of photography, has helped a large proportion of our countrymen to confirm what had previously been shown only to those of great wealth—that in the members of three generations there can be seen a persistent " family likeness," sometimes strong, sometimes feeble, but never entirely absent. By choosing contemporary photographs of each generation the confusing effect of time can be eliminated, and in each family album we can discern the " Robinson ears," the " Smith nose," just as in the past the examination of paintings revealed the history of the " Hapsburg lip." There can be no doubt that facial characteristics, at least, can be handed down from father to son, from mother to daughter, and (more significantly) from father to daughter and from mother to son. Whether *other* characteristics are inherited is a matter of some dispute; whether " Willie gets his brains from his father " or " Susan gets her temper from her grandmother " is rather more difficult to prove, particularly when the protagonists of opposing views have a personal interest in the answer.

" Little Johnny is *so* like his father, but at times you can see a lot of his mother in him." How often have we heard this? The child cannot resemble one parent without differing in some way from the other; he is usually a mixture of the two. This is understandable if both parents contribute to his origin, but a fact that is not easy to explain is that he and his brothers are

not all alike. It is unquestionable that brothers may differ considerably and yet retain the family likeness. The origin of the variability of our species as a whole evidently lies as much *within the family* as outside it.

Forty years of research into the nature of vitamins, and into many other aspects of human nutrition, have shown us how profoundly inadequate diets, just as surely as severe illness, can alter the human frame. The training of athletes, the development of skill in the techniques of modern industry, reveal the capacity of the body to adapt itself to new demands. Can we explain the differences between members of a family entirely by the action of such influences as these? Does, in fact, each married couple produce boys of one hereditary type and girls of another, which are then changed by the accidents of upbringing and the changes of family fortune into the diverse groups that we see in the family reunion photograph? Most parents would not hesitate to answer an emphatic "No," and they would be right, as later chapters will reveal. Heredity, while preserving the general conformity of the human species, produces a great diversity of detail within these limits.

This, and many more of the features of heredity which are discussed later, were discovered in the first place by experiments with species far removed from our own: with sweet-peas, with maize, with grasshoppers, with fowls, with mice, and so on. Even the most insignificant forms of life, like yeasts and fungi, have yielded information which (with that from other organisms) has been pieced together to form a design of heredity common, perhaps, to all living things.

The evidence obtained in many fields of biological

science has been assembled with all the care of a detective reconstructing the course of a crime. Significant observations have had to be sorted from irrelevant ones and then subjected to the closest scrutiny. Each clue has had to be related to the others, finger-prints have been checked and suspicious stains analysed, all the resources of the modern laboratory brought into play, from calculating machines to X-rays. The reader has in his hand not tales of travel, nor a volume of reminiscences, but a detective story. If at the end the criminal is not denounced and justice triumphant, this is because fifty years of scientific research, however brilliant and resourceful, is but a fraction of that which will be needed to give a satisfactory answer to any one of the many problems nature has set for us. Heredity, by which man is linked to the past and to the future, is by no means the least of these.

CHAPTER I

DARWIN AND MENDEL—THE FIRST STEP

IT is now accepted, for reasons which will be given later, that both parents contribute to the inherited characteristics of their offspring. Taking this for granted and leaving aside the difficulties introduced by sexual differences, the simplest assumption about the nature of heredity would be that the offspring represents an average of the two parents. Thus if the father had black hair and the mother blonde, we might suppose that all their children would have brown hair; or if the father was tall and the mother short (for a woman) that the children would all be of medium height.

The chief objection to such a theory of inheritance is that if it were true one would expect that populations would tend to become less diverse as time passed. The tallest individual would necessarily have to marry someone of shorter stature, and so on, so that after a few centuries we would expect to find everyone looking approximately the same. Since we have no reason to believe that this has happened, it becomes necessary to examine the processes which are working in the other direction—that is to say, which encourage *variation* in the population.

When Darwin was writing his *Origin of Species* (nearly a hundred years ago), he began with the knowledge that the members of natural populations varied considerably, and assumed that the environ-

ment among other factors played a big part in producing this effect. Following Lamarck, he thought it most likely that all the individual variations that could be seen in one generation were capable of being transmitted to the next. Among such variations were those due to use or disuse—for example, if an individual developed bigger muscles than his fellows, or (the familiar example) a longer neck by reaching up for food, these advantages would be inherited by his descendants. This was called the "inheritance of acquired characters," and it played an important, though not essential, part in the theory of the origin of new species put forward by Darwin.

That it did so was partly due to uncertainty about the mechanism of heredity which existed at that time. If we assumed the process to be one of averaging, or "blending," as we have just suggested, then these advantageous characteristics would tend to be lost again in the levelling action of inheritance, and to ensure progress in a particular direction a constant repetition of the variation (muscle development or neck stretching) was called for. Thus, in the struggle for survival the same adaptation had to be elicited in generation after generation in order that the whole or a section of the species should change from the old type towards a new one.

By what Darwin called "artificial selection" of particular variable characteristics, cultivated plants and domestic animals had been made to diverge from the original wild type very considerably, and many distinct varieties or breeds had been produced within each species. As examples of these he cited cattle, apples, and in particular pigeons, with which he had

conducted experiments on cross-breeding. Very striking results had been achieved by man's efforts within a biologically short period of time, and, as we now know, this process of artificial improvement of plants and animals was to continue unchecked in the next century and to be a powerful stimulus to the scientific study of heredity.

The experiments which were to form the basis of the new science were performed by a monk, Gregor Mendel, of Brno, in the years immediately following the publication of *The Origin of Species*, but, for reasons discussed later, their full importance was not understood, even by their author, and they were virtually disregarded until the end of the century.

In order to investigate such a complex phenomenon it was necessary to choose as simple a manifestation of it as possible. This Mendel achieved by choosing a cultivated plant (the garden pea), by studying one particular part of it at a time (for example, the seed), and by choosing contrasting characteristics of this part. The first advantage of choosing this plant was that each plant, and indeed each flower, is both male and female, so that there was none of the difficulty we have already met in man of comparing the offspring with its parent of the opposite sex. Secondly, the plant is habitually self-fertilized, so that if he planted a single pea-seed he got a plant capable of producing the next generation unaided. By taking the *colour* of the seed as the characteristic to be studied he chose one which belongs to the embryo in the seed, and therefore to the generation *after* the plant bearing it. This meant that he could compare one generation with the next by a single sowing and harvesting.

He took two strains of pea, one producing consistently nothing but yellow seeds, the other nothing but green, and tried the effect of crossing them. To do this it was necessary to prevent the normal self-pollination and to transfer the pollen from one type of plant to the stigma of the other artificially, a tedious but feasible operation.

He discovered that the seeds produced in this way were all yellow, irrespective of the direction of the cross—i.e., whether the cross was made with " yellow " pollen on " green " stigmas or vice versa. This was unexpected on the theory of " blending " inheritance, from which we might have expected an intermediate colour.

By planting these yellow seeds from either crossing and allowing them to grow to maturity in the normal way, he harvested seeds which were the result of self-fertilization. The yellow seeds of his original strain, it will be remembered, produced nothing but yellow seeds when planted in this way.

However, of 8,023 seeds harvested from 258 plants the results of crossing (once again the direction in which the cross was made did not matter), only 6,022 were yellow, the remaining 2,001 being green. This result is entirely inexplicable on the theory of " blending," because both of the original strains had apparently been recovered.

To test this, some of *these* seeds were grown and the results harvested. The green seeds produced nothing but green seeds—that is to say, they were like the green seeds used in the first place. The 6,022 yellow seeds proved to be of two kinds: those which, like the green seeds, produced nothing but seeds of their own

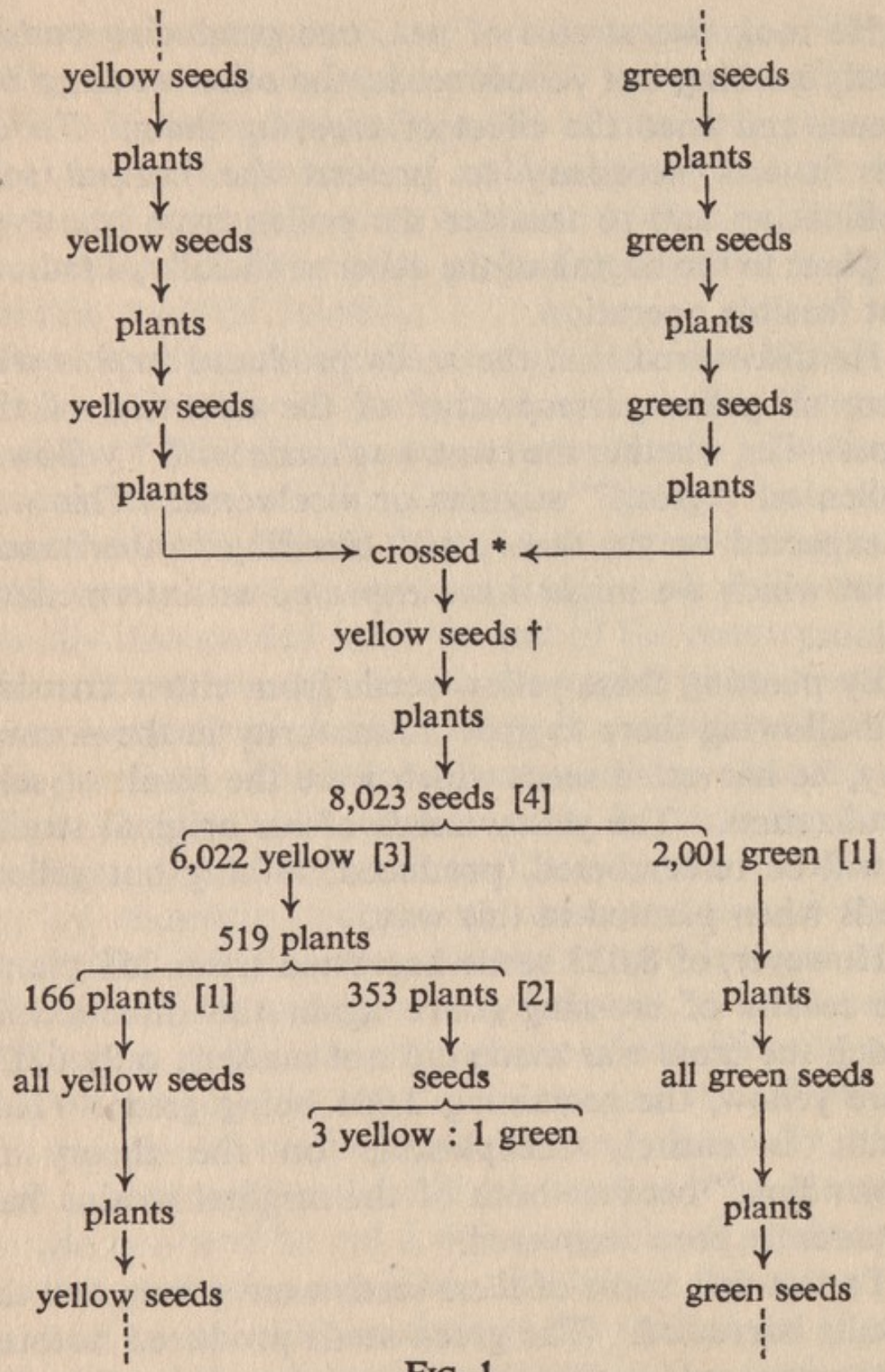


FIG. 1

Numbers in brackets show how of every 4 seeds from the *plants* obtained from the cross (*), 1 bred true for green seeds, 1 bred true for yellow, and 2 resembled the yellow seeds (†) at the cross, giving 3 yellow seeds to 1 green.

colour and resembled the yellow strain used in the original cross, and those which produced a mixture of yellow and green seeds once more.

It thus appeared that *three* kinds of seeds now existed: green ones which yielded nothing but green, yellow ones producing nothing but yellow, and yellow ones which behaved like those resulting from the crossing of yellow and green.

Numerically, also, the results were of great interest. The ratio of yellow to green seeds in the plants from the result of the cross was 6,022 : 2,001, almost exactly 3 : 1. From 519 of these yellow seeds 353 plants were obtained which gave yellow and green seeds in 3 : 1 ratio, and 166 giving nothing but yellow seeds. Roughly speaking, this means a ratio of 2 : 1 of false to true breeding among the yellows. Thus all the seeds from the original crossing of yellow and green were yellow, but out of each four of the seeds harvested from *them* one was green and bred true, another was yellow and bred true, and the remaining two behaved like the seeds from the original cross.

That the 3 : 1 ratio was not an accident was shown by an experiment with plants bearing round or wrinkled seeds; when crossed these gave nothing but round seeds, whose offspring numbered 5,474 round and 1,850 wrinkled. Here "round" behaved like "yellow" in the first experiment.

Again, with a characteristic of the plant, a tall variety crossed with a dwarf one gave plants which were all tall but whose offspring were 787 tall to 277 dwarf.

Mendel had accumulated evidence which could not be fitted in with any existing theories of inheritance,

and to explain it he postulated that the characteristics (henceforward in this book in accordance with the usual scientific practice called the "characters") of peas *were inherited as though they could not be mixed with one another by crossing, and could be recovered in later generations unchanged. Secondly, he suggested that certain characters were so related to others that when both were present in a plant only one was manifested* —e.g., the character "yellow" in the seeds took precedence over the character "green." *The former he called a "dominant" character, and the latter a "recessive" one—that is, one which remained latent in the first result of the cross but returned later.*

These ideas could not be applied to inheritance in general without a considerable amount of work on other plants and on animals, but unfortunately the plants which Mendel chose, with some deliberation, for his next experiments were the hawkweeds. His results lent no support to his earlier conclusions and must have diminished their importance for him.

He died in 1884, eighteen years after the publication of his work on peas; but it was not until the close of the century that three other European scientists, making experimental crosses with other plants, came independently to the same conclusions and announced separately (in 1900) their rediscovery and confirmation of Mendel's work.

We now know that in selecting the hawkweeds he had chosen plants in which the ordinary sexual mechanism rarely operates and in which we could not expect to find the combination and separation of characters which is typical of all sexual reproduction. That Mendel should have made this unfortunate choice,

which cost him the recognition during his lifetime of his great contribution to the science of heredity, was a consequence of the diversionary effect of Darwin's theory (which by its denial of the unchangeability of species temporarily reduced the interest in those characters which served to distinguish them) and of the relative backwardness of certain other branches of biology at that time. Between 1866 and 1900 there were great developmnets in our knowledge of the minute structure of living organisms, which provided the physical basis for an interpretation of Mendel's findings.

It is therefore necessary, at this stage, to describe these developments in some detail, because the whole history of the science since 1900 has depended on the interaction of knowledge gained in the two fields: of cell structure, and of inheritance.

CHAPTER II

THE CELL IN INHERITANCE

THE naked eye was the chief means by which man first studied living creatures, and remains so to this day. The ordinary man's study of life is essentially observational rather than experimental, and it is rarely that he has any aids to his naked senses beyond a magnifying glass.

The development of the microscope made two things possible: the discovery of living forms too small to be seen by the unaided eye, and the examination of the detailed structure of larger forms. From these two fields has emerged a theory—the *cell* theory—which has transformed biology, and unified it.

The microscope has made it possible to discover, and classify by their shape and structure, several groups of tiny organisms, the so-called micro-organisms, including the yeasts, bacteria, and certain plants and animals. A study of the larger organisms showed that they were not like enlargements of the smaller ones, but more like three-dimensional mosaics made from large numbers of them. In plants the boundaries of the units making up the mosaics are marked by a woody material, so making little boxes, and to these enclosed spaces the name of " cells " was originally given. The word " cell " is now used to describe the unit itself—that is to say, the box plus its contents.

The theory that the cell, rather than the individual, was the basic unit of life gained support when it was

discovered that each large " multi-cellular " organism develops from a single cell. The change from this single cell to a full-sized adult takes many forms, varying from a simple multiplication of the cells to give a hollow sphere, to elaborate foldings and dimplings, formation of tubes, and so on, in the more complex forms. To some extent the complexity of the process is related to the place which the particular organism is assigned in the evolutionary series, creatures like sea-anemones having rather simple development, birds a very elaborate one.

The theory of evolution supposes that the earliest forms of life developed into organisms more or less like the micro-organisms we know today, and that these " single-celled," or unicellular, organisms gave rise to simple multicellular ones. The remaining part of the evolutionary process consists of the development of more complex and successful multicellular organisms. However, just as the young forms of our present land-living animals show signs of the aquatic lives which their distant fishy ancestors led, so the multicellular organisms in reproducing their kind commonly return to a unicellular stage, represented by the spore, the egg-cell, the sperm, or the pollen grain.

It is for this reason that the study of cell structure throws so much light on the processes of heredity; because the production of offspring nearly always involves the return of the organism to a single-celled stage. All the direct physical contribution a parent makes to its offspring is boiled down to this tiny particle, within which, therefore, lies the whole secret of heredity.

The typical cell is extremely small, say one-hundredth of the size of a capital " O " on this page, although in certain cases one may be several feet long (e.g., a nerve cell), or in others a whole multicellular organism (e.g., some beetles) may be smaller than a full-stop! The early microscopists found it easy to see the cell *walls* in plants, or the outline of some minute infusorian or diatom from pond water, but knowledge of the internal structure has come more slowly.

This is because the cell contents are semi-transparent and, in most cases, almost colourless, so that light shining through the cell shows little more than lack of uniformity within it. Besides this, unless special precautions are taken the cell-contents disintegrate after a time through spontaneous chemical change. These difficulties are partly got round by using dyes to stain the structures within the cell, and since very often these dyes themselves kill the cells, the cell is first subjected to some treatment harsh enough to kill it, but not, it is hoped, to alter the contents too much. The killing, or " fixing " as it is optimistically called, can be done with heat, or acid, or alcohol, the exact treatment depending on the cells being used and the particular structure which is being studied.

A further difficulty with multicellular organisms is that the microscope can be used to look only at thin slices which can be illuminated strongly by a light placed behind them. (The staining with dyes is also more satisfactory with these thin slices, too.) While plant cells have tough walls, most animal cells have almost invisible walls, easily broken, and it is important to find ways of cutting the material without mangling it. Blocks of *tissue* (the name given to the

agglomerations of cells in multicellular organisms) are sometimes frozen before being cut with a very sharp knife, or alternatively are strengthened by impregnation with wax, which is later dissolved out of the wafer-thin slices. So in dealing with some material it is convenient to " fix " it in blocks before slicing it, while in other cases frozen slices can be fixed after cutting, the freezing itself " fixing " the tissue temporarily.

The job of dyeing the cells, or " staining " them as it is called, has become very specialized, but it depends upon carrying out one or other of three main processes: the first uses a dye which is taken up only by certain cell structures, so that when the cells are afterwards washed these remain coloured; in the second the whole cell is stained and then a special solution is used to remove the stain from some structures but not from others; in the third a substance, which may be colourless, is used (as in the textile industry) as a *mordant* for a particular part of the cell, so that this, which ordinarily would not stain, can now take up the dye.

After this staining process the fixed material, which has become rather opaque, is put into a suitable clear substance, which makes it more or less transparent again and also helps to preserve it. In this way the stained " preparation " can be kept for years without deterioration, mounted on a piece of glass and ready at a moment's notice for examination.

It is, of course, possible to study *living* cells by means of the microscope if special precautions are taken to protect them from the strong illumination normally used. The comparison of living and " fixed " and

" stained " cells should enable one to decide whether the structures seen in the latter do, in fact, correspond with parts of the living cell, or whether they are produced by the action of substances used in the fixing and staining. The most obvious examples of structures " created " by the fixing and staining processes are called *artefacts*, but most of what is seen in the stained preparation differs more or less from what is seen in the living cell.

To a limited extent it is possible to stain parts of the cell while it is still alive and functioning, but the parts with which we are most concerned are very sensitive to any such attempts, and for this reason the picture given by stained preparations has to be checked by studies of unstained living cells made with special techniques. In recent years a particularly successful method, called *phase-contrast* microscopy, has been introduced, by which the relative opacity of the structures in the living cell can be increased. The results so far obtained by this technique confirm the description which follows, which was largely built up through examination of stained preparations. Despite the difficulties thus presented, it is reasonable to assume that the description below approximates to a description of events in living cells.

In all cells there are found one or more bodies distinguishable from the rest of the cell contents by colour, by greater opacity, or by a different index of refraction—that is to say, behaving rather like a lens within the cell. They include the *chloroplasts* in plants, which carry the green pigment *chlorophyll* (responsible both for the colour of green plants and for their ability to transform gaseous carbon dioxide into

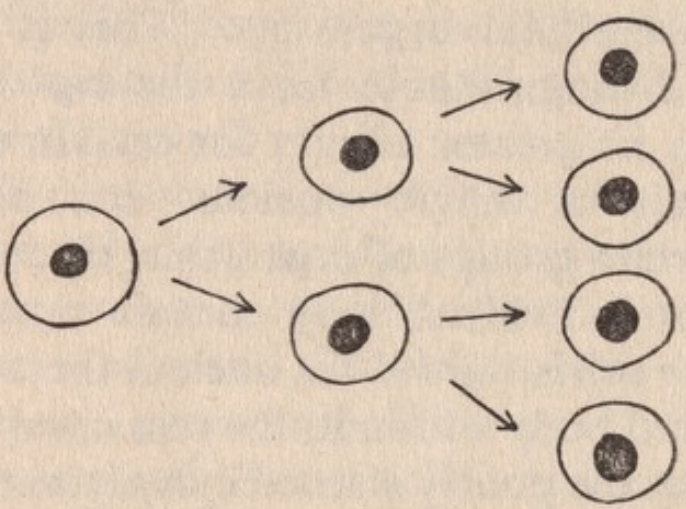
complex compounds of carbon), and also certain classes of foodstuffs, like starch or fats, stored within the cell.

There is, however, one type of body which is found in all cells, except possibly those of some unicellular organisms, particularly bacteria, and certain types of cell in multicellular organisms. This is the *nucleus*, and it is distinguishable from the rest of the cell contents by its greater affinity for certain dyes. Most cells contain a single nucleus, but for differing reasons certain groups of organisms, or certain cells of a particular individual, may contain more than one.

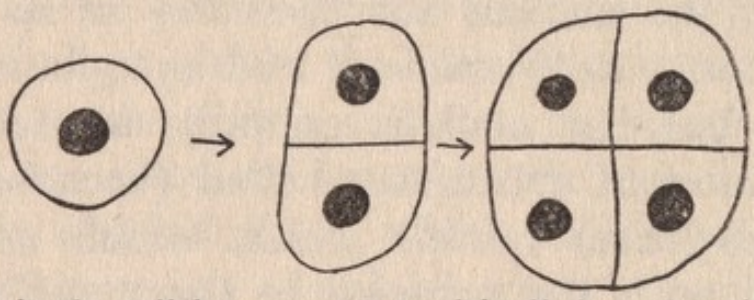
When the cell is stained the nucleus therefore appears as a coloured body within it, the remaining space being occupied by the poorly stained *cytoplasm* within which various additional structures may be found. The affinity of the nucleus for dyes lies in its chemical composition. Both nucleus and cytoplasm contain proteins, but the nucleus contains a much higher concentration of substances called (because of their occurrence here) *nucleic acids*, which are closely associated with the proteins to form *nucleoproteins*. Although the general chemical nature of these substances is known, we have as yet no detailed knowledge of them. It is the nucleic acid in the nucleus which combines with the dye, so that even when the nucleus ceases to be a compact body one can still trace the fate of the nucleoproteins.

The nucleus is of interest in the first place because of its behaviour when the cell divides. We have seen that cell division plays an important part in the formation of the multicellular organism. Cell division is usually accompanied by cell growth—that

is to say, the cell increases in size, divides, the resulting two cells, the *daughter* cells, continue to grow, each then divides, and so on. In some cases considerable growth may take place without any division of the nucleus—for example, with salivary glands of certain insect larvæ.



One unicellular organism becomes four.



A single cell becomes a multicellular organism.

FIG. 2

Cell division in unicellular and multicellular organisms.

In dividing, the cell produces two more or less equal daughter cells so that each of these contains approximately half of the bulk of the mother cell. However, this division of the cell contents is not entirely haphazard. In particular, a body called the centrosome, and the nucleus, go through an elaborate process which can best be interpreted as a careful sharing of the nuclear material. Characteristic changes take

place in the nucleus, the centrosome divides into two, and these take up positions on opposite sides of the nucleus, and the nuclear membrane, separating nuclear contents from cytoplasm, breaks down. At this stage, or a little earlier, a structure known as the " spindle "

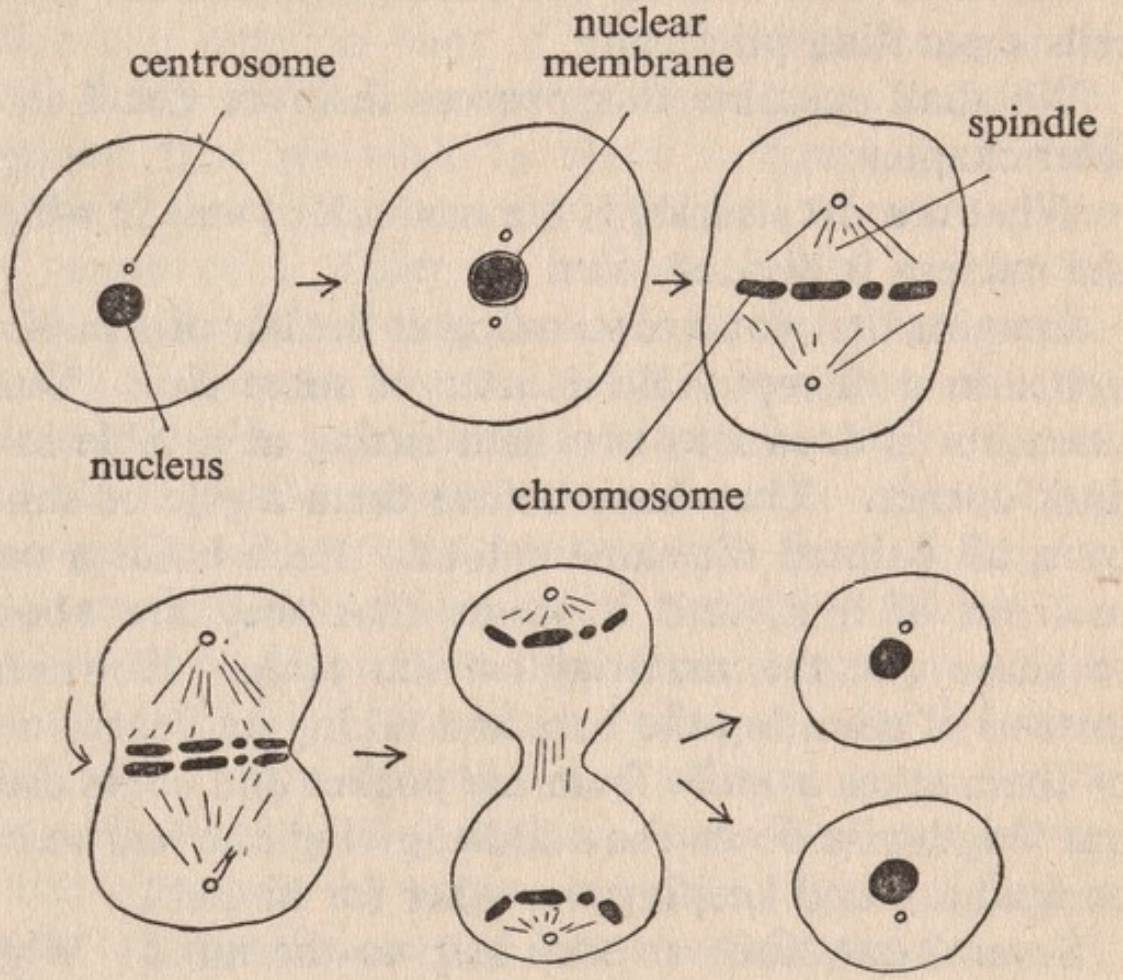


FIG. 3

The division of the cell nucleus; very much simplified and diagrammatic.

forms between the centrosomes, and after preliminary movements the strongly staining material from the nucleus arranges itself in the middle of the spindle in the form of thin, sausage-like bodies, which are called *chromosomes*. These are seen to be split lengthwise, and the halves after a time move to opposite ends of the spindle, where they re-form compact nuclei;

simultaneously the cytoplasm, which has become constricted about the middle of the spindle, separates by a completion of the constriction into two parts, and the cell has completed its division; alternatively, a new cell wall develops between the two separating groups of chromosomes and the cell becomes two without the cells separating physically.

We shall examine this process in more detail in a later chapter.

What is most striking is the meticulous way in which the nucleus is divided.

Imagine that you are standing at the bar of a public-house in a disreputable quarter of some city. Your attention is drawn to two men sitting at a table in a dark corner. They have before them a pile of short bars, all painted the same colour. Each holds a bag in front of him, and it seems that they are about to share out the material on the table. However, instead of counting the bars and taking half each, one of them takes a knife from his pocket and splits each bar lengthwise down the middle, giving one half to his companion and keeping the other for himself.

Several questions at once leap to the mind: What are they sharing? This we cannot see because of the paint which covers it and the dim light, but there is no doubt that this *is* a sharing, from its very nature. Why do they not count the bars and divide by two? Probably because each bar is different in composition from all the others, so that if one man receives a particular bar there is no equivalent to give the other. If this is the case, why is it not sufficient to cut each bar across the middle and share the two shorter bars which would result?

This last question is the most difficult of all. The answer might be that the bars split easily lengthwise but are very difficult to cut across. Another possibility is that the composition of each bar changes from end to end so that cutting it across the middle would give dissimilar halves.

We can imagine bars of material which could be more fairly divided by being cut across the middle. Suppose that we wish to share a dozen pieces of seaside " rock " between two children. Each bar has the name of a different holiday resort, so to be scrupulously fair we cannot, as in the previous instance, give six to one and six to the other. In this case we should cut each bar into two shorter bars, and each child would receive a complete set of half-bars bearing the twelve names. If we split the rock lengthwise one child would have half a bar with " BRIG " all the way through, and the other the corresponding half bar with "HTON" through it, and so on. On the other hand, if we were sharing a roll of wine-gums a slice down the length of it cutting each into two halves would obviously be more equitable than dividing it across the middle into two lots of whole gums.

These examples help to show how the manner of division of the nucleus can suggest the kind of structure of which it is composed. The chromosomes, because each divides separately, may all be different in some important properties, and because they all divide lengthwise may be made up of qualitatively different parts arranged in rows running lengthwise.

The nucleus is of interest in the second place because it is apparently the only part of the cell which is *always* found in the cells from which a new individual arises.

As we have already seen, the multicellular organisms pass through a unicellular stage (the *gamete*) when they reproduce by sexual means. For this purpose the reproductive organs produce numbers of cells of two kinds—small, active cells, which come from the male, called " spermatozoa " or pollen, and larger, comparatively quiescent, female cells, the " ova." For brevity's sake these are usually called, in the animal kingdom, " sperm " and " eggs " respectively.

In the sperm cell the cytoplasm is reduced to negligible proportions and the nucleus occupies most of the " head." Behind it lies a centrosome, " the middle piece," and behind this a long tail which can drive the cell head forward by wriggling movements. The whole of the physical contribution of the male to its offspring is contained in this tiny thing. The egg is better supplied with cytoplasm, in which there is usually a supply of foodstuffs for the *embryo* which develops after fertilization.

The production of a large multicellular organism from these two cells requires, of course, considerable cell division, and these new cells must be adapted to serve many functions. But egg nucleus and cytoplasm do not begin to divide, except in special circumstances which are discussed later, until a significant event has taken place. This is the union of the nuclei of the egg and the sperm, first seen under the microscope in 1875.

In the animal kingdom large numbers of sperm are usually produced for every egg, and by a variety of mechanisms they are eventually brought near it and travel the remaining distance under their own power. As soon as one sperm has touched the egg and pene-

trated it the rest are in some way excluded, so that each egg is fertilized by a single sperm. As the sperm enters the cytoplasm of the egg the two nuclei come together, and almost simultaneously the sperm

TABLE I

The Chromosome Numbers of Species in Various Groups of Organisms

Group.	Commonest haploid number.	Other haploid numbers in the group.
ANIMALS		
Leeches	8	9, 13, 14, 16
Dragonflies	13	9, 10–12, 14
Aphids	4, 6, 7, 10	3, 5, 8, 9, 11, 13, 15, 19
Flies (Diptera)	4, 6	3, 5, 7–9
Moths and butterflies	29, 30, 31	11, 13–15, 19, 21, 23–25, 27, 28, 30–34, 37, 38, 49, 51, 56, 87, 112
Lizards	19	12–18, 20
Marsupials	11	6–8, 10, 14
Other mammals	24	7, 14–28, 30, 31, 35, 39
PLANTS		
Chrysanthemums	18	36, 54, 72, 90
Peonies	10	20
Roses	14	28, 35, 42, 56
Tulips	24	36, 48, 60
Brassicae: Cabbages	18	—
Swedes	38	—
Turnips	20	—
Radishes	18	—
Potato family (*Solanum*)	24, 36, 48	60, 72
Apples, pears, etc.	34	51, 68
Blackberries, raspberries, etc.	14, 28	21, 42, 49, 56
Plums, cherries, etc.	16	24, 32, 487

These figures do not include all the known species or varieties, only those in which the chromosomes have been examined, a much smaller number. It will be noticed (cf. Chapter X) that whereas the plants show chromosome numbers which are mostly multiples of a basic number (e.g., 17 in apples), in animal species no such regularity occurs.

centrosome divides to initiate the first division of the fertilized cell, or *zygote*.

Similarly in plants a single nucleus of the egg-cell combines with a single "generative" nucleus from the pollen-cell. In almost all the forms of life in which gametes are produced their nuclei fuse at the formation of the zygote, the new nucleus thus containing nuclear material from both parents.

The third point of particular interest respecting the nucleus relates to the *number* of chromosomes. If these bodies were simply convenient ways of packaging the nuclear material, we should expect that their number would vary from nucleus to nucleus in the same organism and even more widely if we considered the cells of all the members of a species. In fact, each species is found to have a characteristic number of chromosomes, and the occasional deviations from this number are of a very regular kind (see Table I). Since chromosomes are never seen to fuse together, it is clear that the fusion of *nuclei* at fertilization would double the chromosome number, unless by some mechanism the number in each gamete had been halved. *This "reduction" of the chromosome number in the formation of gametes in the higher plants and animals was predicted by Weismann on these grounds of the constancy of chromosome numbers and was later confirmed by observation. The reduction division at which it takes place is of the utmost importance for the understanding of the mechanism of heredity, because it is an essential part of the formation of gametes.*

Seen in its broad outline, this division resembles the ordinary cell division described above. The usual spindle is formed, but instead of the chromosomes

arranging themselves separately in the middle of this they form pairs, and the two members of these move

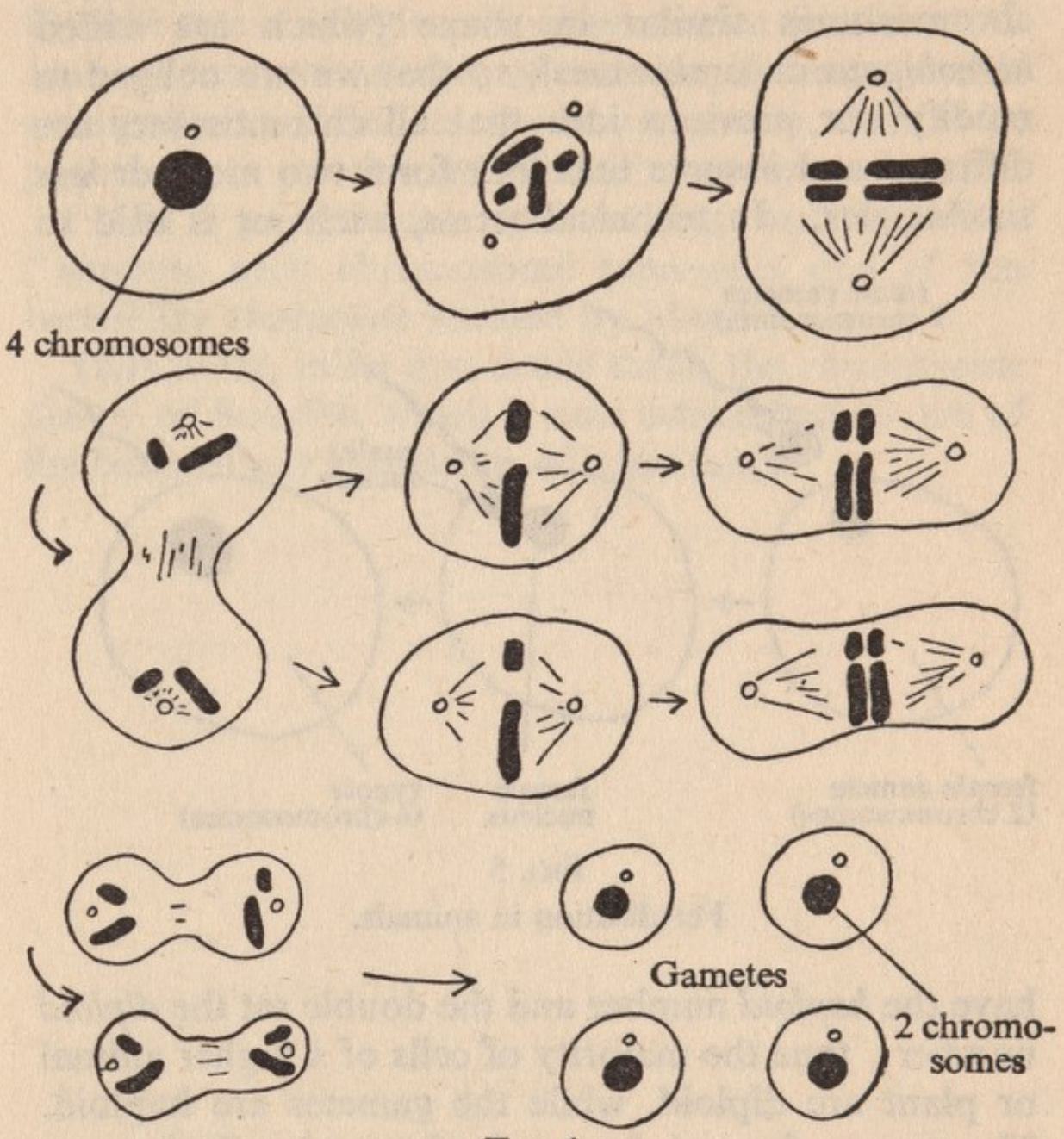


FIG. 4

The reduction division; very much simplified and diagrammatic. In the formation of female gametes three of the four nuclei are lost, with very little cytoplasm (cf. Fig. 9).

apart to opposite ends of the spindle, where a second (normal) division takes place almost at once. In this way four nuclei are produced, each of which contains half the usual number of chromosomes.

The pairing of whole chromosomes which takes place in this form of division can be seen to involve chromosomes similar in shape (which are called *homologous* chromosomes), so that we are obliged to modify our previous idea that all chromosomes are different and assume that they form two more or less similar sets. In technical terms, each set is said to

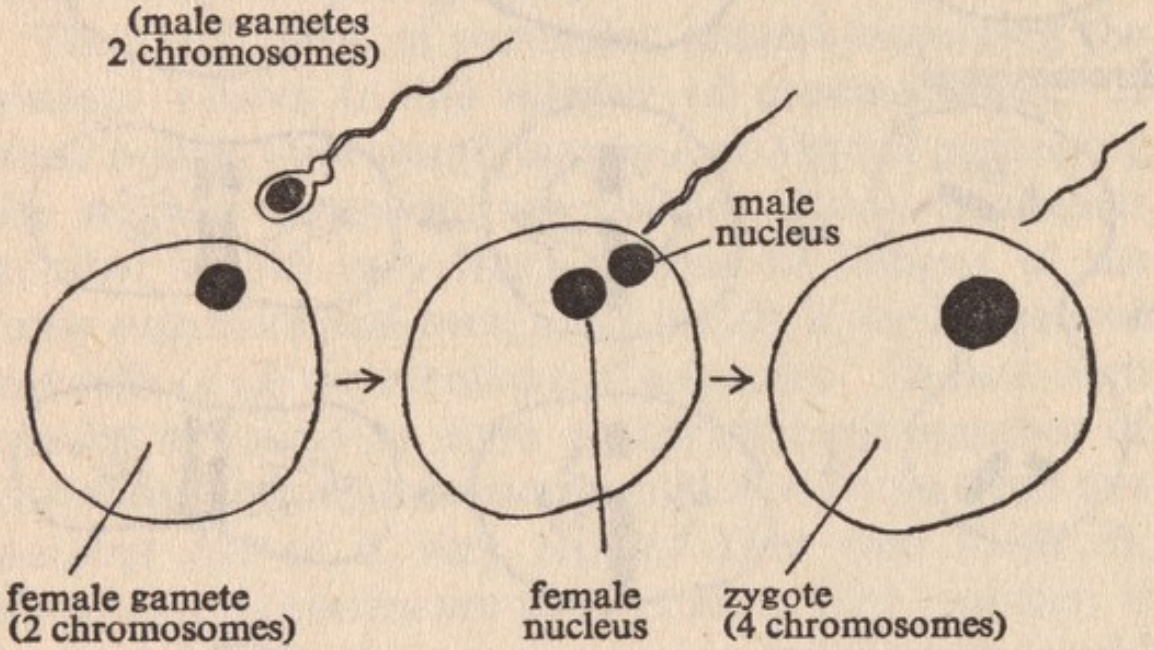


FIG. 5
Fertilization in animals.

have the *haploid* number and the double set the *diploid* number; thus the majority of cells of a higher animal or plant are diploid, while the gametes are haploid. The zygote formed from two haploid cells is once again diploid.

Each diploid cell therefore, because of the careful way in which each chromosome is divided, contains one haploid set of chromosomes from its male parent and another haploid set from its mother. These physical contributions from the nuclei of the two parents lie side by side in the nucleus of the offspring,

but do not fuse. If we follow a particular chromosome (from the male parent, say), it seems quite feasible that it will give rise at successive divisions to a tremendous total number of exact duplicates, and that eventually it will find its way into a gamete, there to be passed on to another generation virtually unchanged.

"Ah!" said those experimenting with heredity, "suppose each chromosome represents one of the hereditary characters studied by Mendel."

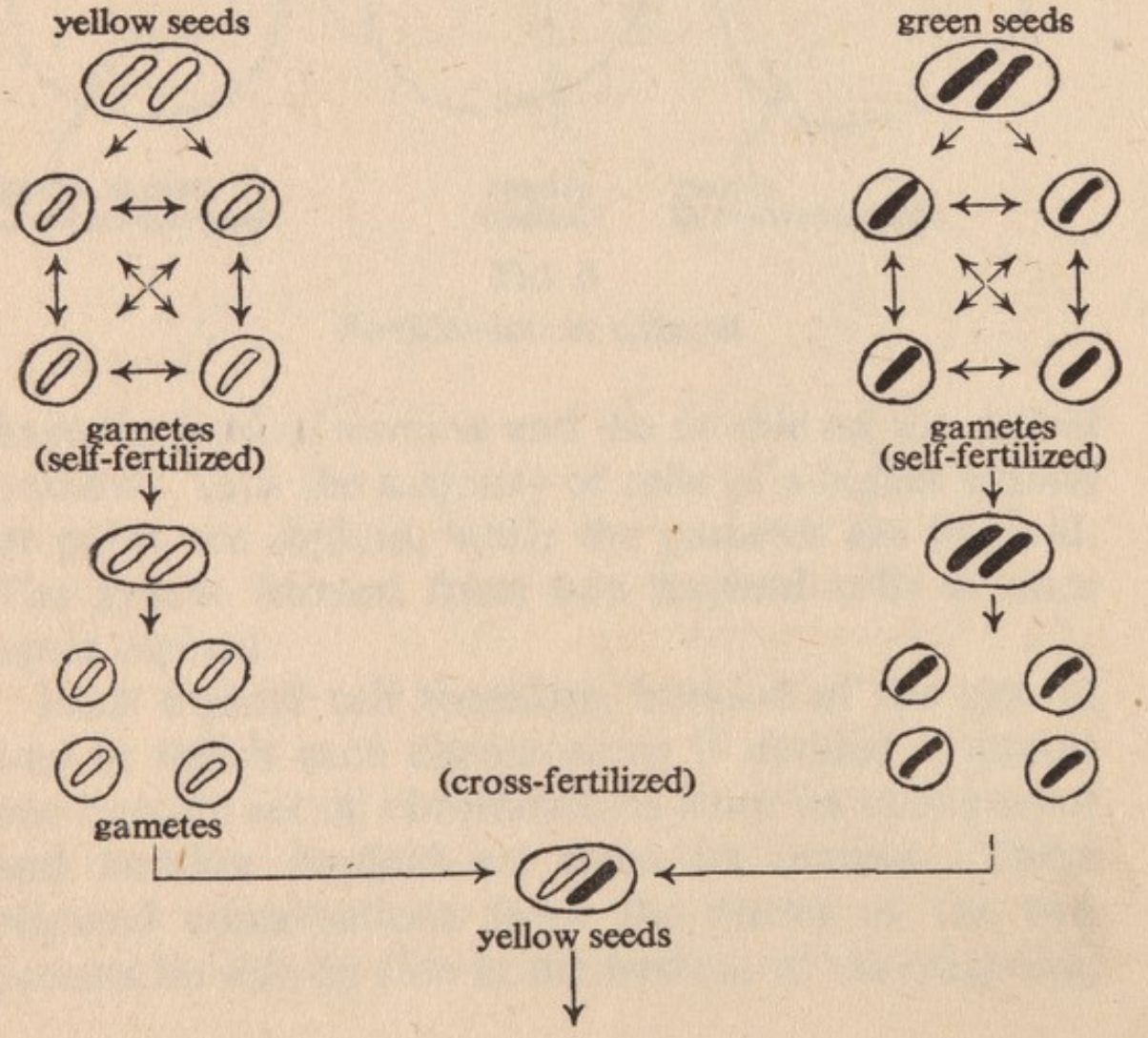
Thus arose, in its first crude form, the *chromosome theory of heredity*, which is now established as one of the bases of our knowledge of inheritance.

CHAPTER III

MENDEL'S LAWS

If we go back to Mendel's experiments with yellow- and green-seeded peas we can see how plausible an explanation was given by the chromosome theory.

Suppose that the colour yellow is due to the possession of a particular chromosome. The true-breeding yellow peas would carry in their cell nuclei a pair of such chromosomes. During the formation of gametes these would be separated, so that each gamete carried



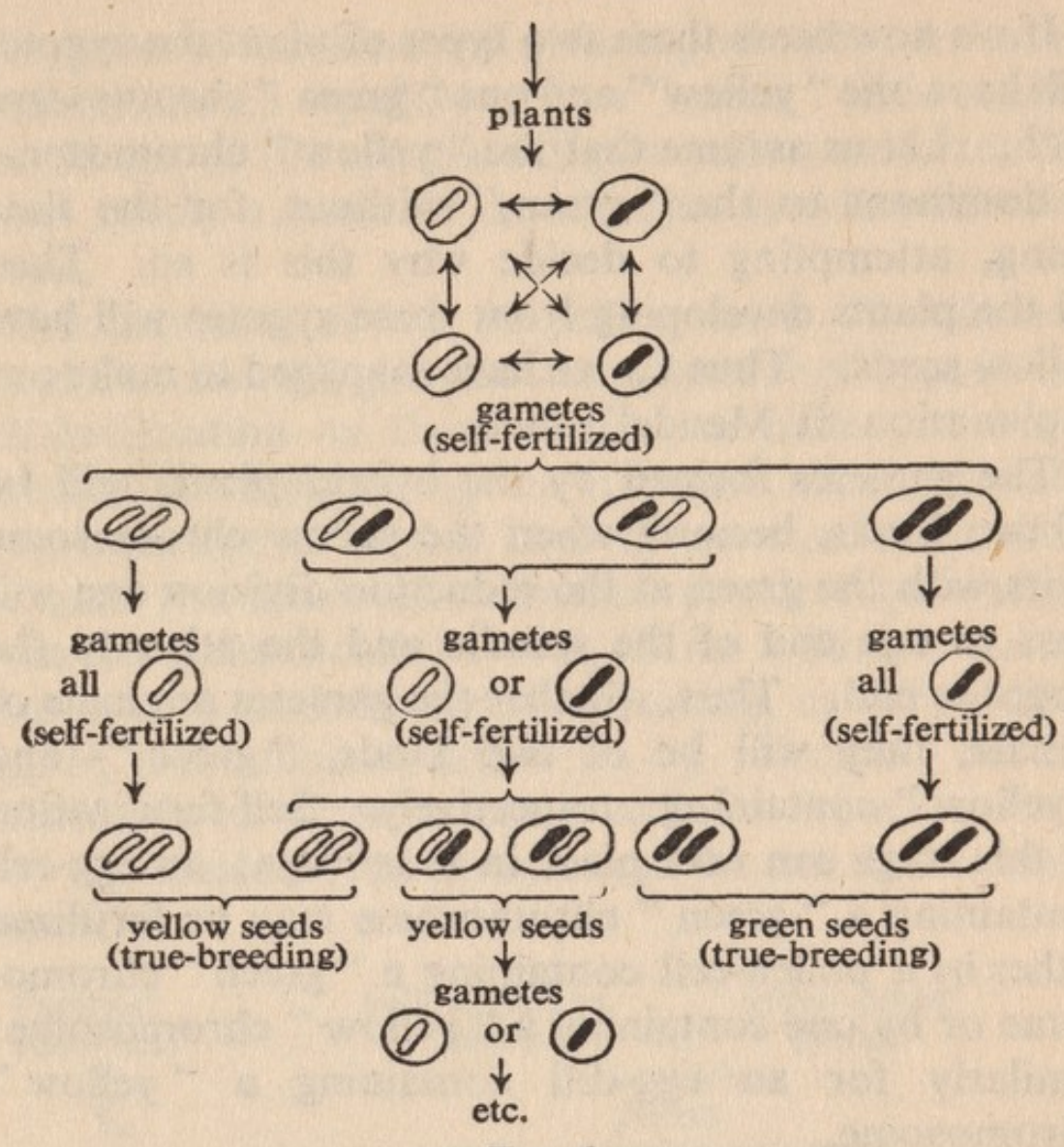


FIG. 6

Mendel's experiment explained by the presence of " yellow " and " green " chromosomes.

one " yellow " chromosome. Self-fertilization would bring two yellow chromosomes together again and give a yellow-seeded plant.

Suppose that in the nuclei of the green-seeded peas the place of these " yellow " chromosomes is taken by chromosomes which confer greenness on the seeds. These plants will also breed true when self-fertilized, each gamete carrying one " green " chromosome (see the first part of Fig. 6).

If we now cross these two types of plant the zygotes will have one " yellow " and one " green " chromosome each. Let us assume that the " yellow " chromosome is dominant to the " green," without, for the time being, attempting to decide why this is so. Then all the plants developing from these zygotes will have yellow seeds. Thus far we have managed to make our explanation fit Mendel's facts.

The gametes formed by the hybrid plants will be of two kinds, because when the yellow chromosome pairs with the green at the reduction division one will pass to one end of the spindle and the other to the opposite end. Thus, whether the gametes are male or female, they will be of two kinds, " green "- and " yellow "-containing respectively. Self-fertilization at this stage can take place in four ways: an egg-cell containing a " green " chromosome may be fertilized either by a pollen-cell containing a " green " chromosome or by one containing a " yellow " chromosome; similarly for an egg-cell containing a " yellow " chromosome.

If we assume, as we are entitled to as a first hypothesis, that nothing interferes with the operation of chance, on an average half the " green " egg-cells will be fertilized one way and half the other; similarly for the " yellow." We can therefore draw up a balance-sheet like this, for every 100 egg-cells fertilized:

100 egg-cells contain 50 " yellows " and 50 " greens ";
of 50 " yellows " 25 fertilized by " yellow " pollen,
and 25 fertilized by " green " pollen;
of 50 " greens " 25 fertilized by " green " pollen,
and 25 fertilized by " yellow " pollen.

We have already assumed that the " yellow–green " pair of chromosomes gives a yellow seed, so that the

50 zygotes of this kind will give, superficially, the same seeds as the 25 " yellow–yellow " ones. This means that 75 out of 100 zygotes will give yellow seeds and 25 green seeds, a ratio of 3 : 1. This is what Mendel found.

Furthermore, of the 75 yellow seeds 50 will not breed true but will give the same mixture of zygotes on self-fertilization as those which we have just been discussing. This also agrees with what Mendel found.

In experiments of this kind where a cross is made between two kinds of individual the first generation from the cross is called the F_1 (F for " filial "—Latin *filius*, a son), and the result of pairing, or self-fertilizing, F_1 individuals is called the F_2. Crossing the F_1 individuals to either parent is called a " back-cross." For convenience the process can be set out in this manner:

Parents: yellow–yellow × green–green
(Gametes yellow × green)
F_1 yellow–green
F_2 pollen

eggs \ pollen	yellow	green
yellow	yellow–yellow (Y)	yellow–green (Y)
green	yellow–green (Y)	green–green (G)

from which we get

1 yellow–yellow : 2 yellow–green : 1 green–green

The actual colour of the seeds, indicated by (Y) and (G), gives a ratio 3 Y : 1 G.

Many other examples of this 3 : 1 ratio have been discovered, and will be mentioned in later chapters.

Here is one from an investigation of heredity in gooseberries: 6 varieties of red gooseberry when self-fertilized gave seeds from which were obtained 164 plants bearing red fruit and 62 bearing fruit that was not red.

We may notice that if the " yellow–green " zygote had neither yellow nor green seeds, but an intermediate colour, it would have been possible to see in the F_1 generation that the plants were different from both parents, and also to see that in the F_2 three types of individuals were produced. An example of this is the Four o'clock, where the result of crossing red- and white-flowered plants is a pink-flowered plant, which on self-fertilization gives 1 red to 2 pink to 1 white. In the animal kingdom we have the Blue Andalusian fowl, which is the result of a cross between black and white strains, and therefore never breeds true, like the F_1 generations we have discussed above. In every brood one gets on the average 1 black to 2 blue to 1 white. Crossing of black and white fowls will give all blues; a programme of breeding based on this will help to keep the majority of birds in a flock in the " blue " state.

If we develop the chromosome theory a stage further we may consider what might happen if two pairs of chromosomes were involved. Mendel carried out another experiment with peas which may help to cast light on this. He crossed yellow smooth-seeded peas with green wrinkled ones. " Round " and " wrinkled," it will be remembered, behave like " yellow " and " green." Let us call the chromosomes by the initial letters of the characters which they are assumed to carry, and the characters by the same

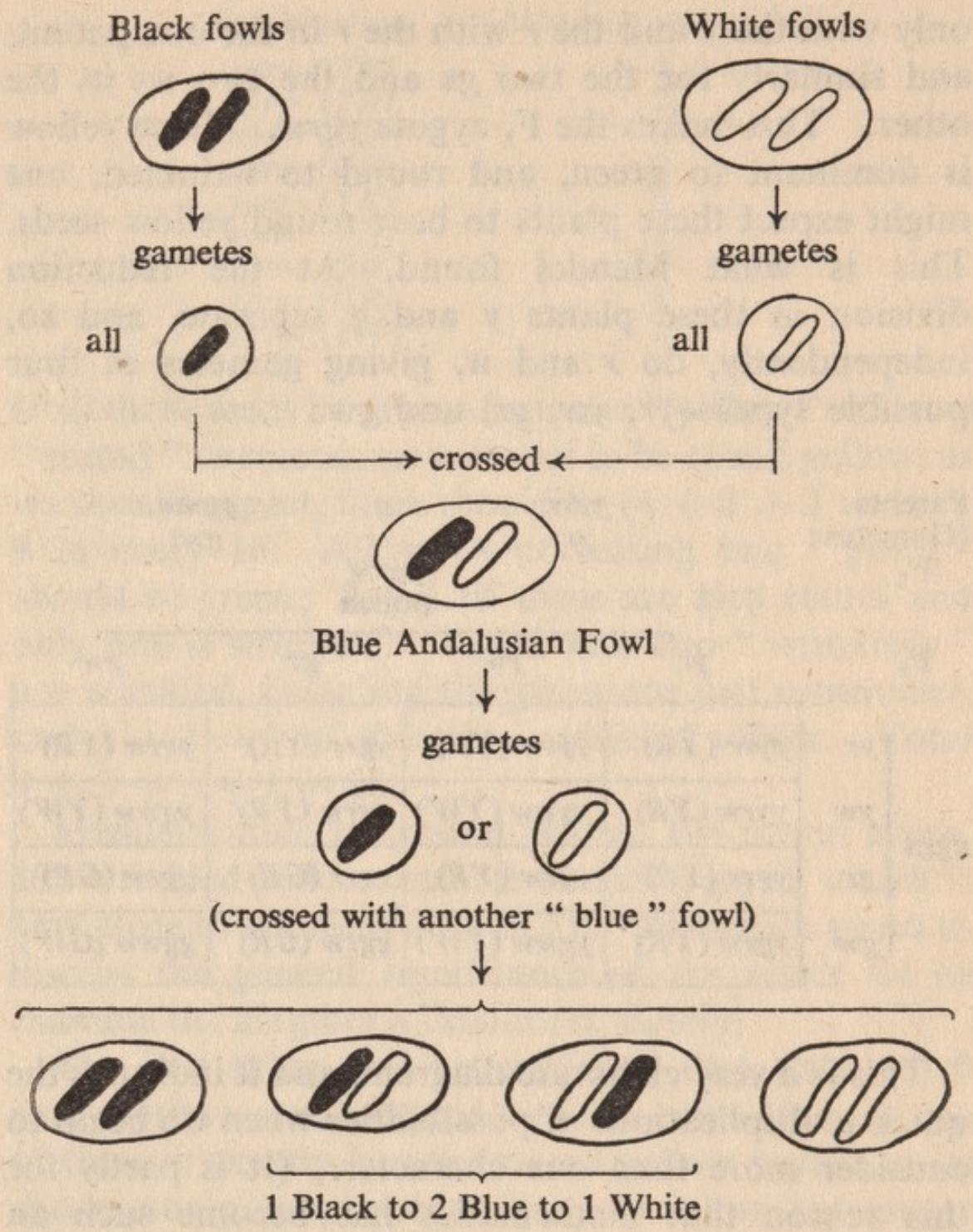


FIG. 7

The Blue Andalusian fowl; an example of an hereditary constitution which is incapable of breeding true.

capital letter—e.g., chromosome *y*, character *Y*. The parents will be *yyrr* and *ggww*, producing gametes *yr* and *gw* respectively, because the *y* chromosome pairs

only with the *y* and the *r* with the *r* in the one parent, and similarly for the two *g*s and the two *w*s in the other. This makes the F_1 zygote *ygrw*. Since yellow is dominant to green, and round to wrinkled, one might expect these plants to bear round yellow seeds. This is what Mendel found. At the reduction division in these plants *y* and *g* separate, and so, independently, do *r* and *w*, giving gametes of four possible types—*yr*, *yw*, *gr*, and *gw*:

Parents: *yyrr* × *ggww*
(Gametes: *yr* *gw*)
F_1 *ygrw*
pollen

F_2 eggs	*yr*	*yw*	*gr*	*gw*
yr	*yyrr* (*YR*)	*yyrw* (*YR*)	*ygrr* (*YR*)	*ygrw* (*YR*)
yw	*yyrw* (*YR*)	*yyww* (*YW*)	*ygrw* (*YR*)	*ygww* (*YW*)
gr	*ygrr* (*YR*)	*ygrw* (*YR*)	*ggrr* (*GR*)	*ggrw* (*GR*)
gw	*ygrw* (*YR*)	*ygww* (*YW*)	*ggrw* (*GR*)	*ggww* (*GW*)

This is a very elaborate diagram, and it indicates the quick multiplications of possibilities when we begin to consider more than one character. (It is partly for this reason that mathematics has become such an essential part of the science of genetics, providing, as it does, simpler ways of arriving at these conclusions than the laborious method of writing all the possible combinations down and adding similar things together.) Some of the F_2 offspring are the same; we can pick out the following different combinations of chromosomes:

Combination	Numbers (out of 16)
ygrw (*YR*)	4
yyrw (*YR*)	2
ygww (*YW*)	2
ggrw (*GR*)	2
ygrr (*YR*)	2
yyrr (*YR*)	1
ggww (*GW*)	1
ggrr (*GR*)	1
yyww (*YW*)	1

If all those seeds having *at least* one " yellow " and one " round " chromosome turn out to be round yellow, as we should expect, there should be $(4 + 2 + 2 + 1) = 9$ in every 16. All seeds possessing two " green " should be green; $2 + 1$ of these are also round and only one is wrinkled. Those with two " wrinkleds " are wrinkled, including the green one just mentioned, and $2 + 1 = 3$ of them are wrinkled yellow. Total $9 + 3 + 3 + 1 = 16$.

Mendel found 315 round yellow, 108 round green, 101 wrinkled yellow, and 32 wrinkled green, which is very close to the ratio 9 : 3 : 3 : 1. Before we go on to discuss the general significance of the result let us examine the diagram a little more closely.

The first thing that we notice is that although 9 round yellow seeds are produced in every 16, only *one* of these is exactly like the round yellow parent in its chromosome complement—i.e., *yyrr*. For that matter there is only one of the same constitution as the green wrinkled parent. These two lots of seeds will breed true when self-fertilized. What of the rest?

Among them are two new types of seed, the round green and the wrinkled yellow (3 each in every 16). But from their chromosome constitution it is clear that one only out of each three will breed true, *ggrr* and *yyww*.

Thus from our original true-breeding strains we have obtained two new ones. (The importance of this will be seen when we come to consider the application of Mendel's discoveries to plant-breeding; it provides a means whereby characters desirable to the farmer may be combined in one plant although originally discovered in separate strains.)

The remainder include no true-breeding strains, but the chromosome constitution of the F_1 generation *ygrw* reappears 4 times in 16. The truth of these predictions could be established by suitable crosses between the F_2 plants and (best) the wrinkled green parent, as will be seen later.

The time is now ripe for a review of the theories and assumptions which we have been using.

In the first place, an examination of the cell nucleus has led to the suggestion that it is a structure concerned with the transmission of hereditary characters. Within it are the chromosomes, which pair before the formation of gametes and are shared equally among them. In fertilization the nuclei of these gametes fuse, so that the zygote has once again the number of chromosomes characteristic of the species.

This, in brief, is the essence of the knowledge gained between 1866 and 1900, which led to the rediscovery and revaluation of Mendel's work. His work would have been of small importance though if his ideas about inheritance had applied to peas only. In fact, they were confirmed first in several genera of plants and shortly afterwards in animals, and so came to have a general significance.

His conclusions were essentially as follows: *First, that the hereditary characters of peas are not amalga-*

mated when crossing takes place (F_1) but are somehow kept distinct, so that THEY REAPPEAR UNCHANGED IN DEFINITE PROPORTIONS *in the F_2 generation. Secondly, that some of these characters stand in such a relationship to one another that when both are present in the same plant only one of them is manifested (is dominant). Thirdly, that when these characters reappear in the F_2 generation the separation of one pair of characters does not influence the separation of the other.* This last conclusion has been named the Law of Independent Assortment. In terms of the experiment we have been discussing it means that if a gamete from *ygrw* carries the character *y* it has an equal chance of carrying *r* or *w*. This would mean that half the *y* gametes were *yr* and half *yw*. Since for every *y* gamete there is also produced a *g* gamete, and each of these may be either *gr* or *gw* (on the same reasoning), one would expect one quarter each of *yr*, *yw*, *gr*, *gw*. Mendel tested the gametes from the F_1 of the cross round-yellow × wrinkled-green to see whether the four kinds of gametes were, in fact, produced in equal numbers. This he did by crossing the F_1 to the wrinkled-green parent—that is, by a " back-cross." In theory it should work out as follows:

Parents: *ggww* × *ygrw*

pollen

eggs		*yr*	*gr*	*yw*	*gw*
	gw	*ygrw* (*YR*)	*ggrw* (*GR*)	*ygww* (*YW*)	*ggww* (*GW*)

The four kinds of seeds should be produced in equal numbers. He found 55, 51, 49, and 53 respectively out of a total of 208.

In the behaviour of chromosomes there is a possible parallel to the behaviour of these characters, if one assumes that the distribution of the members of each chromosome pair in the " reduction division " is at random. Each pair of chromosomes consists of one from the male parent and one from the female; random distribution would mean that if the paternal chromosome of one pair moved towards a particular end of the spindle the paternal chromosome of another pair might move either in that direction or in the opposite. In the example we have worked out this has been assumed. In the formation of gametes from the F_1 generation (*ygrw*) the chromosomes *g* and *y* were capable of moving to one or other end of the spindle like this:

$$g \longleftrightarrow y \quad \text{or} \quad y \longleftrightarrow g$$

At the same time the chromosomes *r* and *w* were assumed to move independently. Thus, while $g \longleftrightarrow y$ took place, the *r* and *w* chromosomes could move either

$$\begin{matrix} w \longleftrightarrow r & & r \longleftrightarrow w \\ & \text{or} & \\ g \longleftrightarrow y & & g \longleftrightarrow y \end{matrix}$$

giving four kinds of gametes:

gw *yr* *gr* *yw*.

Similarly for the opposite movement of *g* and *y*,

$$\begin{matrix} w \longleftrightarrow r & & r \longleftrightarrow w \\ & \text{or} & \\ y \longleftrightarrow g & & y \longleftrightarrow g, \end{matrix}$$

one gets the same four kinds of gametes

yw *gr* *yr* *gw*.

This is a rather long-winded way of showing that either the paternal (and therefore the maternal) chromosomes move in the same direction, giving *yr* and *gw*, or in opposite directions, giving *yw* and *gr*. Occasionally it is possible to *observe* this behaviour in chromosomes; thus in a certain grasshopper the members of one pair of chromosomes are sufficiently different in size to be distinguishable, and another chromosome (a special one to which reference will be made below) has no partner. In a series of observations the larger member of the dissimilar pair moved to the same end of the spindle as the single one in 154 and to the opposite end in 146 out of 300 cells studied, which amounts to saying that they move independently.

So in instance after instance the experimental evidence we have so far considered makes it possible to talk of Mendel's "factors" as though they were chromosomes, but we have no proof of any physical connection between them. This proof, in the usual paradoxical way of nature, has come to us through a knowledge of the ways in which hereditary characters do not behave like chromosomes.

CHAPTER IV

DROSOPHILA—GENES AND CHROMOSOMES

THE greatest hindrance to the progress of experimental work in heredity is offered by the length of time needed to complete each life cycle. Thus the time for a human being to grow to physical maturity is fourteen years or more, so that an experiment like those performed by Mendel would take nearly thirty years to complete if the characters investigated were immediately perceptible in the new-born child, or more than forty years if the F_2 generation had to become adult before the character revealed itself.

For this, and other reasons, quite different techniques are required to study inheritance in man, or in the larger mammals. It is, however, possible to find, in other groups of the animal kingdom, species in which the length of a generation is much shorter even than that of the pea plant and which for this reason are eminently suitable for experiments involving a study of successive generations.

The organism which was originally chosen by the American scientist, T. H. Morgan, and has since dominated the study of heredity, is the tiny fly Drosophila, of which there are several species, widely distributed in the temperate and sub-tropical regions. Of these the most famous is *Drosophila melanogaster*, which can be found in the British Isles by the observant. It is about the size of the small letters on this page,

with a yellow body and bright red eyes, and colourless transparent wings. It is an insect, belonging to the order Diptera. This large group includes the common house-flies and the familiar " clegs " of this country, as well as the tsetse flies of South Africa and many others parasitic on man and his domestic animals. All possess a single pair of wings and, instead of the hind pair found in other winged insects (e.g., bees, dragonflies, butterflies), have small rod-like structures with knobs at their ends, called *halteres* or " balancers." All pass through a larval and pupal stage in their development from the egg, much in the way that butterflies first hatch as caterpillars, then turn to chrysalids, before emerging as the adult form.

Drosophila is a comparatively harmless member of its group, as far as man is concerned, its food, and the food of its larva, being fermenting fruit. For this reason its numbers fluctuate considerably through the year, reaching a maximum during the fruit season of late summer and autumn. It is then that one is likely to notice it, attracted by the products of fermentation. It is very cosmopolitan in its distribution, and when found in the wild state shows few variations in its outward appearance whether from the Old or New Worlds.

Under laboratory conditions a generation of this insect can be reared within ten days, without any great expense either from the cost of its food or from apparatus to accommodate it. It is most commonly grown in half-pint milk bottles stoppered by a plug of cotton-wool; the food for the larvæ is placed at the bottom of the bottle and the whole set-up sterilized,

so that a stock of bottles can be kept ready to hand. When a generation is to be reared the food material has a yeast added to it and the selected male and female flies are introduced. The larvæ hatch from the eggs, feed upon the fermenting material, pupate, and emerge as adult flies all within the compass of the bottle. They can be killed for examination under the microscope, or, more conveniently, anæsthetized for a short period and later used for further breeding experiments. If the necessity arises, a fly can be kept until the next generation has been completed, so that crosses can be made between successive generations.

If we add to this the information that *Drosophila melanogaster* has a haploid chromosome number of only four, and other species of Drosophila at most one or two more, it will already be seen that it provides an excellent basis for breeding experiments. Since it was originally chosen for research purposes another property has been discovered which has increased still further the information which can be derived from it. This is the presence of relatively enormous chromosomes in the salivary glands of the larvæ, to which reference will be made later.

It is no exaggeration to say that Drosophila has been the leading figure in the science of heredity, so much so that there has been a danger that other less convenient organisms might be neglected and a one-sided view of phenomena obtained. For example, certain features of chromosome behaviour in Drosophila (and in its fellow dipterans) are not found elsewhere, and its method of sex-determination is not found in all insects, let alone all animals. More obviously, information gained from Drosophila cannot explain

the special features of plant, as against animal, inheritance.

Important though these peculiarities are for a consideration of special aspects of heredity, they are far outweighed by the general similarity of hereditary processes in living organisms, and the results obtained with a few related species of flies have had a significance far wider than the most optimistic could have hoped for at the beginning of the century. So in turning from experiments on peas to experiments on Drosophila we are not changing our ground significantly.

Mendel's observations on the inheritance of single pairs of characters were soon confirmed, but when more than one pair was considered at once a new phenomenon came to light. Let us take, for example, flies which have purple eyes and very stunted wings, instead of the red eyes and normal wings of the wild-type fly. Both purple eyes (*p*) and stunted wings ("vestigial" wings—*v*) are due to the possession of recessive characters, so that a fly showing both characters breeds true like the green wrinkled peas discussed earlier. Its hereditary constitution can be represented as *ppvv*, and if we use the same letters *in capitals* for the corresponding dominant characters the wild-type fly would be *PPVV*. The cross between them (F_1) would be *PpVv*, as far as its hereditary characters went, but it would not differ *outwardly* from its wild-type parent.

If we now cross a male fly from this F_1 generation with a *ppvv* female we would expect a result like that given at the end of the last chapter (p. 40): four types of offspring in equal numbers, thus:

vvpp × *VvPp*

sperm

Eggs *vp*	*VP*	*vP*	*Vp*	*vp*
	VvPp	*vvPp*	*Vvpp*	*vvpp*

i.e., from left to right (in outward appearance)

wild-type flies;
flies with normal eyes, but vestigial wings;
flies with purple eyes, but normal wings;
flies with purple eyes and vestigial wings.

Typical results from this experiment are:

VvPp	519
vvPp	0
Vvpp	0
vvpp	552

This contradicts Mendel's principle of independent assortment, which was expressed earlier by saying that " when characters reappear in the F_2 the separation of one pair of characters does not influence the separation of the other." It therefore becomes necessary to decide whether this experiment invalidates the general application of Mendel's ideas, or whether some reconciliation can be achieved between them and the chromosome theory.

The latter in its crudest form postulated that Mendel's characters corresponded to chromosomes. An early objection to this, however, was that it would not permit an organism to have more pairs of hereditary characters than it had pairs of chromosomes. In fact, Drosophila was soon discovered to have many more pairs of characters than its four pairs of chromosomes, and the total now known to exist exceeds four hundred.

What has happened is that Mendel's "Law" of independent assortment has been superseded, and the chromosome theory has been modified. If the chromosomes, in fact, carry hereditary characters, then it is obvious that in Drosophila at least each one must carry more than one character, and consequently the characters on a particular chromosome must be linked together physically. It can easily be seen that such a linkage will explain the results with purple eyes and vestigial wings that we have just examined. If both *v* and *p* are carried in the same chromosome the doubly recessive fly will be more correctly represented by $\frac{p \quad v}{p \quad v}$, where the lines represent homologous chromosomes. At the reduction division each gamete will receive one of these chromosomes. Similarly the wild-type fly will be more correctly represented by $\frac{P \quad V}{P \quad V}$ and each gamete will receive one chromosome $\frac{P \quad V}{\quad}$. The F_1 generation will then be $\frac{P \quad V}{p \quad v}$, and when mated with a $\frac{p \quad v}{p \quad v}$ female an F_1 male will give offspring as follows:

		sperm	
		$\frac{P \quad V}{\quad}$	$\frac{p \quad v}{\quad}$
eggs	$\frac{p \quad v}{\quad}$	$\frac{P \quad V}{p \quad v}$	$\frac{p \quad v}{p \quad v}$

that is to say, will give only two types of offspring:

wild-type and purple vestigial flies, which should appear in approximately equal numbers (compare 519 to 552).

This hypothesis therefore enables us to explain the experimental results without abandoning the essence either of Mendel's ideas or of the chromosome theory. If it were correct we would expect that the hereditary characters of an organism should not always separate independently in the F_2 generation, but should be bound together by linkage into as many groups as there are chromosome pairs—i.e., the *haploid number* of chromosomes. In *Drosophila melanogaster*, although many hundred pairs of characters have been discovered they make up only four groups, corresponding to the haploid four chromosomes. Two closely related species show five and six linkage groups, and cytological examination reveals five and six haploid chromosomes respectively. In species with larger haploid numbers it is necessary to study correspondingly larger numbers of characters to stand a chance of determining all the linkage groups. Maize, which has received a good deal of attention, shows ten groups and a haploid number of ten chromosomes; but in man, with a haploid number of twenty-four, the evidence so far accumulated is insufficient to establish anything like this number of linkage groups. One can appreciate that in species with more than a hundred haploid chromosomes—for example, certain moths—it will be a long time before the hypothesis can be tested satisfactorily.

Nevertheless, we can now say with some certainty that the chromosomes are in some way the bearers of hereditary characters, but that each chromosome may

" *carry* " *many hundreds of them.* It will be remembered that in discussing the division of chromosomes at cell division (mitosis), the longitudinal splitting was suggested as evidence that whatever was being shared between the daughter cells was arranged along the chromosome in a linear manner. As an example of this a roll of wine-gums was mentioned; a similar arrangement can be found in a queue of people waiting for a bus. So, in speculating about the arrangement of those things in the chromosomes which are responsible for the transmission of hereditary characters in the sexual process (abbreviated to " which ' carry ' hereditary characters "), it is this type which first springs to mind. The characters are assumed to be " carried " in physical particles, which either themselves make up the chromosome or represent a layer on the outside of the main rod-like structure—that is to say, like wine-gums, or like people standing on the continuous line of curb- and paving-stones. For the present we will not attempt to distinguish between these alternatives.

To these particles, carriers of hereditary characters, the name of *genes* has been given. It does not follow that the possession of a gene always confers some visible or otherwise immediately detectable characteristic upon the individual organism; thus a *recessive* gene can be detected only by suitable breeding experiments. For example, in Chapter III, by crossing round yellow and wrinkled green peas we got in the F_2 generation *four* kinds of round yellow peas, similar in their outward appearance but differing in the genes they carried. (They were *rryy*, *rwyy*, *rwyg*, and *rryg* respectively; only the first would breed true if self-

fertilized.) Similarly, in the Drosophila example quoted above, the flies $\frac{P \quad V}{p \quad v}$ and $\frac{P \quad V}{P \quad V}$ are both wild-type in appearance, although crossing with a $\frac{p \quad v}{p \quad v}$ individual would at once distinguish them.

For this and other reasons a distinction is made between the collection of genes which an organism carries in its chromosomes and the characters which it displays when reared in a particular environment. The first we call its *genotype*, the second its *phenotype*.

We know for certain that the phenotype can be altered by changing the conditions under which the organism is reared. In plants the results of unfavourable surroundings are probably familiar to most of us: the same seed will give good or bad crops according to the ground in which it is sown and the care taken in its cultivation. In animals such effects are also seen but are not so well marked, because the animal is often able to move in search of its food and thus to mitigate the effects of unfavourable circumstances. An example of a different type of effect of external conditions on the phenotype is seen in the Himalayan breed of rabbit, in which the characteristic black-tipped ears, nose, and paws do not develop unless the temperature of its surroundings is below 33 degrees centigrade.

On the other hand, we cannot be so certain about the effect of changed conditions on the genotype, but there is little direct evidence that the ordinary variations in living conditions encountered by most plants and animals have any effect at all. This means that *the*

genotype is a comparatively stable property of the individual organism, all the cells of which carry essentially the same collection of genes.

In the diploid nucleus the collection of genes consists of a series of *pairs*, one member of each pair being carried on one chromosome and the other on its homologue, so that at the formation of the haploid gametes the gene pairs are separated, just as Mendel's characters were separated. Dissimilar genes which are members of such a pair are called *allelomorphs*—for example, we may take the recessive gene *p* for purple eye-colour and the corresponding dominant gene *P* which is responsible for the red eye-colour of the wild-type Drosophila. *P* and *p* are said to be an allelomorphic pair. For convenience we can write the gene composition of flies in the form *P*/*pV*/*v*, corresponding to $\frac{P \quad V}{p \quad v}$, and so on.

In order to distinguish genotypes in which the *same* allelomorph occurs twice, we refer to these as *homozygotes*, thus *P*/*PV*/*v* is homozygous for *P*; while those carrying differing allelomorphs are called *heterozygotes*, thus *P*/*pV*/*v* is heterozygous for *P*. A fly with a genotype *P*/*pV*/*V* would be heterozygous for *P* and *p*, but homozygous for *V*. Purple-eyed flies are thus homozygous, since the purple-eye character is shown only when two of the recessive genes *p* are present. When crossed they will breed true for the character, this being the case with all homozygous organisms. Heterozygotes, on the other hand, always produce two kinds of gametes, carrying one or other allelomorph, and hence never breed true but give the familiar 1 : 2 : 1 ratio when crossed with one another,

or a 1 : 1 ratio in the back-cross to the homozygous recessive. Another look at the diagrams on pp. 33 and 40 will help the reader to understand this.

Let us now return to the problems which arise when more than one gene is carried in the same chromosome. We saw that the doubly recessive flies *p*/*pv*/*v* gave when crossed to wild-type flies (*P*/*PV*/*V*) an F_1 generation *P*/*pV*/*v*, and that a male of this generation when crossed to a doubly recessive female gave only two kinds of offspring, *p*/*pv*/*v* and *P*/*pV*/*v*, with no signs of the *P*/*pv*/*v* and *p*/*pV*/*v* types which might have been expected if the allelomorphic pairs in the heterozygous F_1 had separated independently. The explanation was found in *linkage* of the recessive and dominant genes respectively, so that the F_1 genotype was $\frac{P \quad V}{p \quad v}$.

We could imagine a fly of similar "total" genetic constitution but with the linkage the other way round: $\frac{P \quad v}{p \quad V}$. This would also give only two kinds of offspring when crossed with a female $\frac{p \quad v}{p \quad v}$, in this case flies with purple eyes but normal wings $\frac{p \quad V}{p \quad v}$, and flies with normal eyes but stunted wings $\frac{P \quad v}{p \quad v}$. In other words, linkage could either hold *P* and *V* together or *P* and *v*. Experiment has confirmed this, which means that there is no question of one homologous chromosome carrying nothing but dominant genes and the other nothing but

recessives. A chromosome can carry any given mixture of recessives and dominants.

It may be noticed that nothing in the theory of linkage abolishes the Mendelian idea of dominant and recessive characters. Thus the flies $p/pV/V$ (purple eyes, normal wings) and $P/Pv/v$ (normal eyes, stunted wings) when crossed give wild-type offspring, as would be expected from the dominance of the wild-type genes P and V. The $p/pV/V$ flies contribute a $\underline{p \quad V}$ chromosome to the F_1 generation, the $P/Pv/v$ flies a $\underline{P \quad v}$ chromosome, giving the $\frac{P \quad v}{p \quad V}$ flies we have just discussed.

A very important question now arises: Are genes like p and v in our earlier example tied together for eternity in the same chromosome, so that none of their descendants will ever lack the $\underline{p \quad v}$ chromosome, or does some mechanism exist by which they can be separated? This might be a very important question for the plant or animal breeder, who found that a gene conferring a useful characteristic was linked to a deleterious one. To stretch a point somewhat, he might be attempting to get a true-breeding strain of purple-eyed Drosophila. Unless he can separate p from v he will never get a purple-eyed fly without stunted wings, because every time p is made homozygous, v is made homozygous also. For "fly" read "wheat," for "purpled-eyed" read "disease-resistant," for "stunted wings" read "susceptibility to drought," or any other such combination of qualities.

If genes sometimes underwent transformations, so

that *v* could be transformed to *V*, that would be one way out of the difficulty. (In later chapters we shall discuss the probability of this happening.) However, it is not necessary to go into that problem to get an answer to our question, as the following experiment shows:

If instead of crossing a male of the genetic constitution $\frac{P \quad V}{p \quad v}$ with a female $\frac{p \quad v}{p \quad v}$ we make the reverse cross (of $\frac{P \quad V}{p \quad v}$ female to $\frac{p \quad v}{p \quad v}$ male) the results are somewhat different. The offspring turn out to be of four types (the four expected from independent separation of the allelomorphic pairs), but the numbers of each kind are not the same. Thus, for this back-cross the offspring are typically:

wild-type	1,339	(519)	*P/p V/v*
purple eyes	154	(0)	*p/p V/v*
stunted wings . . .	151	(0)	*P/p v/v*
purple eyes, stunted wings .	1,195	(552)	*p/p v/v*

In brackets are given the figures of the reverse cross, which we discussed earlier. After each type is given its genetic constitution (each can receive only *p* and *v* from its father). In a more expanded form these genotypes are:

$$\frac{P \quad V}{p \quad v}, \quad \frac{p \quad V}{p \quad v}, \quad \frac{P \quad v}{p \quad v}, \quad \frac{p \quad v}{p \quad v},$$

If we cross a *P/pV/v* female of the opposite constitution, viz., $\frac{P \quad v}{p \quad V}$, with a $\frac{p \quad v}{p \quad v}$ male the results are

typically:

wild-type	157	(0)	$\frac{P\ V}{p\ v}$
purple eyes	1,067	(364)	$\frac{p\ V}{p\ v}$
stunted wings . . .	965	(358)	$\frac{P\ v}{p\ v}$
purple eyes, stunted wings .	146	(0)	$\frac{p\ v}{p\ v}$

In the offspring of both these crosses the original combinations of genes are most frequent, *but they are no longer the only ones.* In other words, linkage still exists but it is no longer complete. A certain proportion of the genes behave as though they were not linked.

The suspicion in this matter rests with the female gametes, since the homozygous male can contribute only a chromosome carrying *p* and *v* genes, and these are not decisive in constituting the four genotypes. The gametes produced by the female were clearly of four kinds: the majority were formed by the normal separation of $\frac{p\ v}{}$ and $\frac{P\ V}{}$ chromosomes to give gametes carrying one or other of these two chromosome types; the rest carried $\frac{P\ v}{}$ and $\frac{p\ V}{}$ chromosomes respectively. It is significant that in each cross the new combinations occurred in approximately equal numbers; there was no net loss of either dominant or recessive genes. They have apparently been exchanged in some way; technically, they are said to have *recombined.* Furthermore, the process can apparently

take place in either direction, either separating *p* and *v*, as in the first cross, or bringing them together, as in the second.

If we lump all the results together we get 608 new combinations out of 5,174 chromosomes tested (by the appearance of the fly which carries the chromosome together with a $\underline{p \quad v}$ chromosome)—that is to say, about 11 per cent.

The question thus arises: *How permanent is the arrangement of genes in a particular chromosome? What evidence can cytology produce for an exchange of material between chromosomes?* In order to answer these questions it is necessary to examine the processes of cell division in more detail, in particular the divisions which precede the formation of gametes.

CHAPTER V

CLOSE-UP OF THE NUCLEUS

BEFORE beginning to describe the process of nuclear division in greater detail, it is as well to point out once more the difficulty of deciding the relation between events in the living cell and the successive immobilized stages of the process revealed by fixing and staining it. One must add to this the difficulty of getting a true picture of structures at the limits of the resolving power of the ordinary light microscope. By the use of ultra-violet light, which involves using photographic plates in place of the eye, it is possible to extend these limits so that smaller structures can be distinguished. The reason for the inadequacy of the microscope is not some technical difficulty arising in its construction, but a more fundamental one connected with the wave-length of visible light. For this reason there is not much hope of increasing our knowledge of the minute structures in the cell by improvements in the existing microscope; instead we must await the development of new types of microscope, such as the electron microscope. Up to the present, chromosome structure has been studied by light microscopes, and the description which follows is based on such work. All description contains an element of interpretation, and this is exaggerated by the difficulties of observing the cell nucleus. The modifications which future discoveries will make necessary seem unlikely, however, to alter the general picture here presented.

The reader may profitably prepare himself for the description which follows by looking through the diagrams on pp. 59 and 67.

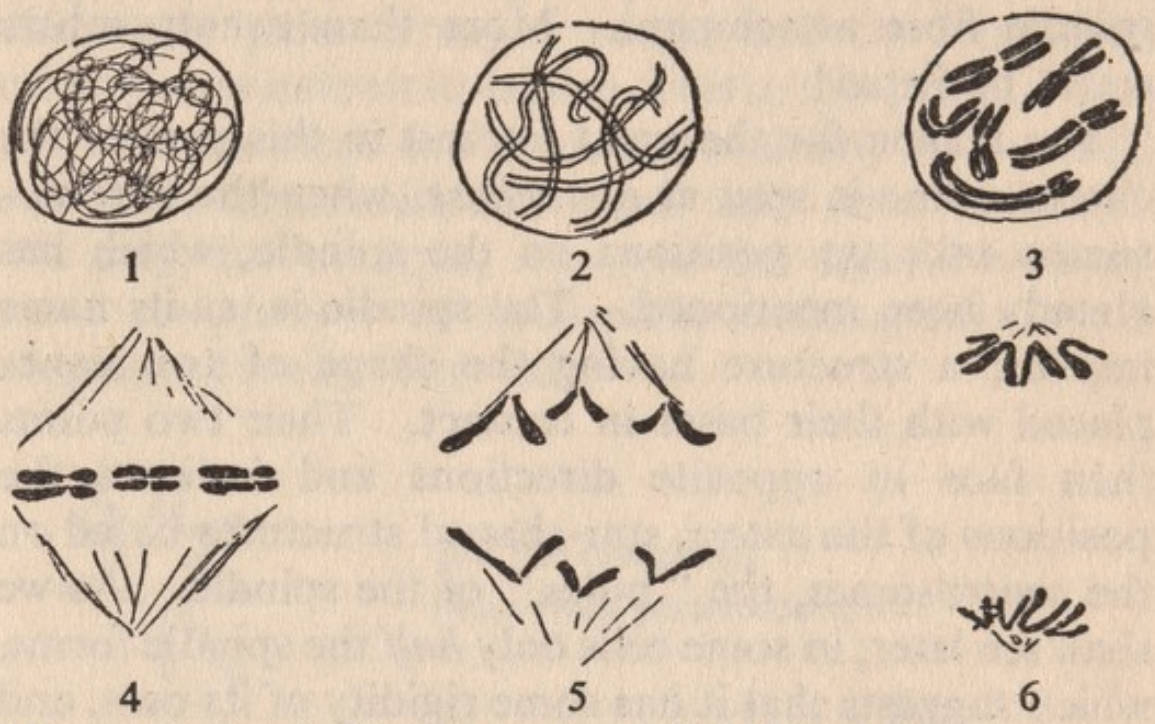
In Chapter II it was noted that two kinds of nuclear division occur in higher plants and animals, one of which is found only in the stages leading to the production of gametes before sexual reproduction. This, the reduction division, is called *meiosis*, while the commoner kind of cell division, found at all stages of growth and differentiation, is called *mitosis*. For convenience, the stages of division are distinguished in order of time, as *prophase*, *metaphase*, *anaphase*, and *telophase*.

There is a general similarity in the events which make up *mitosis* and *meiosis*, so that it is possible to talk of mitotic and meiotic prophase, metaphase, and so on, but the behaviour of the chromosomes is different in some respects. It has been suggested that meiosis can plausibly be derived from mitosis by assuming that the individual chromosomes go through the same series of changes as in mitosis, but that the time relations of division are altered. It does not seem necessary, though, to introduce a note of controversy at this level of presentation, and for present purposes the two processes will be treated separately.

Figs. 8 and 10 show successively mitotic and meiotic divisions and are semi-diagrammatic. They represent a reconstruction of the essential features of each stage as they are understood at present, all of which would not necessarily be seen in a single dividing nucleus by an untrained eye.

First, *mitosis*, the type of division seen in the body cells and in most stages of the production of germ cells.

In mitotic prophase the nucleus loses its more or less homogeneous appearance and granules appear within it. The chromosomes become visible as double threads, much coiled and twisted. Each of these threads is referred to as a *chromatid.*



Mitosis (1–6). 1. Resting nucleus; 2–3. Prophase. 4. Metaphase. 5. Anaphase. 6. Telophase.

FIG. 8

The stages of mitosis and meiosis ; semi-diagrammatic.

During prophase the chromatids contract to one-tenth or less of their length at their first appearance. This they achieve by forming a close spiral, in which successive coils practically touch one another. By this contraction the threads are converted to rod-like bodies, distinguishable from those of other pairs by size, shape, and by the presence of constrictions. The latter are of two kinds—those associated with the *centromere* and those which indicate the position of *nucleoli* (see later).

The *centromere* is of great importance in cell

division. Many names have been given to it, or to the point in the chromosome at which it occurs. In case the reader should meet it under one of these aliases, here are some of the terms: attachment body, centric constriction, kinetochore, primary constriction, spindle fibre attachment. More than twenty others could be listed!

The reason for the great interest in this part of the chromosome is seen at *metaphase*, when the chromosomes take up positions on the spindle, which has already been mentioned. The spindle is, as its name implies, a structure having the shape of two cones placed with their bases in contact. Their two points then face in opposite directions and indicate the positions of the *asters*, star-shaped structures based on the centrosomes, the " poles " of the spindle. As we shall see later, in some cells only *half* the spindle forms, which suggests that it has some rigidity of its own, and experiments in which whole cells were compressed also suggest that it is harder to distort than the surrounding cytoplasm.

The pairs of chromatids, which are still held together by the fact that the centromere is either undivided or that its halves show great cohesion, and which are to some extent coiled round one another, move so that the centromeres arrange themselves on the *equatorial plate* of the spindle. The plate corresponds to the bases of the two cones, just as the cut surfaces of a grapefruit correspond to the bases of two hemispheres. While the centromeres lie in the plate, the rest of the chromatids may either lie outside the spindle, free in the cytoplasm (the nuclear membrane, it will be remembered, disappears when the spindle is

formed), as in many of the higher animals, or else more or less wholly in the plate also, only the ends of the larger ones projecting into the cytoplasm, as in most plants. Intermediate arrangements also occur.

Looking from either pole (aster), one now sees the chromatid pairs arranged round a circle with their centromeres nearest its centre. It is in this position that the chromosomes can most conveniently be counted and their characteristic shapes and sizes observed. We may, for example, *represent* the diploid *chromosome complement* of *Drosophila melanogaster* semi-diagrammatically like this:

and the related fly
Drosophila pseudoobscura:

(Note: In these diagrams the chromosomes are not shown in the divided state, and the homologous chromosomes are shown side by side.)

Of course, the chromosomes do not lie in such a regular pattern in every cell at metaphase, even when the number is small. In organisms with many chromosomes the picture becomes very confused, the smaller ones usually lying nearer the centre of the circle, the larger ones outside.

The chromosomes, which since prophase have been almost split in two, now lose their last connection by dividing at the centromere, and daughter chromatids

move towards opposite poles. The centromere leads the way, so that during this stage, *anaphase*, the ends of the chromatids away from the centromere still lie close together, while their middle parts move in opposite directions. The movement seems to be due both to the repulsion between daughter chromatids and to the pressure towards the poles exerted by the portion of the spindle between them.

On reaching the poles the chromatids form a compact mass, and may perhaps be assumed to go through a process representing a reversal of prophase. *Telophase* is thus normally the formation of a characteristic *resting* nucleus, though occasionally the chromosomes remain separated, in little compartments called *vesicles*, until the next division.

Much interest attaches to the state of the chromosomes during the resting stage, but from certain observations (made in favourable material) it seems likely that they do not break up, but remain as such, and have been observed to " reappear " in approximately the same positions at the next prophase as those they occupied at the previous telophase. In many flowering plants the proximal parts of the chromosomes, nearest to the centromeres, persist as strongly staining bodies throughout the resting stage. They are distinct from nucleoli, which, as has been mentioned above, are attached to certain of the chromosomes, and are prominent in the resting stage, but usually disappear at an early stage of mitosis in most organisms, although in some plants they may persist to metaphase. The apparent disappearance and reappearance of the chromosomes in most organisms is put down to alternate loss and absorption of nucleic

acid or some similar process, which makes the chromosomes less or more stainable respectively. Just as in living cells of some organisms it is sometimes possible to see the mitotic chromosomes easily, while in nearly related organisms they may be practically invisible, in a few organisms chromosomes have been seen in resting nuclei. Faced with evidence of this kind, and with a body of genetical evidence which cannot easily be explained on any other hypothesis, it is now generally accepted that *the chromosomes are permanent structures within the nucleus and carry out their biological function without losing their characteristic thread-like structure.*

The time taken by cells to pass through the various stages of mitosis is extremely variable and may vary from half an hour to days. This order of magnitude makes it possible, as we shall see later, to subject dividing cells to physical and chemical treatments, and by the subsequent behaviour of the chromosomes to make deductions about their nature and also about the changes produced in them. This is one way in which cell division can be studied experimentally; other methods include such diverse procedures as direct mechanical interference, using minute dissecting instruments; centrifuging, by which nucleoli can be dragged out of the nucleus; and genetical methods, such as hybridization which takes chromosomes into "unfamiliar" cytoplasm. This latter method is sometimes very illuminating, and more about it will be found later.

If the cell nuclei continued to divide by mitosis, indefinitely, there would be little chance of exchanges between homologous chromosomes, since at each

mitotic division they behave more or less independently. A tendency of homologous chromosomes to associate in pairs during mitosis has been noticed in certain organisms, particularly in Diptera, but this pairing does not bring the partners into contact.

However, in the formation of gametes a special type of division, *meiosis*, takes place, and here the homologous chromosomes come into a much more intimate relationship. The main outlines of the process have been given above (in Chapter II), and before we proceed to detailed description a few remarks about the cells in which it occurs may help to emphasize its importance.

In the higher animals and plants gametes of two kinds are produced, male and female. There is a general similarity in the processes which occur in the generative organs of both sexes: testis and ovary in animals, anther and ovary in plants. After a series of mitotic divisions there are produced the cells from which the gametes are to arise. These cells divide twice in fairly rapid succession, producing four nuclei with the haploid number of chromosomes; these two divisions constitute *meiosis*.

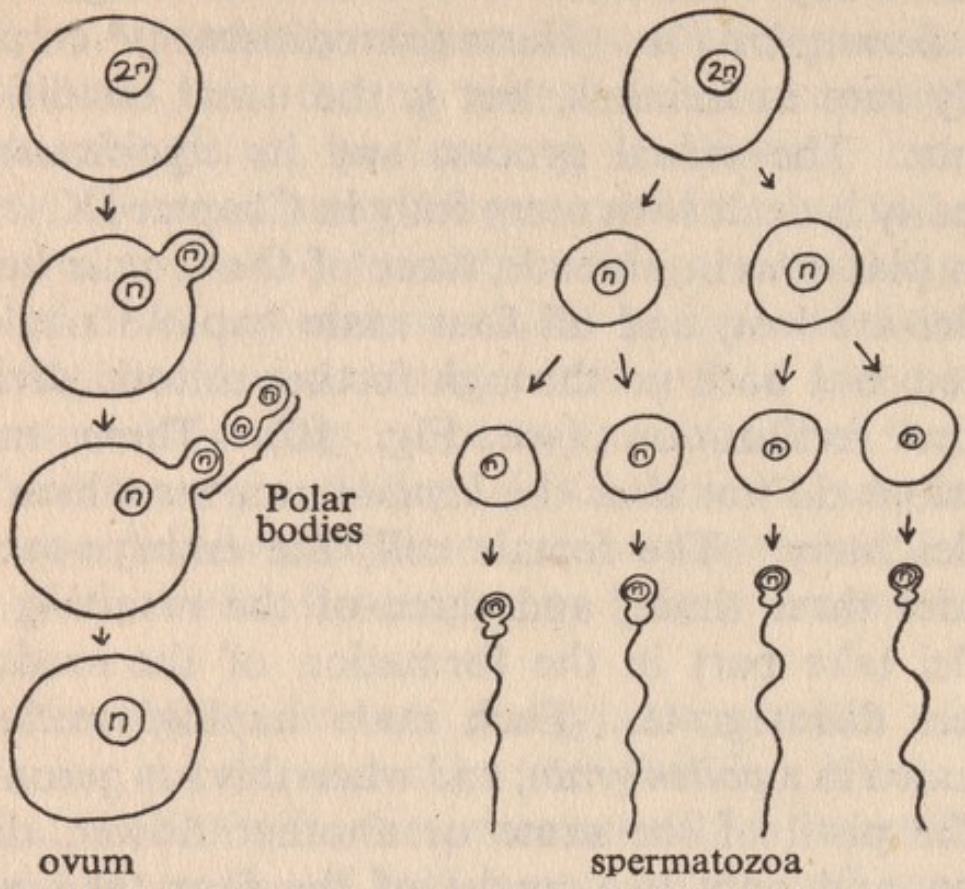
In female animals three of these four nuclei are discarded, with a minimum of cytoplasm (so-called *polar bodies*), the fourth becoming an ovum; in the male all four nuclei go to form spermatozoa. The ova and spermatozoa undergo no further division before fertilization. (Ova, which in a few organisms develop without fertilization, are said to develop by *parthenogenesis*, see Chapter IX.) The fertilization of an ovum by a sperm from the same animal is called *self-fertilization* and can occur only in those animals

which carry both male and female sex organs—i.e., are *hermaphrodite*. Hermaphroditism is comparatively rare in animals, but is the usual condition in plants. The sexual process and its significance for heredity is dealt with more fully in Chapter IX.

In plants, as in animals, three of the female haploid nuclei are lost, and all four male haploid nuclei retained, but both go through further mitotic divisions before fertilization (see Fig. 10). These mitotic divisions do not alter the *haploid* number which these nuclei carry. The female cell, the embryo-sac cell, divides three times, and three of the resulting eight nuclei take part in the formation of the seed; the others disintegrate. Each male haploid nucleus is included in a *pollen grain*, and when this has germinated in the pistil of the same or another flower, divides twice, and only two nuclei of the four take part in fertilization. One fuses with one of the female nuclei and gives rise to the embryo, the other fuses with two haploid nuclei from the female to form the *endosperm* nucleus from which the endosperm develops. From this it is clear that the embryo will have diploid nuclei, the endosperm *triploid* (three times the haploid) *nuclei ;* or, put another way, the embryo, which will give rise to the new plant, receives one chromosome of each homologous pair from each parent, but the endosperm, which provides the reserve of foodstuff for the seedling, has one from the male parent and two from the female parent in each triplet of homologous chromosomes.

At the beginning of meiotic division the chromosomes once again appear in the nucleus as at previous mitotic divisions, but *not* this time as double threads. Each chromosome is seen to have a granular structure.

(1) In animals



(2) In plants

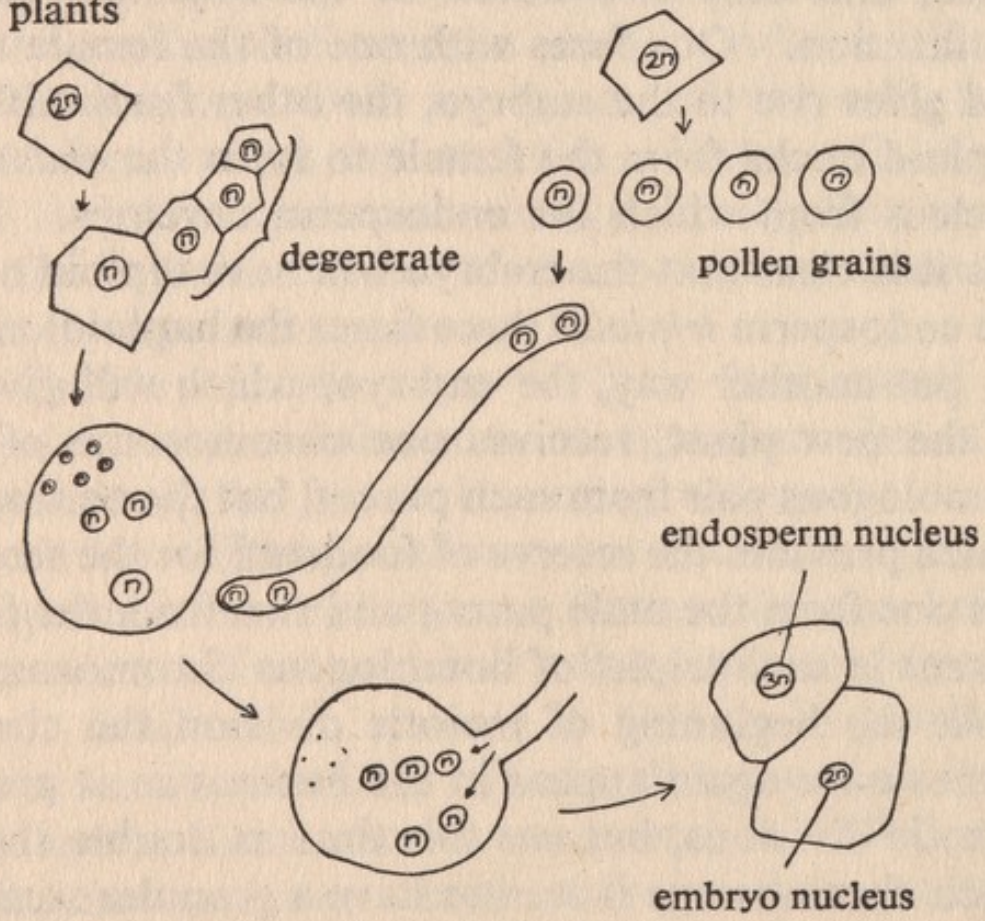
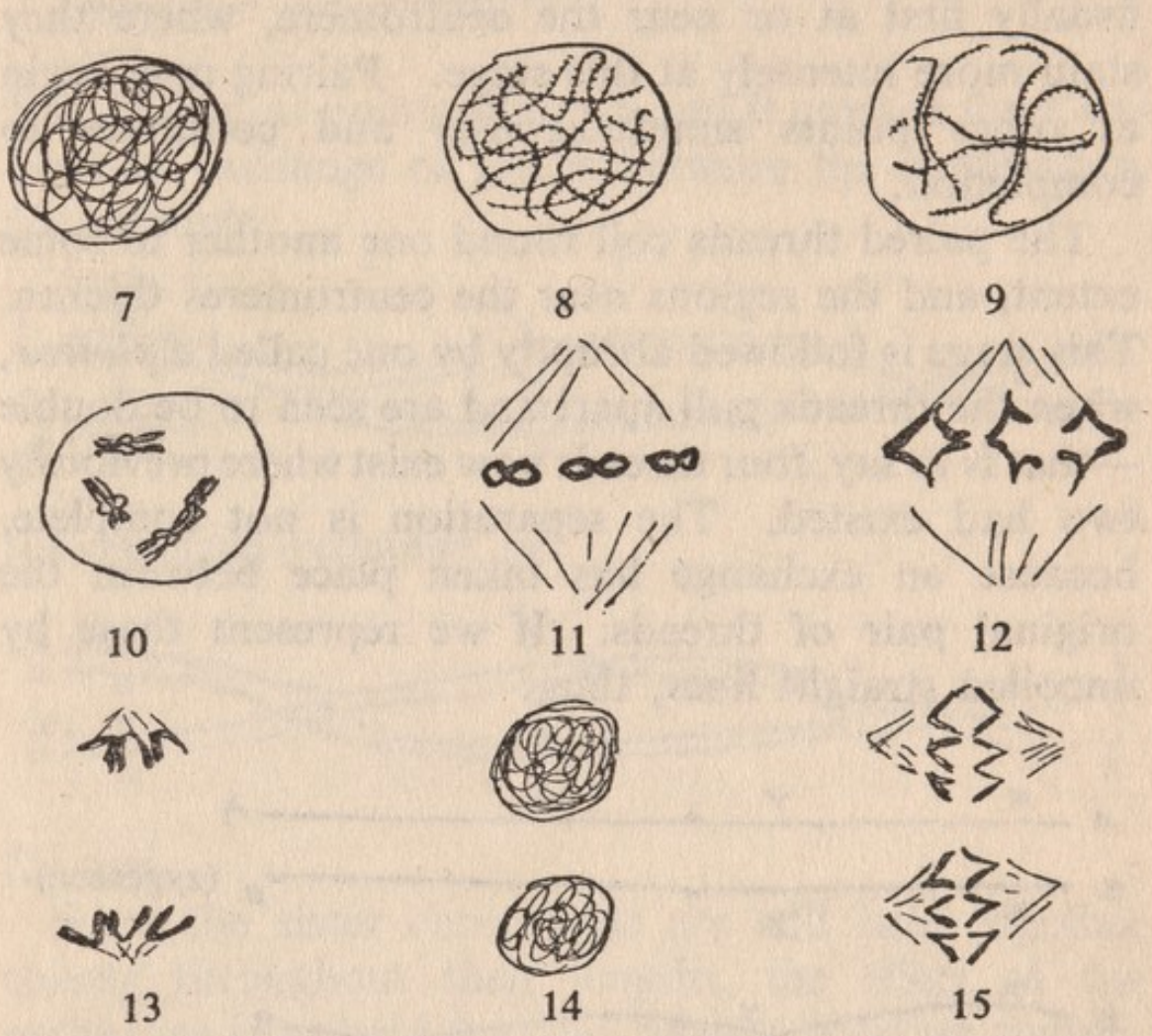


FIG. 9.—Gamete formation and fertilization: diagrammatic.

In the stained preparations the chromatid appears to consist of deeply staining granules, the *chromomeres*, arranged in the manner of a loose bead necklace. It



Meiosis (7–15). 7. Resting nucleus. 8. Zygotene.
9. Pachytene. 10. Diplotene.
11–12. Metaphase (1st). 13. Anaphase (1st).
14–15. Telophase (1st) and second division.

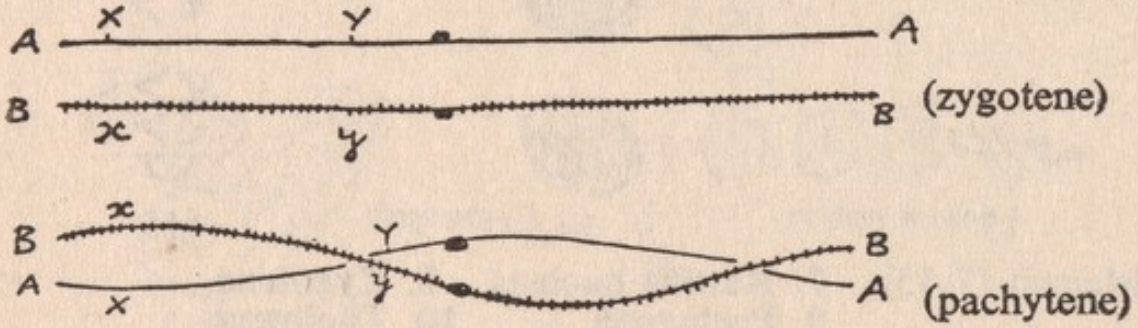
FIG. 10
The stages of mitosis and meiosis; semi-diagrammatic.

seems possible that the gaps between the " beads " are exaggerated by the staining techniques and that the living chromatid is more continuous in structure. The arrangement of chromomeres is the same in each chromosome of a homologous pair, though differences exist between members of different pairs. The

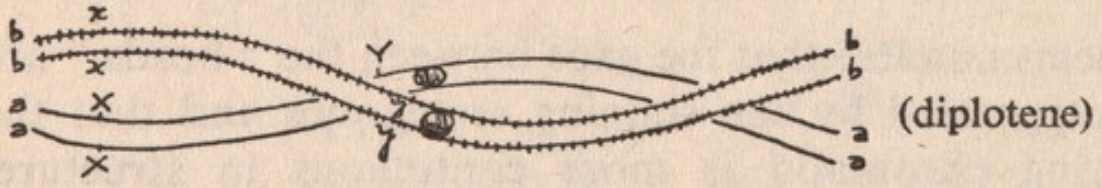
chromosomes are arranged at random within the nuclear membrane.

The homologous chromosomes begin to pair, usually first at or near the centromere, where they stain more intensely at this stage. Pairing may begin at other points simultaneously and continues to completion.

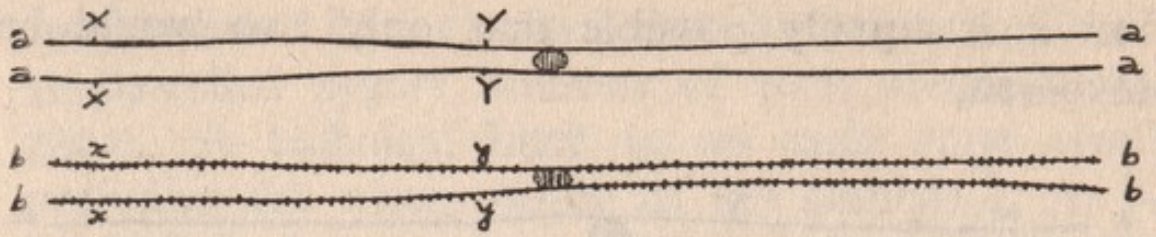
The paired threads coil round one another to some extent, and the regions near the centromeres thicken. This stage is followed abruptly by one called *diplotene*, when the threads pull apart and are seen to be double —that is to say, four threads now exist where previously two had existed. The separation is not complete, because an exchange has taken place between the original pair of threads. If we represent these by uncoiled straight lines, thus:



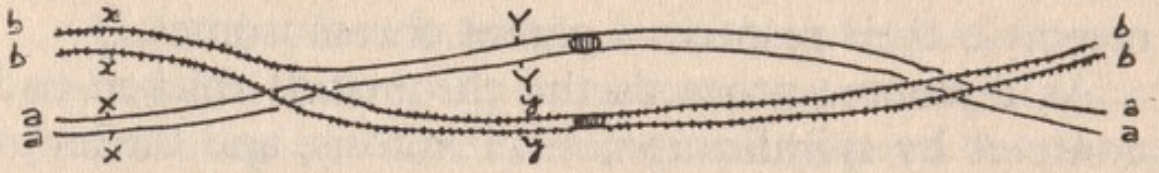
between pachytene and diplotene each has doubled,



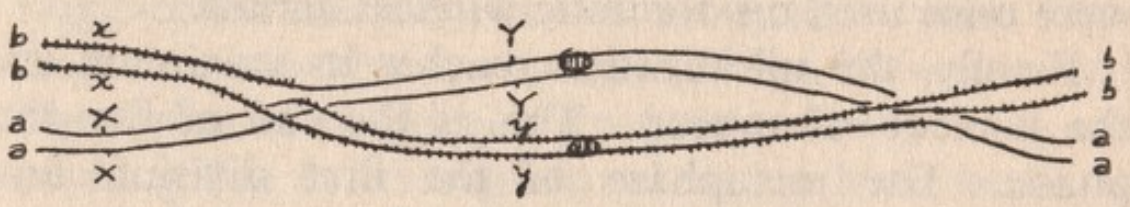
so that if no other change had occurred the separation at diplotene would give



But, in fact, at points where A and B crossed there has been an exchange of pieces between the chromatids, for example:



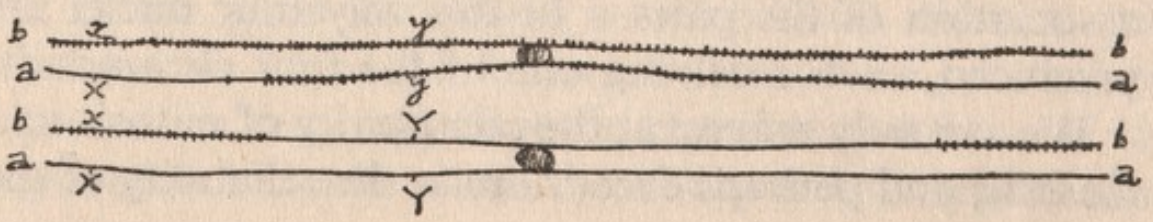
for one such exchange, or



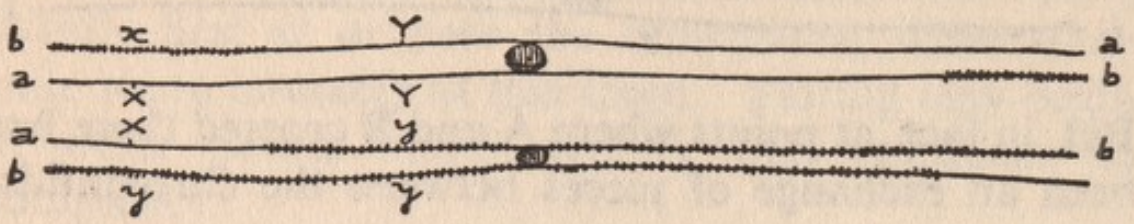
for two.

Since the sister chromatids are still held together closely throughout their lengths, the effect of the exchanges is to hold the four threads together tightly. The points at which the newly constituted threads cross over are called *chiasmata*, and can be seen clearly in the cells, especially in the latter part of diplotene.

We have drawn these exchanges so that all four chromatids are involved; thus if we were to separate them we should get



but it is equally possible that only two would be involved,



in which case two of the daughter chromatids will resemble their respective parent chromosomes.

As diplotene proceeds the chromatids thicken and contract by spiralization, as in mitosis, and the loops between the chiasmata come to lie at right angles, rather like the holes in the porcelain insulators that were once used on domestic wireless aerials.

Finally, the spiralization reaches its maximum and the nucleoli disappear. This is the end of the prophase. The metaphase of the first division now begins, and the *bivalents*, as they are called, arrange themselves so that the two centromeres lie on each side of the equatorial plate.

At the succeeding anaphase the centromeres move to opposite poles, and the pairs of chromatids attached to them move after them.

At telophase the chromatids uncoil and pass into a resting stage.

The second division resembles an ordinary mitosis, the chromosomes appearing as double threads and separating at metaphase without any very complete association of the pairs. In this way four nuclei are produced, each receiving one of the four chromatids.

We can only marvel at the complexity of mitosis and meiosis, and perhaps even more at the reliability of the

mechanism. In the growth of a human being from a single-celled zygote millions of such divisions take place. A technical hitch at an early stage would prejudice the whole future of the embryo. As we shall see in later chapters, hitches do occur, and these must often kill the new individual long before birth; but by and large the complex and meticulous division of chromosomes is repeated countless times without error.

As to the forces which lead the chromosomes in their weird dance, we cannot yet say much of value. Speeded up by the cinematograph camera the movements appear almost frantic, but usually they are slow by comparison with, for example, the movements of single-celled animals, like amœbæ, and much slower than the muscular movements of the higher animals. The forces of electrical attraction and repulsion, or of swelling due to absorption of water, have been suggested as possibilities.

Let us now return to our problems of heredity and in particular to that of incomplete linkage of genes. (Turn back to the diagrams on pp. 68-70 while reading this.) Consider the fate of two allelomorphic pairs of genes, which we will assume to be located at the points *X* and *Y* on this chromosome, *X* and *x* and *Y* and *y*. For the sake of this illustration both wild-type genes are on the same chromosome. Let us also assume that they are exactly reproduced at the doubling of the threads.

If the gene *Xx* alone is considered, then it will behave as Mendel's factors behaved—i.e., it will be present in the single form in equal proportions of the gametes and will show the characteristic segregation

ratio in the offspring of self-fertilization. But if we consider both genes it is clear that they will emerge from this process in new combinations. Thus the parent could originally be described by $\frac{XY}{xy}$, but the gametes which have been illustrated above are of four kinds: *XY*, *xy*, *xY*, and *Xy*. This exchange is caused by a single chiasma, the left-hand one, occurring *between the places* which we have assigned to the genes; the other chiasma has no effect on their segregation.

In other words, *in the phenomenon of chiasma formation is revealed a mechanism by which the incomplete linkage seen in Drosophila* (Chapter IV) *could be explained. By an examination of the implications of this idea it is possible to learn much more of the nature of the genes, and their behaviour, than our earlier evidence has provided.*

CHAPTER VI

MAPPING CHROMOSOMES

WHAT has been said of the effect of chiasma formation is enough to demonstrate that in it we have a possible explanation of incomplete linkage, an explanation based upon the observed behaviour of the chromatids at meiosis, and upon certain assumptions about the arrangement of genes within the chromosome. Before investigating these assumptions more closely it is worth noticing that if the theory is correct, then where no crossing-over is detected genetically (as in the crosses discussed at the beginning of the previous chapter) no chiasma formation should occur. This is, in fact, found to be the case in the males of Drosophila, where the reduction divisions preceding the formation of spermatozoa show practically no chiasmata. In the female, on the other hand, chiasma formation takes place, as it does in both sexes of most higher animals and plants. This is another example of the way in which the much-studied fly differs from the majority of insects and from other animals. It explains why the results of back-crossing the F_1 flies to the purple-vestigial parent type differed according to the direction of the cross.

This agreement of cytological and genetical evidence makes the whole idea very plausible, and it will be seen later that other examples of absence of crossing-over can be correlated with cytological findings. The *chiasmatype theory* has been in existence for several

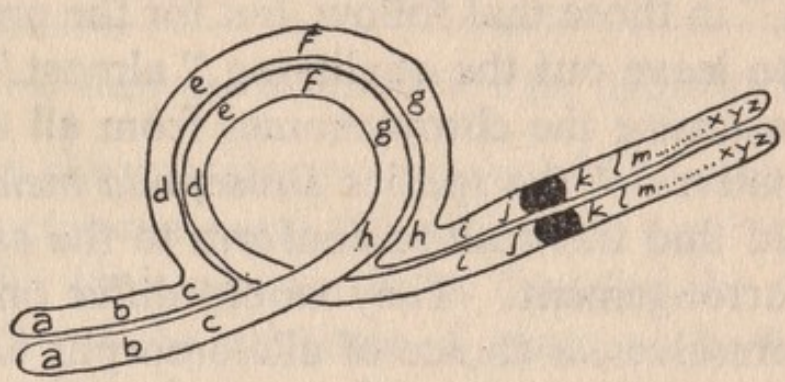
decades, and its usefulness as a foundation for new interpretations of genetical experience makes it unlikely that future investigations will ever contradict its basic assumptions.

The chief of these is that the genes are arranged in linear order in the chromosomes, as one might write *abcdefghi . . . xyz*, and that usually when the chromosomes reproduce themselves by splitting, the two daughter chromosomes have identical arrangements of genes, which lie side by side $\begin{matrix} abcdefghi \ . \ . \ . \ xyz \\ abcdefghi \ . \ . \ . \ xyz \end{matrix}$ when the split first occurs. The position which a particular gene occupies in a chromosome is called its *locus*; in a corresponding locus on the homologous chromosome one may find the same gene or some allelomorph of it. Thus any one of a series of allelomorphs may occupy the same locus in a given chromosome, and at meiosis a pair of allelomorphs are brought together when the chromosomes pair. One might compare the homologous chromosomes to two tape-measures: when they are laid side by side the gene loci lie opposite one another, just as each number on one tape-measure lies opposite the same number on the other. This means that the attraction between homologous chromosomes seen at meiosis must take account of the arrangement of genes on each, otherwise they might come together:

abcdefghijkl . . . uvwxyz
zyxwvutsrqpo . . . fedcba

The simplest assumption to explain what happens at chromosome pairing is that the allelomorphic genes attract one another, although we have very little idea

of the nature of the attraction. This assumption is confirmed by the discovery that where portions of a chromosome are reversed—as, for example, *abcdefghijk . . . uvwxyz* might become *abchgfedijk . . . uvwxyz* —the pairing chromosomes make up this configuration:



If, as sometimes happens, a chromosome is formed from broken pieces of two different (not homologous) chromosomes, it will pair with the corresponding part of either homologous chromosome. So at meiosis a chromosome of this kind is seen " paired " with *two* other chromosomes, thus:

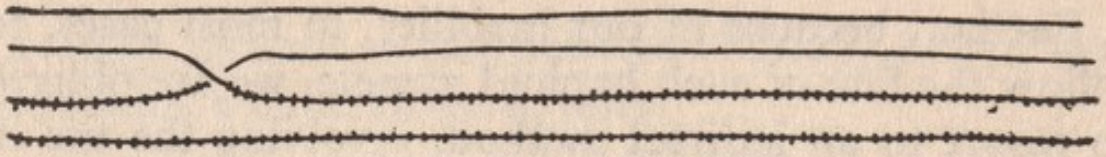
We have noted already that all members of a species have the same chromosome complement, a characteristic number, and characteristic shapes of chromosomes. We may now go farther and say that (according to the hypothesis we are discussing) each of these chromosomes has a characteristic plan, according to which its gene loci are arranged. If, for example, we were able to identify a gene by looking at it through a

microscope, we should see that the gene for Bar eyes always occurred at a particular point on the chromosome of Drosophila, and that genes for forked bristles and fused wing-veins lie near it on either side of it. (We shall find it necessary in a later chapter to modify the " always " in the last sentence and the implied " always " in those that follow, but for the present it is simpler to leave out the qualifying " almost.") If we were to examine the chromosomes from all the living representatives of the species *Drosophila melanogaster* we should find them all to conform to the same plan of gene arrangement. They would differ only in the *genes* themselves, a choice of allelomorphs existing at each locus. Most of the chromosomes will carry a majority of wild-type genes, and any particular chromosome will have, perhaps, one or two recessive allelomorphs. The species as a whole can be regarded as a collection of genes, most of them wild-type, each with its characteristic place in the chromosome complement.

The death of individuals will cause continual changes in this collection, so that the species will never be quite the same thing from one day to the next. What will preserve its uniformity is, on the one hand, the existence of a " working majority " of genes of the wild-type—that is, which determine the characteristics of the type-specimen of the species—and on the other the constancy of its chromosome complement and of the arrangement of genes within the chromosomes. What happens when this arrangement is disrupted we shall see in later chapters.

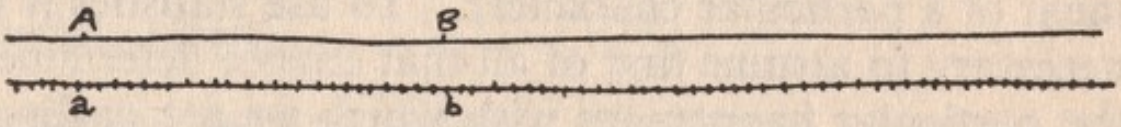
The second assumption made in the chiasmatype hypothesis is that often two of the four chromatids

formed at meiosis break between the loci of particular pairs of adjacent genes and, instead of rejoining to give the original chromatids, swap partners, thus:

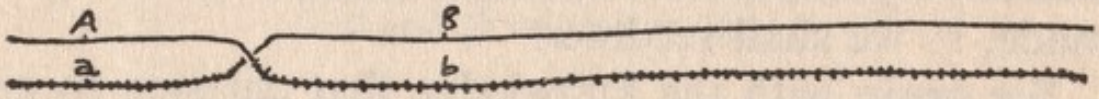


(No centromeres drawn here for simplicity.)

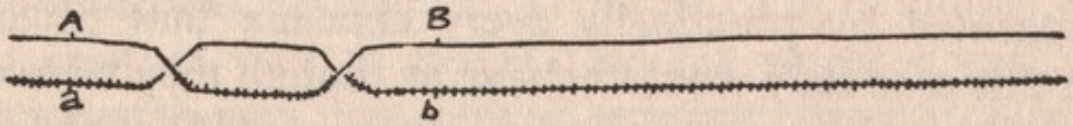
If the two chromatids are identical (they may be from the same chromosome) this swap will not be noticed. In fact, for the exchange to be detected the geneticist must know of the existence of genes on *both* sides of the point of breakage, and these must be present in the heterozygous condition. Thus an exchange between



giving



would be shown genetically as crossing-over between the genes *a* and *b*. It will be noticed that *two* exchanges taking place in the segment of chromosome between *A* and *B* would not be detected, thus:



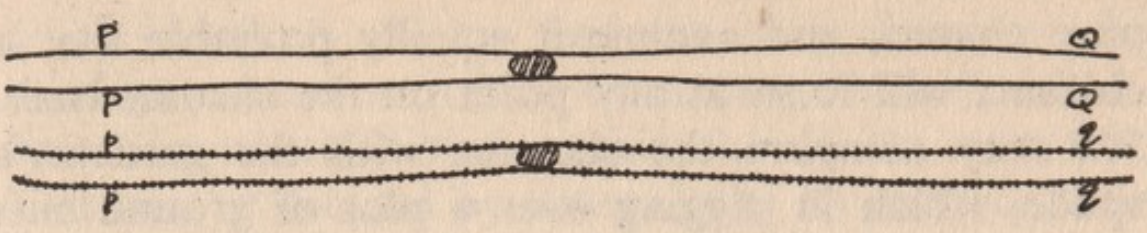
The importance of this tedious exploration of possibilities is that in crossing-over can be found a clue to the order and position of the genes within the chromo-

some. We have no way of recognizing the genes by sight, let alone distinguishing between allelomorphs; consequently, any clue, however unsatisfactory, is welcome.

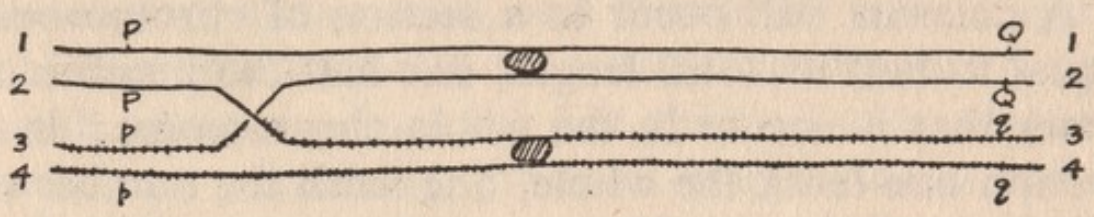
Further, because of our inability, in most cases, to follow the fate of each haploid gamete, we are obliged to resort to an indirect method, involving the use of statistics. Statistics are the mathematics of chance happenings, such as the combination of gametes in the F_2 generations we have already discussed, which can be tested mathematically to distinguish between ratios of the expected types that are the result of chance variations, and ratios that mean that the initial assumptions are incorrect (for example, that two gene pairs and not one might be responsible for the development of a particular character). To use statistics it is necessary to assume first of all that chance determines the particular happenings with which we are dealing. If it later appears that chance plays a major, but not an exclusive part, then suitable modifications must be made, as we shall see later.

We begin with the knowledge that chiasma formation is comparatively frequent, at least one chiasma being seen in most chromosome pairs at meiosis, often three or four.

If two genes are at opposite ends of a long chromosome it seems reasonable to assume that they will be separated by practically every chiasma that occurs. In this case they would behave as though they were on separate chromosomes—i.e., they would show no linkage at all. Let us look once more at the four chromatids of meiosis, considering this time genes *P*, *p* and *Q*, *q* at extreme ends of the chromosomes:



If a single chiasma occurs between *P* and *Q* two of the chromatids will be affected, thus:



and the chromatids will be of four kinds—*pq*, *PQ*, *Pq*, and *pQ*. In other words, 50 per cent of the gametes will show recombination. If another chiasma now takes place we can draw up a balance sheet of its possible effects:

Between 1 and 2 no change.
„ 3 „ 4 „
„ 2 „ 3 original positions of *P* and *Q* restored.
„ 1 „ 4 a second chromatid showing crossing-over of *P* and *Q* will be produced.

Taken together, if each is equally probable, the net effect of a second chiasma is to leave the situation unchanged, so that the greatest possible percentage of recombination (on the average) shown by genes at opposite ends of a chromosome is 50 per cent. (A recombination percentage of 50 per cent, of course, is just another way of saying that the genes *P* and *Q* behave as though they were on separate chromosomes.)

In considering the effect of chiasmata on genes which are separated by a distance less than the whole length of the chromosome, we invoke the operation of

pure chance, and assume it equally probable that a chiasma will form at any point on the chromosome. We may compare the chiasma with the gardener's spade, which in digging over a plot of ground cuts worms in two pieces entirely at random, sometimes producing two nearly equal pieces, sometimes two very unequal ones.

A chiasma will occur in a section of chromosome equal to half its total length, one-half the number of times that it occurs in the whole chromosome; in a section one-tenth the whole, one-tenth the number of times; and so on. Consequently, if two genes are separated by (say) one-tenth of the total length of the chromosome, one chiasma in ten will occur between them (on the average), and half this number of gametes will show recombination (because the other two chromatids of the four are unaffected).

The bigger the distance between the gene loci the greater the chance of recombination, up to the 50 per cent maximum. (Also, of course, the greater the chance of *two* chiasmata between them. This can be allowed for, mathematically.) This relationship has been used to construct *chromosome maps*.

Each chromosome is represented by a line, and the position of various genes is marked along it in units equivalent to a 1 per cent recombination frequency. This means that loci 1 unit apart show 1 per cent recombination. In the example quoted in Chapter IV the recombination frequency is about 12 per cent, so that the two genes are mapped about 12 units apart on the second chromosome.

We will have, at first, no idea where to put our two genes on the line, nor even which end of the chromo-

some is which. If we find the map distance of a third gene from one of the other two, we shall still not know in which direction this should be measured. This can be decided by determining its distance from both genes.

It can be imagined that all the crosses necessary to establish the map of a single chromosome will constitute a formidable total, and that in its early stages a chromosome map will be a very sketchy affair, with small sections completed but their relative positions unknown. Similarly, the exact map distances will be adjusted as more data accumulate and the statistical correlations can be made. A most odd feature of this map-making is that the chromosomes of a species can be mapped without being identified under the microscope; thus we could say that twenty genes occurred in the same chromosome, and were arranged in a particular order of spacing, without being able to point to the actual chromosome involved. In certain cases, as in the sex chromosomes, we have a ready method of identification (see Chapter IX), but in other cases we have to await the appearance in the chromosome of some physical abnormality which also shows itself genetically.

Maps have been compiled for all four chromosomes of *Drosophila melanogaster* and for the ten chromosomes of maize, but in many organisms—for instance, in man—the data so far accumulated are not sufficient to permit the establishment of the number of linkage groups, let alone a mapping of the chromosome.

Before leaving this subject it is necessary to point out that an even spacing of loci on the map does not necessarily imply that the genes are spaced evenly in

the chromosomes. The contrary assumption that a bunching to one end of the map represents a bunching of genes is equally doubtful. This is because the mathematics has been done on the assumption that chiasmata can occur at all points in the chromatids and that they were equally frequent at all points. Cytological examination, in fact, suggests that crossing-over occurs more frequently in some parts of chromosomes than in others, and that some chromosomes regularly carry more chiasmata than others. The former will make genes which are regularly spaced in the chromosomes appear irregularly spaced in the maps, and the latter will make the maps relatively longer in terms of units. It is as though a traveller across a large city judged the distance he had travelled by the number of changes of bus he had made. By looking at the punch-holes in his tickets he could tell the order of the places through which he passed, but unfortunately the bus companies charge different rates for journeys by different routes, so that a twopenny ticket pays for a mile's ride on one bus and for three miles on another. He might think it probable that total fares of three shillings on one occasion represented a longer journey than one-and-sixpence worth on another, but he could not be sure without some other terms of reference.

Although, as we have seen earlier in this chapter, the biggest possible average recombination value is 50 per cent, this does not mean that all chromosomes are 50 units long, or shorter. By adding together smaller distances one can build up map lengths within which several chiasmata can occur. Many chromosomes (three out of four in Drosophila) are already known to

be more than 50 units long, and some have been found of nearly 200 units.

The methods used to establish the identity of these genetical maps with the chromosomes seen under the microscope, and the methods by which the size of genes and therefore the approximate number of genes for which there is room on a given chromosome complement have been estimated, but must be left for a later chapter. *Here in recapitulation it is necessary only to stress the importance of the conception of the chromosome as a thread-like structure, carrying at fixed positions along it the genes which are responsible for the transmission of hereditary characters. In most of what follows this conception is implicit, and without it any attempt to unravel the complexities of inheritance would be indescribably difficult.*

CHAPTER VII

GENES IN ACTION

THE gene, in previous chapters, has been described mainly indirectly by its expression in the phenotype or by its behaviour as a part of chromosome structure. Having got this far, it is only natural to ask *whether the gene can be seen in the chromosome and how it determines the nature of the adult organisms.*

One is used to the idea of adaptation to function. The limbs of a mammal may be modified for use in swimming (as in the seals or whales) or for flying (as in bats), and it is possible to make a good guess at the function of such an organ from an examination of its structure. Occasionally, of course, a careful study of the animal or plant in its natural habitat is necessary before this can be proved. So far, in our examination of the cell, we have seen the nucleus as a mechanism for the sharing of the nucleoprotein and associated substances, the splitting and pairing of the chromosomes having an essential part in this.

In the case of the internal structure of the chromosomes we have already some idea of function, but little of structure. It is as though we knew that a particular animal excavated tunnels in the soil but could not decide exactly how this was done, because none of the usual adaptations for digging were discernible, and the animal refused to dig if kept under observation. For the chromosome we have a theory that it carries particles of inheritance arranged side by side throughout

its length; a theory by which many of the results of experiments in animal and plant breeding can be explained. How is the structure of the chromosome adapted to carrying hereditary units? How are they reproduced when the chromosome splits? What are the special relations between allelomorphs? Why does one often dominate the other when they are both present in diploid cells? How do the genes exercise their influence on the cells in which they occur? These are but a few of the questions which arise.

The most elementary question is whether one can see anything which might correspond with the gene *arrangement*. In following the phenomena of mitosis and meiosis, we have seen that the chromosomes appear as thin threads, carrying bead-like chromomeres at intervals throughout their length. By one of the most fortunate accidents in the history of any science, Drosophila (like other Diptera) happens to develop a peculiar type of cell in which the chromosomes exist more or less permanently in this state. The organs in which they occur, the salivary glands of the larva, appear to grow in size, not by the multiplication of their constituent cells, but by their *enlargement*. The cell nuclei also enlarge and contain correspondingly enlarged chromosomes. These are so big that if one represented the normal metaphase second chromosome by a small " i " on this page, its homologue in the salivary gland cell would be 15–20 inches long. The chromosomes are paired, as if they were at an early stage of meiosis, showing the normal haploid number of pairs; but during the subsequent metamorphosis (by which the adult fly is produced) the

cells in which they are contained break down, and, in fact, no division ever takes place.

We thus have in these chromosomes what amounts to enlargements of the ordinary *somatic* (body-cell) chromosomes, although we cannot be certain that they represent *exactly* their smaller prototypes in the original zygote. For instance, we should not be justified in referring to them as undergoing the first stages of *meiosis*, because in the Diptera generally there is always a tendency of the homologous chromosomes to associate closely. This is called *somatic pairing*, to distinguish it from the close pairing at meiosis which is universal in the higher forms of life (see Chapter X).

After making these allowances, the salivary gland chromosomes still offer an exceptional opportunity for the study of chromosome structure, all the more useful because they are present in Drosophila, the geneticist's best friend. When examined in the living state, or in stained preparations, these giant chromosomes are seen to possess a banded structure. The bands, discs seen edgeways on, are of varying thickness, spaced at varying intervals, and the width of the chromosomes also varies from point to point, so that characteristic bulges often coincide with a particular arrangement of bands.

The particular orders of thick and thin, widely and closely spaced, bands are the same for the same chromosome pairs from different cells; or, to put it another way, these arrangements are specific for a particular chromosome of the haploid set. Since each gene is assumed to occur only once in each haploid set, and the gene *order* of a particular chromosome to be constant, the genes have what would seem to be more

than an accidental resemblance to the bands. From the chemical point of view these bands correspond to the points at which nucleoprotein is concentrated.

The chromosomes lie in a tangle in the salivary gland cells, but the pairing of homologues is more or less complete. This pairing is between similar bands in the two chromosomes, suggesting that a special affinity exists between them. Once again this would fit in with the assumptions made earlier that allelomorphs occupy similar positions in the homologous chromosomes and lie in contact at meiotic pairing. If therefore a band were in some way removed from one of the pair, one would expect a slight buckle in the other at this point. If a portion of a chromosome were taken out and turned round so that it " read " from right to left, instead of from left to right, it should produce some detectable alteration in the pairing over this region.

Thus the discovery, made a little over ten years ago, that these structures in the gland cells were chromosomes had a tremendous significance for genetics, and immediately suggested the possibility that each band corresponds in some way with a gene. If this were true it has been estimated that *Drosophila melanogaster* would possess a total of nearly 4,000 genes.

A second way of approaching the question of the nature of the gene is to ask the question: What does it do? The answer obviously falls under two headings. In the first place the gene grows and divides in intimate relation with the dynamic internal activity of the cell, so that every cell of the organism, except the gamete, carries a duplicate of it; in the second place, it influences the activities of the cells in which it finds itself.

The first statement is not quite true, because if it were so it would be very difficult to explain the existence of allelomorphs, even if the existence of many thousands of genes for each species was taken for granted. These allelomorphs, with which geneticists (including Mendel) have worked, were " discovered " in the original wild population and often retained to the virtual exclusion of the wild-type alleles. For example, albino strains of rabbits or rats have been maintained for generations, although the gene for albinism is a recessive and would show in a wild population only when, by chance, an individual became homozygous for it.

The idea of a wild population with a certain proportion of individuals heterozygous for particular genes has been explained in terms of chromosome structure in Chapter VI. Here we are looking for the *origin* of these comparatively rare alleles. In particular, because of the overwhelming evidence for an evolutionary process leading to our present-day wild species, it seems likely that *new* characters have been acquired by organisms in the past, and although this does not *necessarily* mean the acquisition of new genes (it could mean the creation of new combinations of pre-existing genes), it is difficult to believe that all living creatures are the results of countless re-arrangements of an eternal, unchangeable, set of genes.

Fortunately, the question whether the gene is unchangeable or not has been decided in a very direct way. In the many thousands of generations of Drosophila raised experimentally it has occasionally happened that an individual has appeared showing a character not carried by either parent. *The process is*

called " mutation," but it would not have been practicable to study it extensively unless a method of increasing the number of mutations artificially had been discovered. The organism showing such a changed gene is called a *mutant,* and the changed gene is called a mutant gene.

Because the various recessives known from breeding experiments are presumed to have arisen originally in this way, the term " mutant " is sometimes used loosely to indicate all deviations from the wild-type allele. Some genes seem to mutate more frequently than others (a particular mutating gene was studied in maize thirty years ago), but it was not until *Muller showed in* 1927 *that treatment with X-rays speeded up the rate of mutation* in Drosophila that the subject could be studied as a general phenomenon. Even under the influence of X-rays, rays from radioactive elements, ultra-violet light, increased temperature, certain chemical agents, and so on, some genes are less prone to mutation than others, but the field of investigation has been immeasurably widened by employing such treatments.

As will be seen later, the explanation for mutations, as they are seen in the resulting *phenotypes*, can include several changes in the chromosome only; but here we are concerned with the effect on single genes. The nature of the action of, for instance, X-rays is probably that they produce chemical changes in small regions of the chromosome, and these are sufficient to alter the gene which occupies that locus. It is possible to make an estimate of the size of the structure that is affected from the dose of X-rays which is needed to produce a mutation, assuming that a single alteration of its

chemical structure is sufficient. This is roughly equivalent to deciding the size of a target by dropping bombs at random over the target and its surroundings and seeing how many bombs are needed, on the average, to hit it. Thus, if the target is only one hundredth of the area bombed at random, on the average only one in every hundred bombs will hit it. The sort of size which is calculated for the part of the chromosome carrying the gene is not greater than the space occupied by one band, although it may be somewhat smaller; a nucleoprotein molecule of this size would compare with the plant viruses, which can be seen clearly with the electron microscope but not with the ordinary light microscope.

The evidence from mutations is therefore of two kinds: *on the one hand it suggests that the gene is not immortal, although on the whole it reproduces itself with a fair degree of reliability, and that a chemical change in the part of the chromosome where it is situated will convert it to an allelomorph; on the other it gives an independent estimate of the length of the chromosome occupied by the gene.*

Next we may consider the nature of the effects which the gene produces, as a possible clue to the nature of its action in the cell. In doing this we must avoid the conception of the gene acting independently of its surroundings. Obviously if the environmental conditions are adverse enough the organism will not survive and a particular gene may never find its expression; similarly the presence of other genes may, in the extreme case, lead to early death, or in others reduce considerably the chances of the gene producing its full effect.

The early work on genes was done with characters which are easily recognized in the organism concerned —as, for instance, pigmentation (of the petals in plants, of the eyes in Drosophila)—and at first it was thought that a single gene could be associated with a single colour change. It soon became apparent though that more than one gene might be acting. Thus in the sweet-pea it was found that when two white-flowered plants (Emily Henderson) were crossed (because they had pollen grains of different shapes) the F_1 was purple. This was because *two* different dominant genes are necessary for colour production, and each must be present at least once. Each white parent carried one of the genes in the doubly dominant, the other in the doubly recessive, condition. Representing the dominants as *C* and *R*, the parents were *C*/*C r*/*r* and *c*/*c R*/*R*, the F_1 being *C*/*c R*/*r*. In other plants more than two genes have been found necessary for colour production, and in maize at least *eighteen* dominant genes are needed to ensure the production of yellow pigments and chlorophyll in the plastids.

In Drosophila the cross of a true-breeding white-eyed strain (recessive *w*) with a true-breeding vermilion-eyed strain (recessive gene *v*) gives an F_1 with the wild-type eye colour. Here the parents are *w*/*w V*/*V* and *W*/*W v*/*v* and the F_1 is *W*/*w V*/*v*. In the white strain the vermilion gene has no effect even if present in its dominant form. In other words, at least two dominant genes are responsible for the normal wild-type eye colour. In this way even the "simple" character differences can often be broken down to smaller differences which may have no effects *singly* on the phenotype. For such reasons as these care must

be taken not to confuse the condition where a gene is not expressed with its recessive condition. In the former case the reasons for its failure to show in the phenotype lie primarily in conditions *outside* the gene; in the latter case they lie primarily within it.

It does not follow, however, that a single recessive gene can never show itself in the organism possessing it, nor in fact that the heterozygous condition is always phenotypically the same as the homozygous. The evidence for this falls under two headings.

The first is the existence of *phenocopies* of dominant genes. By a phenocopy is meant an organism made to resemble one *genotypically* different by submitting it to some change of environment. It must be distinguished from the mutant which is produced by X-ray treatment of the germ cells of one of its parents.

Among the earliest and most striking phenocopies were those produced in the common Small Tortoiseshell butterfly. The wing-pattern was found to alter if the chrysalids were subjected for a period to temperatures higher or lower than that at which they usually develop. Cold produced a pattern resembling that of a related species found in Lapland; heat that of a Sardinian species. Similarly by the use of heat the Central European form of the Swallow-tail butterfly was made to resemble species found in Syria and Turkestan.

More interesting for our argument, however, is the case of vestigial wings in Drosophila. Here it was found that by raising the temperature in which the larvæ developed, the wing-size could be increased in flies homozygous for the recessive " vestigial " gene. In males the wing-length could be increased nearly

three times by raising the temperature by 13 degrees centigrade. This case is of exceptional interest because *vg* is one of a series of several alleles occupying the same locus in the second chromosome. These *multiple alleles* show graded effects on the adult wing, varying from a slight *nick* in the top of the wing to no wing worth mentioning. The many combinations of the alleles which are possible give a complete series of wings, progressively reduced in size and changed in shape. Vestigial is not quite at the end of the series, which is occupied by " no-wing " (meaning a tiny rudiment with no internal structure); the effect of increased temperature is to make the wing " ascend " the series until it reaches the nicked stage. At the temperature required to do this a general adverse effect on the organism intervenes and it is not possible to take the final step to a normal wing. The general effect of increased temperature is thus to reduce the effect of the possession of the two vestigial genes and make the wing more like the normal wild-type.

The opposite type of effect is seen in the " Himalayan " rabbit. The gene responsible for this condition—in which a rabbit, in other respects resembling an albino, has black tips to its nose, paws, ears, and tail—is probably an allele intermediate between wild-type and albinism. Rabbits homozygous for the Himalayan coat develop no black pigment unless the temperature of the skin drops below 33 degrees centigrade (see Chapter IV). Those heterozygous for Himalayan coat and albinism require a lower temperature still. Consequently, the pigment develops only in the parts of the body where the skin temperature is low—i.e., at the extremities. Here the effect of

increased temperature is to shift the effect of the gene *away* from the pigmented wild-type.

These examples serve to show that the expression of a gene can be modified by changes in the environment of the individual carrying it ; they also suggest that dominance is not necessarily complete or unchangeable. This was known already from straightforward genetical experience. A familiar example is that of the Blue Andalusian fowl (quoted earlier), which is a heterozygote. When mated together, " blue " birds produce black, " blue," and white offspring in the expected ratio 1 : 2 : 1—i.e., neither black nor white is dominant. Many other examples could be cited, in which the heterozygous form is intermediate; in some of them it is possible to measure the effect of the single dominant gene, as by number of facets in the compound eyes of Drosophila or the shape of starch grains in the seedlings of peas.

A peculiar phenomenon is the change in dominance seen in some organisms. Thus from a crossing of red and yellow snails young snails are produced which at first are yellow but later become red. In a certain moth the crossing of races having caterpillars with transparent and pigmented outer skins respectively gives caterpillars which have transparent skins to begin with but later develop pigmentation.

Finally, we must mention the phenomenon of *penetrance*. Certain genes in the homozygous condition do not exert their characteristic effects in all individuals but only in a certain percentage of them.

All these aspects of gene expression demonstrate that dominance has not the hard-and-fast meaning which was originally attached to it. This conclusion

leads to the conception of gene action as *quantitative* in character, particularly when multiple alleles are considered, the dominant allele exerting more effect than the corresponding recessive, but the effect of both capable of alteration by suitable changes in the conditions of life of the individual concerned. Further light is shed on the interaction between genes at different loci by the observation that two genes, *Bar* and *Lobe*, which are dominant in *Drosophila melanogaster*, are no longer dominant in the offspring of crosses with the related species *D. simulans*.

The conception of genes as things controlling the rate at which things happen in the organism was introduced by Goldschmidt, who used the development of pigment in caterpillars (mentioned above) to support his idea. In axolotls and goldfish the *rate* of development of pigment cells is reduced by genes which give albinotic and transparent individuals respectively. In the fresh-water shrimp (*Gammarus*) a red-eyed form corresponds to an early stage in the pigmentation process in the normal eye, where the red substance changes through brown to black before the process is terminated; in the mutant the rate of development of pigment is slower and the adult eye remains red.

Goldschmidt has also interpreted the *vestigial* series in Drosophila as the effect of progressively earlier interference with the normal development of the wing, the allele with the most drastic effect coming into action earliest. The effect of a " tail-less " gene in mice could also be explained along these lines, degeneration of the primitive backbone beginning earlier in the homozygote and proceeding so far that normal development becomes impossible and the embryo dies.

In the heterozygote, which survives, the effect is confined to the tail and the hind limbs and is not lethal.

Closely related to the idea of genes controlling the rates of processes in the organism is the study of the effect of different doses of genes. An early explanation of recessive genes, put forward by Bateson, was that they represented the *absence* of the dominant gene; if this were the case the heterozygous form would carry one dose of the gene effect and the homozygous dominant two. This explanation cannot hold in the case of multiple alleles, such as the *vestigial* wing series or the eye-colour series at the *white* locus in Drosophila, because it allows for only one recessive to each dominant. It seems much more likely that the recessive gene is relatively less active than its dominant allele, perhaps to the point of inactivity, but not necessarily so. Experiments have been carried out in which the small fourth chromosome of Drosophila was incorporated one, three, and four times in the otherwise diploid complement of chromosomes, instead of the usual twice. Under these conditions the effect of a recessive gene (*shaven*) in the chromosome varied. When present once its effect (the removal of bristles and hairs) was more pronounced, but in doses higher than normal the flies approached the dominant wild-type more closely. This would suggest that the gene represented a form of the dominant with reduced activity. That all genes found at the same locus may not have identical activity is suggested by some other experiments with Drosophila. White-eyed mutant flies are relatively frequent in occurrence, but when these flies, which are homozygous for a recessive gene, are crossed with apricot-eyed flies, which are homo-

zygous for another recessive gene at the same locus, they do not all give the same eye-colour in the F_1.

In plants the endosperm, as was mentioned earlier, is *triploid*—that is to say, it contains three haploid sets of chromosomes: one from the male parent and two from the female. " Waxy maize," in which the starch of the kernels stains red with iodine, is due to a gene recessive to the normal one for blue-staining starch. By suitable crosses it is possible to get endosperm carrying three recessives (self-fertilization of waxy plants), two recessives (waxy ova × normal pollen), one recessive (normal ova × waxy pollen), or no recessives. Of these only the first is of the waxy type, showing that one normal gene can " dominate " two recessives. On the other hand, when one considers the dominant gene giving yellowness in the endosperm, there is a steady increase in the amount of vitamin A (part of the yellow pigments) for each increase in the number of " yellow " genes. Thus, while the triple dominant contains an appreciable amount of the vitamin, the endosperm with two dominants has only two-thirds of this, that with one dominant one-third, and the triple recessive (white) endosperm less than a hundredth.

From these and many similar results it is clear *that the effects of many genes have a quantitative aspect and that many recessive genes represent a reduced activity of the corresponding dominant allele.* One obvious question remains: What happens if a gene is omitted altogether?

This can best be studied in Drosophila, where it has been shown, for instance, that the removal of certain short sections of the *X*-chromosome always coincides

with the removal of the wild-type allele at the *white* locus. This was discovered by examination of the salivary gland chromosomes of progeny from X-ray-treated males, the genetical effects being checked by suitable breeding tests. In addition to showing a definite correlation of a particular gene locus with a particular band structure in the chromosome, this kind of experiment makes it possible to distinguish between the genetically observed *change* in a gene, a gene mutation, which cannot be detected in the salivary gland chromosomes, and the loss of a section of the chromosome, a *deletion*, which results in a loss of bands, and a fault in the pairing of the homologous chromosomes. Many deletions have been detected in this way; most of them lead to the death of the zygote carrying them, even in the heterozygous condition, when the homologous chromosome is still intact, but some small deletions are not lethal and have distinct phenotypic effects.

It follows, of course, that after meiosis the chromosome with a deficiency is left on its own and half the gametes will carry it. They are therefore as badly off as a zygote homozygous for the deficiency, and in higher plants, where the male gamete is in effect a separate generation, it is unusual for a deficiency to survive this stage. Similarly, it is unusual for a zygote homozygous for a deficiency to survive, although one or two such cases are known (one including the loss of a known gene, *yellow*) in Drosophila.

In general we may say that *the complete loss of a gene has a deleterious effect* and is not to be compared with the homozygous recessive state. An organism which has lost completely more than a few gene loci in this

manner will probably not live, although an organism heterozygous for the deletion may survive. Thus a small deletion will show as a *recessive lethal.* Losses of more than fifty or so salivary chromosome bands have not been seen, and it is assumed that these are lethal even in the heterozygous state—i.e., are *dominant lethals ;* their existence in cells treated with X-rays can be inferred from other chromosome changes which take place.

Summing up, we can find evidence that the genes may correspond to the bands in the salivary-gland chromosomes, to structures of the size of large filter-passing viruses. Their actions may be so limited in scope that many genes are needed to accomplish the synthesis of a single chemical substance, like chlorophyll. They are self-perpetuating, but not infallible in this respect, mutations sometimes occurring, usually to a recessive form. Their effects can sometimes be paralleled by suitable treatment of a different genotype, and in this way dominance can be reduced or enhanced. Several alleles of a particular locus may exist, giving a graded series of characters, and increasing dosage of a particular gene, whether recessive or dominant, may lead to increasing effects in the individuals carrying them. Finally, the elimination of the section of a chromosome carrying a particular gene does not lead to the kind of results which follow mutation from dominant to recessive, but to a position in which homozygosity may cause death or, at the best, reduced chances of survival.

Above all, the possession of a particular gene does not lead automatically to the appearance of the character associated with it, but merely confers on the individual

the capacity to develop this characteristic when placed in a suitable environment. Putting it very crudely, the genes determine the potentialities of the organism; the environment decides which of these shall be realized. Gene and environment, of course, could not exist and act in such isolation as this statement suggests, as we shall see in the next chapter. The two factors are opposites in the sense that when the environment varies the genotype puts a limit on the variability of the organism, or alternatively, when the environment remains constant the gene has still the capacity for variation.

CHAPTER VIII

THE GENE AND ITS RELATIVES

ONE of the features of gene action which attracted attention very early was the association of genes with simple chemical changes in living organisms. The biochemist has demonstrated amply that such changes, involving usually a single step from one chemical structure to another, are brought about through the action of *enzymes*. These substances make possible chemical changes that could not otherwise take place in living tissues. The amount of an enzyme present can determine the rate at which the chemical change proceeds. *Thus the attractive theory presented itself that the genes were themselves enzymes, or at least responsible for the production of particular enzymes, and in this way influenced single steps in chemical processes, either by making them possible or by controlling the rate at which they took place.*

One of the pieces of evidence which supports this idea is the discovery that in *albino* varieties of animals the formation of black pigment from a colourless substance called *tyrosine* does not take place because the enzyme necessary for it is not present in the appropriate tissues. Consequently, although the raw material for pigment production is present throughout the body, no means exist to convert it to the finished product in the skin and the eyes. The skin remains white, and the colour of the eyes is simply the colour of the blood circulating through them, pink. On the

other hand, in *dominant* whiteness (as opposed to albinism which is recessive) the enzyme *is* present, but in addition there is a further substance which prevents it from acting.

There are several conditions, ascribed to the presence of recessive genes, in which the human body fails to deal with a single food constituent in the normal way. Thus, a substance related to tyrosine, *phenyl-alanine*, is normally used up completely by the tissues of the body and converted to carbon dioxide, water, and ammonia; but certain individuals fail to complete the process and the partly-changed substance is excreted in the urine, presumably because one or more enzymes is missing. Again, in most dogs the products of breakdown of nucleic acids include the substance *allantoin*, which appears in the urine. In the Dalmatian coach-hound (or plum-pudding dog) the process is not carried as far and *uric acid* is excreted. Here the enzyme responsible for converting uric acid to allantoin is missing (as it is in man and his near relatives among the apes), the gene corresponding to its absence being a recessive one.

In plants the chemistry of flower pigmentation has been extensively studied and the changes produced by the presence of certain genes reduced to chemical terms. It has already been noted above that more than one gene is needed for purple wild-type colour in sweet peas. The genes *C* and *R* are needed before any of the coloured *anthocyanins* are produced, and without them the flowers are white. In the absence of two other dominant genes there are no *anthoxanthins*, practically colourless substances which act as *co-pigments* in the wild-type flower, modifying the petal colours produced by the anthocyanins and making them

fast to sunlight. The anthocyanins, if they are present, then give the flowers a maroon colour, which fades in sunlight. If another dominant gene is missing the kind of anthocyanin produced is different (by the loss of a single chemical grouping) and the flowers are red. Absence of this and another dominant gene leads to the absence of a further grouping in the anthocyanin molecule, and the flowers are salmon pink. To these one must add genes which alter the amount of pigment produced, or its distribution in the petals, and others which reduce the acidity of the petal sap, making the pigment more blue.

Investigations of this type have been conducted on the flower colour of several garden plants, and Haldane has classified the genes on the basis of their chemical effects, showing that for certain types of chemical change the dominant gene tends to make the flowers more blue, as by decreasing the acidity, while for others, as by increasing the production of co-pigment, the dominant tends to make them more red.

By far *the most direct evidence for association of genes with enzymes has been obtained with micro-organisms*, in particular with yeasts and fungi. The method of inducing mutations by ultra-violet light has been applied, particularly to the fungus *Neurospora sitophila*, and in this way a large number of mutant forms has been produced. Because many micro-organisms are single-celled and do not show the elaborate division of labour among different tissues seen in multi-cellular organisms, their most characteristic features, apart from their shape and life-history, are the chemical changes which they bring about; for example, the yeasts have long been known for their

capacity to ferment sugars to alcohol, and have been classified by their ability or failure to ferment *particular* sugars.

Both fungi and yeasts live by absorbing foodstuffs from their watery surroundings, having no mouths or digestive systems with which to tackle solid particles. It is therefore possible to grow them on solutions of suitable chemical substances, some inorganic, like sodium chloride or magnesium sulphate, others organic, like glucose. Generally speaking, wild-type *Neurospora* requires no elaborate foodstuffs for growth and reproduction, making what it requires from relatively simple compounds, but many of the mutants from X-ray treatment are found to have lost the capacity to make some essential substance for themselves. This has then to be supplied to the fungus before it can grow.

By examining the nature of the substances which have become necessary it has been possible to relate the gene changes to single steps in their manufacture. The loss of ability to carry out one such step will mean that the fungus mutant can take the process so far, the substance representing this stage in the synthesis accumulating in the culture fluid, but can go no farther. Thus in a process starting from *A* and going to *G* through *B*, *C*, *D*, *E*, and *F*, the fungus may fail to change *D* to *E*, and thus *D* accumulates; if *E* is supplied it can make *G* from that.

In addition to throwing light on the ways in which substances are transformed in the fungus, these experiments also pose a difficult question about the origin of such synthetic chains. If the organism needs *G* to form vital parts of its structure, how did it first acquire

the power to make *G*? If each step is controlled by a separate gene, as seems very likely, genes responsible for the whole transformation of *A* to *G* would have to be acquired simultaneously. The chances of this are astronomically small and nothing short of the whole set would be of any " use." It has therefore been suggested that the course of evolution has not proceeded in the direction here indicated, but that the ancestral organisms had an external source of *G* to begin with and later acquired the power to synthesize it, thus dispensing with the need for an outside supply. That is to say, from being dependent on an outside source of *G* they became independent of it, rather than doing without a supply originally and coming to need this when the necessary power to synthesize *G* had been subsequently lost. This is the more plausible explanation, because some of the substances concerned, the *amino-acids*, are so essential to life as we know it that it is difficult to believe that any living organism could ever have done without them. An alternative explanation would be that the capacity to synthesize a substance, and its incorporation in the vital structure of the organism, have developed by mutual interaction.

However, whatever conclusions can be drawn about the evolutionary history of Neurospora, there is no doubt that as it exists today it possesses many genes controlling its chemical processes, and that when these genes mutate under the influence of radiation the power to carry out specific chemical changes may be lost bit by bit.

In the yeasts both haploid and diploid cultures can be produced. The normal culture of a yeast contains millions of separate cells, all diploid in the *genetical*

sense (the chromosome structure cannot be made out), but under suitable conditions it forms haploid spores, presumably by meiosis. Each spore can be made to grow and divide, forming a population of haploid cells. These cells will show directly the effect of each gene they carry (just as a haploid pollen cell carrying the recessive gene for waxy maize has brown-staining starch, while that carrying the dominant has blue-staining starch), because there is no question of dominance or of a heterozygous pair of allelomorphs. Many experiments have been made which show that the genetics of yeast resemble those of higher plants and animals, segregation following the expected pattern.

Recent work has revealed a peculiar phenomenon which may throw considerable light on the mechanism of gene action. Although all yeasts ferment the sugar *glucose*, forming alcohol and carbon dioxide, the capacity of a particular culture to ferment other sugars, such as *galactose* and *melibiose*, depends partly on the yeast being previously grown in its presence. In this sense it is a phenotypic character, but it is gene-controlled in that some yeasts are capable of responding to the presence of an unfamiliar sugar by the formation of an *adaptive enzyme*, while others are not. This adaptive enzyme is required to ferment the sugar in question, so that a yeast which cannot develop the enzyme when grown in the presence of the sugar can never ferment it. The *capacity* to form an adaptive enzyme (from scratch) is thus gene-controlled.

Confirming this, it is found that a cross between a yeast which can adapt to ferment melibiose and one which cannot yields a diploid culture capable of

adapting to ferment the sugar, and of each four haploid spores produced by meiotic division in this culture two give haploid cultures which can adapt, two give cultures which cannot. In other words, the capacity to adapt is dominant over the failure to adapt, and shows the expected 1 : 1 ratio in the haploid " gametes." It was found, however, that when the spore formation took place in the presence of melibiose all *four* spores produced cultures capable of fermenting the sugar. If these haploid cultures were deprived of melibiose for a time, only two out of each four retained the ability to ferment it; the Mendelian ratio was restored.

The interpretation of these results is not easy, a possible explanation being that the adaptive enzyme is capable of reproducing itself as long as it is in the presence of the substances on which it acts. Whether this is correct or not, the fact remains that in these haploid cultures the enzymes required for fermentation of melibiose persisted in spite of the absence of the dominant gene responsible for their production. There would thus seem to be a more complex relation between gene and enzyme than has hitherto been suspected.

In the same field of biochemistry the discovery of the " transforming factor " for pneumococci, and the recent work on plant viruses, may also help in the understanding of gene action.

The bacteria called *pneumococci*, responsible for pneumonia in man and other animals, can be divided into groups (called Type I, II, III, etc.) according to the differing chemical nature of the capsules which surround the cells. The capsular substances are

complex materials made up of simpler sugar units. They are found only in " smooth " cultures of the bacteria (so called because when growing on the surface of a nutrient medium they form colonies with a smooth appearance). The " rough " strains lacking the capsular substance arise from the smooth when the bacteria are grown in the laboratory, and sometimes change back spontaneously into the smooth form, but always to the same type from which they arose.

Following some experiments made in animals, Avery and his co-workers managed to isolate from several types of smooth pneumococci, nucleic acids which had the property of transforming rough strains of several types to a smooth strain *of a type corresponding to that from which the nucleic acid was obtained.* (Several detailed points of their procedure are omitted in this description; they do not affect the main argument.)

The analogy here is obvious. It is as though specific genes which control the formation of the capsular substances in smooth strains were being transferred to the cells of a rough strain, converting them to whatever type the gene previously determined. It remains an analogy, though, because there is (as yet) no definite evidence for the existence of a sexual process in bacteria, and consequently no evidence for a genetic mechanism of the normal type.

The plant viruses, which are among the simpler viruses, are agents which carry disease from plant to plant. They are extremely small in size, and some of them, when isolated from infected plants, have turned out to be simply nucleoproteins. A minute amount transferred to a new plant leads to the development of

characteristic mottlings in the leaves, from which relatively large quantities of the infective nucleoprotein can be isolated. The virus has therefore increased in amount within the cells of the plant host, just as disease-carrying bacteria multiply in the body of their victim.

This multiplication of a specific nucleoprotein within the cells of the plant can be compared with the multiplication of genes which the cells also contain. In fact, the analogy is still closer, since by X-ray treatment one can obtain mutants of the virus, differing in infectivity and in the effects they produce. Unfortunately, as yet, there is little information about the ways in which the virus upsets the cells in which it finds itself; whether, for instance, it has some damaging enzymic action, or whether it simply throws the system out of gear by speeding up a chemical change which occurs normally.

On assembling these pieces of evidence we are inclined to suggest that *the gene is in some way connected with nucleoprotein in the chromosome, and that it produces its effect on the organism by its control over the production of an enzyme in the cytoplasm, but that in special circumstances nucleoprotein outside the nucleus can take over its function temporarily.* The gene, on this assumption, would have the power of self-reproduction regardless of whether the particular process which it controlled were in operation in the cell or not, in this way differing from the self-reproducing enzyme in the cytoplasm, which requires the constant presence of the substance on which it acts. Such a picture of gene action would help to explain why, although the gene is present in every cell of

the body, its effects may be limited to one or two tissues.

It would be dangerous, though, to get the idea that because genes have been *described* as responsible for single effects, such as a change in eye-colour or bristle length, their total effects are necessarily covered by this description. The gene vestigial in Drosophila, in addition to affecting the wings, alters the angle of certain bristles, causes the balancers to become rudimentary, prolongs the time of development, and decreases the general chances of life of the flies which carry it in the homozygous condition. The gene for red eyes in the flour moth has effects on the pigmentation of the male sex glands, of the skin and simple eyes of the caterpillar, of certain parts of the nervous system, and, in addition to weakening its constitution, *decreases* the time taken to develop to maturity.

Such multiple effects of a single gene may often be traced to a single primary effect. Thus the gene for " frizzle " in the domestic fowl causes an abnormality in the development of the feathers, which fail to protect the bird from cold as effectively as normal feathers, and a whole series of changes in bodily heat production, rate of heart beat, volume of circulating blood, and so on, can be traced back to the abnormal feathers. A recessive lethal which kills young rats appears to do so through its action on the cells which produce cartilage. These work overtime, and produce a whole series of abnormalities, including thickening and stiffening of the ribs so that they cannot assist in breathing, and the animals, which suffer from chronic shortness of breath, usually die from bleeding into the lungs produced by the violence of the efforts to breathe by means of the

diaphragm alone. The heart enlarges and more red blood corpuscles appear in the blood, apparently as an attempt at compensation for the small, inefficient lungs and the unsatisfactory breathing mechanism.

Multiple alleles may differ both in their effects on a single character and on the degree to which they influence other characters. Thus the wild-type gene *W* gives eye and testis colours in *Drosophila obscura* of red and orange respectively. The gene for eosin eyes w^e produces colourless testes, while with the gene *w* both eyes and testes are white.

An example of the phenomenon in plants is the connection between pigmentation and disease-resistance in the onion. Here the substance responsible for resistance to a fungal disease is chemically related to the pigments, and it seems plausible to associate both effects with the same gene action.

So, despite the variety of effects produced by a single gene, these may often be reduced to a single *primary* effect. Whether each primary effect can be reduced to a single enzymic process is for the future to decide.

We shall have to wait, too, for the explanation of gene *mutation* in chemical terms. *Tentatively, we might infer that chemical changes in both nucleic acid and protein components might lead to mutation, but whether we are to regard gene changes as superficial modifications of a large molecule, or as a radical alteration in its structure, is uncertain.* Nor can we say with any certainty why the removal of the gene, recessive or dominant, should have such deleterious effects.

In a later chapter some evidence will be presented

which indicates that the genes exert some effects on their neighbours, and that the activity of an individual gene alters if it is moved to a different part of the chromosome. This underlines the complexity of the gene, which, despite its powers of reproduction and its capacity to emerge unchanged from genetic combination, cannot in the last resort exist apart from the dynamic processes of the living cell.

CHAPTER IX

THE DETERMINATION OF SEX

ALTHOUGH it is possible to describe the behaviour of genes as though they were inherited independently of one another, in fact the *chromosomes* are the physical units which are shared out at cell-division.

Through the mechanism of chiasma formation the genes are given a certain measure of independence, but they may spend several generations with the same genes on either side of them, and often emerge from meiosis in chromosomes identical with that in which their "ancestors" entered it. Because we can watch the chromosomes with the aid of a microscope we can learn a good deal about their behaviour, and hence of the packets of genes which they represent. As we have already seen, the number of chromosomes in the nucleus is alternately halved and doubled through meiosis followed by fusion of gametes. In this chapter we shall trace the connection between this process and the phenomenon which in the higher plants and animals we call *sex*, beginning with its most primitive manifestation in the yeasts.

Here the haplophase cultures become diploid by the fusion of two haploid cells. This process does not occur often between cells originating from the same spore, so that a culture from a single isolated spore may remain in the haplophase condition for a good length of time. By growing it in the presence of another haplophase culture the formation of diploid cells may

or may not be induced; generally speaking, half the cultures tested will fuse with it and half will not. Most diploid cultures are heterozygous for a gene which controls the fusion, so that of the four spores produced at a meiotic division two are of one *mating type* and two of the other.

In Neurospora, which has a more complex life-history, the same condition exists, and haploid cultures of the two types (*A* and *a*) may be kept separate in the laboratory, growing vegetatively—that is to say, without meiotic divisions. On mixing cultures of the two kinds, cells from each fuse, and diploid structures with the constitution *Aa* are formed. These produce spores by the usual meiotic divisions, followed by a mitotic division of each of the four haploid nuclei, the divisions taking place regularly along a narrow spore sac, so that the origin of each spore can be traced. If there is no crossing-over between the centromere and the locus of *A*, the first meiotic division will separate them, and the final spore sac will contain certain spores arranged thus:

$$(\overline{A\,A\,A\,A\,a\,a\,a\,a}) \qquad \text{or} \qquad (\overline{a\,a\,a\,a\,A\,A\,A\,A})$$

If there is crossing over in this region, the arrangements will be:

$$(\overline{A\,A\,a\,a\,A\,A\,a\,a}), \qquad (\overline{A\,A\,a\,a\,a\,a\,A\,A}),$$

or

$$(\overline{a\,a\,A\,A\,A\,A\,a\,a}), \qquad (\overline{a\,a\,A\,A\,a\,a\,A\,A}).$$

Each spore can be isolated and the haploid culture from it tested to find the mating type to which it belongs. Thus in addition to verifying the existence of a gene

pair controlling cell-fusion, this examination of spores provides a convincing demonstration of the correctness of Mendel's idea of segregation of characters and also of the effects of crossing-over. Each *pair* of spores corresponds to one of the four chromatids in each bivalent at meiosis. Only one of the seven haploid chromosomes of Neurospora must be involved in this process of segregation of mating characters.

In these micro-organisms we have the beginnings of a phenomenon which in the higher animals and plants is called SEX. The essence of the sexual process is the alternation of haploid and diploid conditions of the cell nucleus, often with some mechanism operating to prevent haploid cells of identical genetical constitution from combining. Such processes probably occur in all but the simplest forms of life.

Yeasts spend the greater part of their life-history in the diploid stage, occasionally producing haploid spores, while Neurospora and many other fungi always assume the diploid form for the purpose of spore formation, but may be either haploid or diploid at other stages in their life-history. The moss plant with which we are familiar is a haploid stage, while in ferns the diploid stage is the one which attracts attention, the haploid stage being small and inconspicuous.

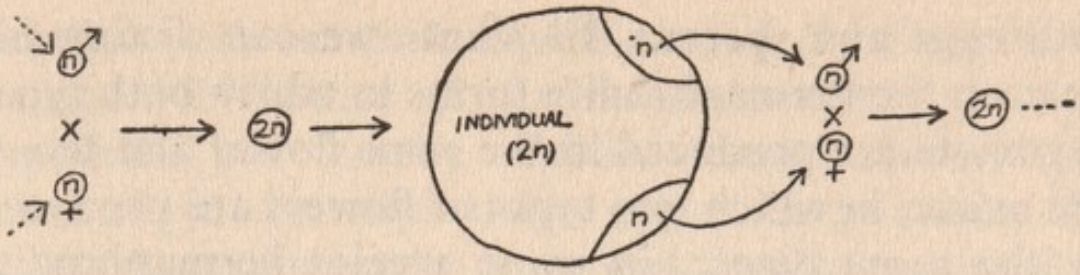
In higher plants the diploid stage is the conspicuous one, and the haploid stage is much compressed, being represented by a few divisions of the nucleus of the embryo-sac cell and by the germination of the pollen grain on the pistil. In animals the haploid stage is almost always restricted to a single cell, the gamete, and after fertilization the diploid state is resumed.

The transition from diploid to haploid is always

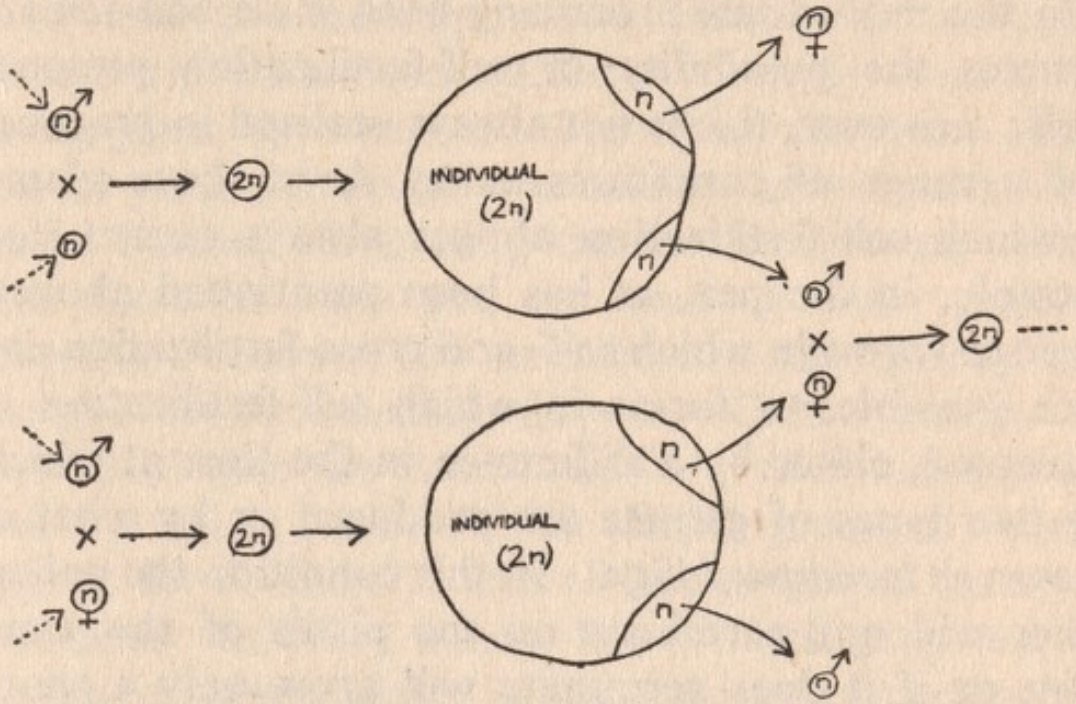
accomplished by meiosis, but occasionally, as in certain fungi, the two haploid nuclei do not fuse at once in the diploid stage, each cell being for a time effectively diploid through the possession of *two* haploid nuclei. In general, however, the change from haploid to diploid involves the fusion of two nuclei, as in the fertilizations which we considered in earlier chapters.

As a kind of division of labour, in the higher organisms the haploid cells which undergo this fusion (the gametes) are of two types, one comparatively immobile, carrying a store of foodstuffs for the zygote formed on fusion, the other active in finding its partner and often reduced to little more than a nucleus and some locomotory device. Conventionally the former is called the female and the latter the male, because in the higher animals the individuals producing the gametes are often similarly distinguished, the female being responsible for the rearing of the zygote, and consequently less active than the male.

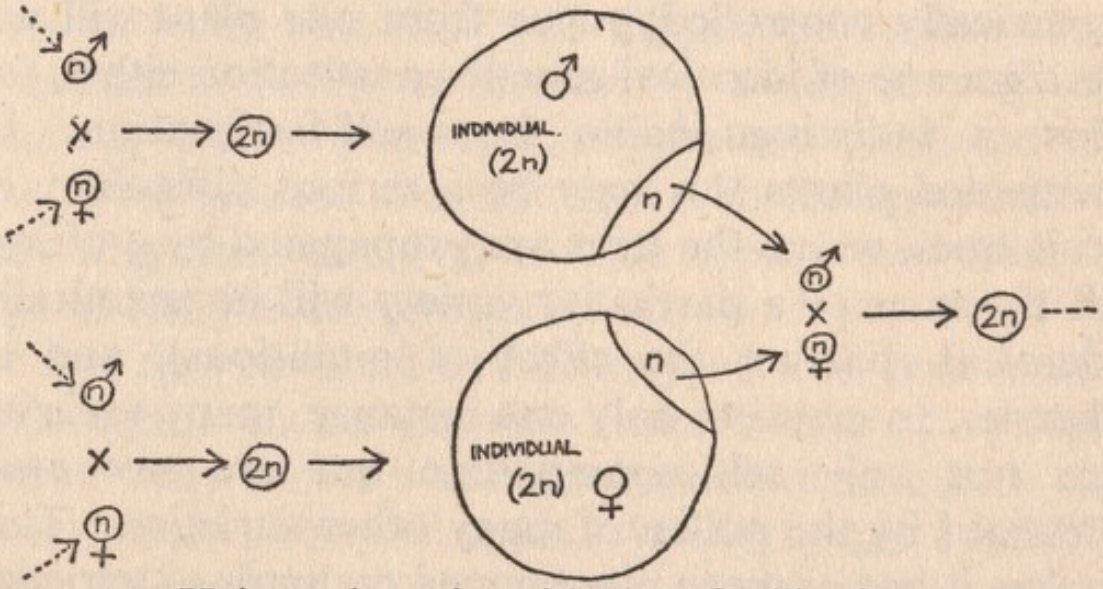
Such separation of the species into two sexes, into individuals which produce either one or the other type of gamete, is by no means general. In the higher plants and animals both types may be formed by the same individual. Thus most flowering plants produce both pollen and ova on the same plant, while in most of the higher animals one individual produces sperm, the other ova. There are notable exceptions in both groups. The male and female flowers of the poplar are borne on separate trees, and most people will have noticed that willow flowers are of two kinds, one more "pussy" than the other—they grow on different bushes. Snails and many of the lower animals are *hermaphrodite*—that is to say, each individual produces



Hermaphrodite species which is self-compatible



Hermaphrodite species which is not self-compatible



Unisexual species with cross-fertilization

FIG. 11
Types of reproduction.

both eggs and sperm. In plants we can distinguish between the hermaphrodite forms in which both types of gamete are produced in the same flower and those, like maize, in which two types of flowers are produced on the same plant; in some species hermaphrodite and unisexual flowers occur on the same plant.

In the individuals producing both male and female gametes the possibility of self-fertilization presents itself; however, this is not always realized in practice, and a range of conditions exists, from those plants in which self-fertilization almost always occurs (for example, in the pea, as has been mentioned above), through forms in which self- and cross-fertilization are both possible, to forms in which self-fertilization is prevented, either by a difference in the time at which the two types of gamete are produced or by what is known as *incompatibility*. In this condition the pollen either will not germinate on the pistils of the same plant or if it does germinate will grow only a short distance down the pistil. Since the condition is genetically controlled, pollen from one plant will not fertilize one of identical genetic constitution either, for this is indistinguishable from self-fertilization. In cultivated plants this may be a serious difficulty; in fruit-trees, where the trees are propagated by grafting, all the trees of a particular variety will be genetically identical (barring the effect of mutations), and in cherries, to mention only one instance, many varieties are not only self-incompatible but are not even fertilized by the pollen of many other varieties. This makes it necessary to plant mixed orchards of varieties chosen for their compatibility.

Where cross-fertilization takes place the plant has

usually to rely on the help of the wind, or of insects, to transport the pollen. In animals, where the individual organisms are usually mobile, cross-fertilization is common in hermaphrodite organisms; snails, for example, conjugate in pairs and fertilize each other simultaneously.

In maize, a hermaphrodite plant with unisexual *flowers* which has been studied extensively, some interesting genes have been discovered by which the *plants* can be made unisexual. A recessive gene *b* makes the stalks barren, eliminating the female flowers, which first show as *silks* and set seed as *cobs*; another recessive *t* converts the male flowers (the tassels) into female, seed-producing flowers. Consequently, an individual with the constitution $t/t\ b/b$ is female, and one $T/t\ b/b$ is male. Their offspring are all homozygous for *b*, and T/t and t/t are produced in equal numbers. In other words, this is a self-perpetuating system in which plants of the two sexes continually appear in equal numbers.

As it turns out, this type of genetic mechanism, produced in maize artificially, is a simple way of ensuring that two unisexual types are produced in equal proportions. At first sight it would appear that such a system would give three types: two homozygotes and the heterozygote; but this is prevented by the fact that no plant can be crossed with one of the same type. In the example from maize, t/t can be crossed only with T/t and vice versa, the crosses of t/t to t/t (female to female) and of T/t to T/t (male to male) being impossible. The first would give nothing but females, the second the usual 1 : 2 : 1 ratio, which in this case would be one female plant to three males.

Since these are excluded the ratio is always 1 : 1, male to female, a situation resembling that found in most higher animals, particularly the vertebrates, and of course including man.

Summarizing, we may say that *the requirements of the sexual process, being essentially a mechanism ensuring the alternation of haploid and diploid conditions of the cell nucleus, can be satisfied by species whose individual members are hermaphrodite and in which fertilization* (the haploid to diploid change) *may take place either between gametes from the same individual or between those from different individuals.* In all these species, however, the organs of a particular individual in which the gametes are produced (the diploid to haploid change) differ in their detailed structure (their *histology*), but not genetically. This follows because all the cells of a single individual arise from a single cell, the zygote, by mitosis. However, we have seen that, by a suitable trick involving certain recessive genes, it is possible to transform maize, a hermaphrodite species, into a bisexual one; when this is done, the male plant differs from the female plant *genetically*, being *T*/*t b*/*b* instead of *t*/*t b*/*b*.

This raises the question whether in habitually *bisexual* species each male individual differs *genetically* from a female individual by a constant factor; or, putting it another way, *whether the sex of a particular individual is genetically determined.* In the example from maize the genes *T* and *t* are separated at meiosis, so that pollen grains of two kinds are produced. These fertilize ova which all carry *t*, so that one kind of pollen (carrying *T*) gives male plants and the other (carrying *t*) gives females. This is a typical example of

sex determined by a genetic mechanism; to what extent is this mechanism found in naturally occurring bisexual species?

In a few species sex determination does not seem to have a genetical basis at all. Thus, in a certain marine worm it seems likely that chemical factors decide the issue: a fertilized egg falling on the sea bottom develops into a female, one falling on the proboscis of a female develops into a male. In another marine worm the female produces two sizes of eggs, the large ones (after fertilization) giving females and the small ones males. Apart from these rare instances, however, a genetical mechanism seems to be the general rule. *It also seems to be fairly certain that the hermaphrodite condition is the more primitive one, and that bisexual species have arisen through modifications of this.*

The simplest case would therefore be one in which a pair of allelomorphs was responsible (cf. *T*, *t* above), and in which one sex was heterozygous, the other homozygous. In fishes and amphibia it is suspected that very few genes are concerned, although it is not yet possible to say exactly how many. In the axolotl it has recently been shown that the female may be made to produce sperm by transplanting sperm-producing tissue (*testis*) from a male into it. Under its influence, sperm was then produced from what would normally have been the female gonad (*ovary*), and was used to fertilize the eggs of a normal female. The offspring were 74 per cent female and 26 per cent male, a result which can be explained if the female is heterozygous and the male homozygous. Thus, if the female was represented by *XY*, then the artificially produced cross would be *XY* by *XY*, and would give 1 *XX*; 2 *XY*;

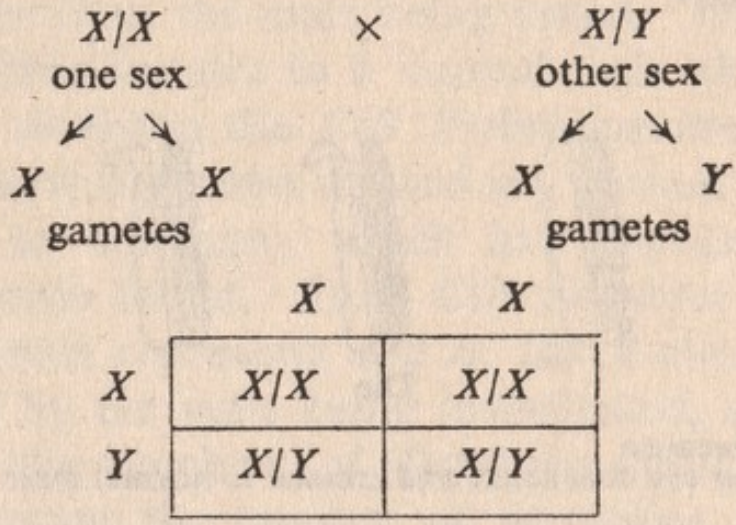
1 *YY*. *XX* is male, and apparently in this case *YY* is a female (cf. the maize cross above, p. 119).

If *X* represents a whole series of genes, and *Y* the corresponding allelomorphs, crossing-over in this section of the particular chromosomes involved would " mix " the genes, destroy the simple 1 : 1 ratio of the sexes, and give rise to all sorts of nondescript individuals. It seems probable that a species with such a defective arrangement would be eliminated in the course of evolution. Consequently, it is not surprising that where any considerable length of chromosome is involved, these sections do not pair at meiosis in the *XY* sex. In the *XX* sex crossing-over would not upset the mechanism and, in fact, occurs.

It follows that if a portion of a particular chromosome is concerned in the determination of sex, then the other genes on it will be linked to either *X* or *Y*, and may therefore appear mostly in one sex of the offspring, hardly at all in the other. This is seen most clearly in the organisms which have special *sex chromosomes*. These chromosomes are readily distinguished by their shape in some species, and were recognized as having a connection with sex before the idea of genes had been put forward.

The extreme type of sex determination by a chromosome pair is that seen in grasshoppers. Here one sex chromosome, the *X* (as it is usually called), is large and conspicuous, while the other, the *Y*, is non-existent. There is therefore one more chromosome in the females, which are *XX*, than in the males, which are *XO*. The sperm differ in a similar manner, one kind, female-determining, carrying the large *X*, the other without it. In Drosophila the *Y*-chromosome is present but is

genetically almost inert—that is to say, it carries none of the alleles of genes on the *X*. The Drosophila type, where the male is *XY*, is the most common. In the butterflies and moths, in one other group of insects, in birds, and in some fishes and amphibia, the female is *XY*, the male *XX*, a situation which caused some confusion in the early days of genetical research, because



i.e., 2 of one sex *X*/*X* to 2 of other sex *X*/*Y*.

FIG. 12

Scheme for production of sexes in equal numbers; *X* and *Y* represent either allelomorphic genes, or homologous chromosomes.

the English school, led by Bateson, were, as it happened, working on birds and butterflies, and thus could not reconcile their results with those of workers who were studying Drosophila and other organisms of that type.

There is reason to believe that as a general rule the *X*-chromosome does not carry many genes other than those directly responsible for sex-determination, but in Drosophila it carries a considerable number of genes controlling non-sexual characters. This gives rise to the useful situation that a recessive gene on the *X*-chromosome shows its effects in the male, because the

Y carries none of the corresponding alleles. Thus a "recessive lethal" gene on the *X*-chromosome will

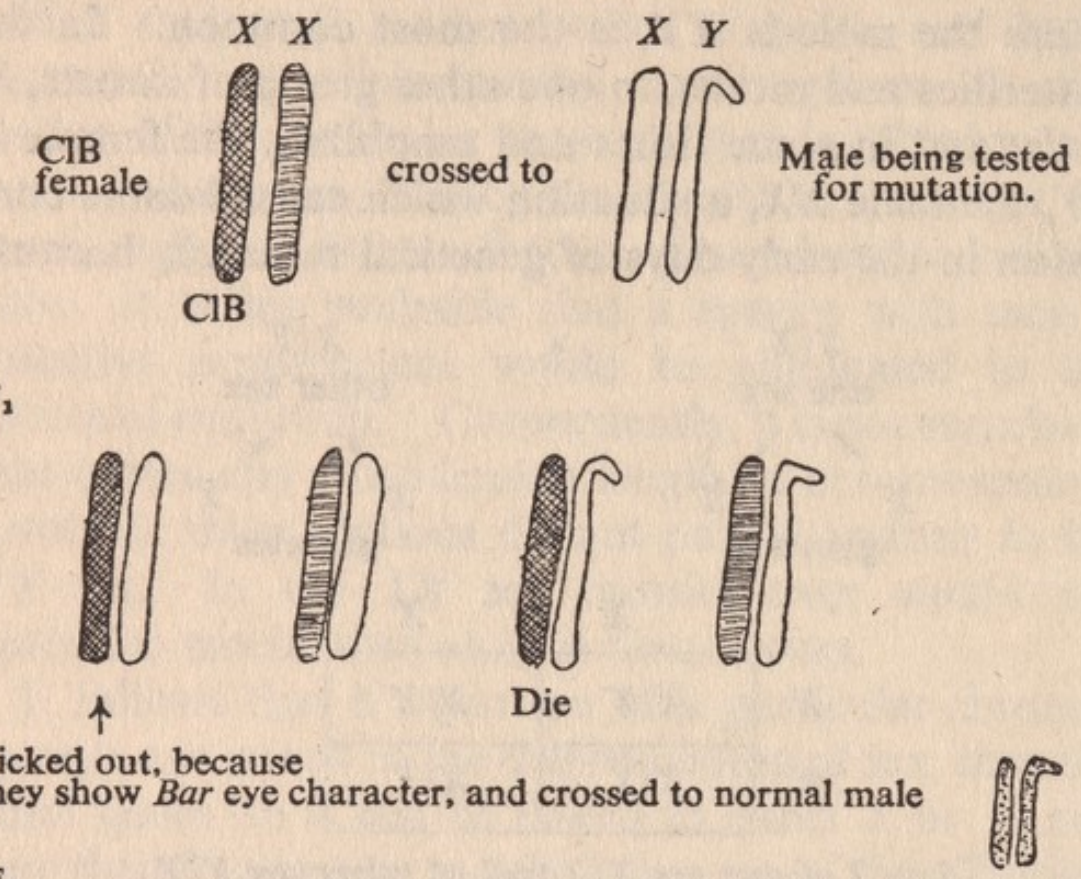
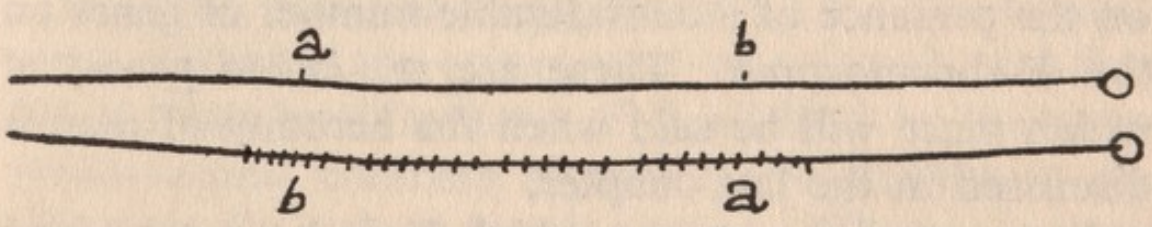


FIG. 13

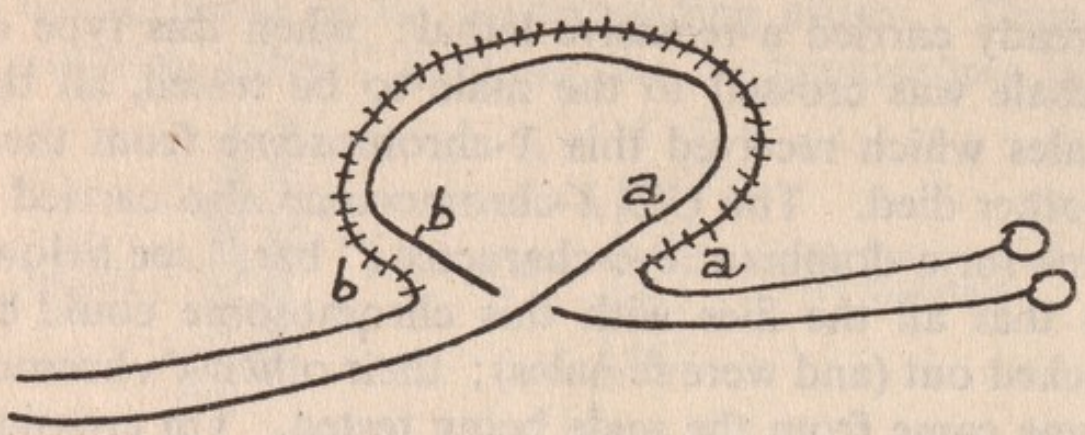
Muller's scheme for detecting mutations in the *X*-chromosome.

kill all the males in which it occurs. Muller took advantage of this in studying the rate at which mutations occurred in Drosophila, whether spontaneously or under the influence of X-rays. He used a special stock of female flies (*ClB*) in which one *X*-chromosome

already carried a recessive lethal; when this type of female was crossed to the male to be tested, all the males which received this *X*-chromosome from their mother died. The *ClB* *X*-chromosome also carried a gene for a dominant eye-character (" bar," see below) so that all the flies with this chromosome could be picked out (and were females); their other *X*-chromosome came from the male being tested. On crossing each of these females to a normal male all the male offspring receiving the *ClB* *X*-chromosome died, so that the surviving males showed any mutant character, recessive or dominant, which had appeared in the original male tested. Each *ClB* daughter from the original cross represents one of the *X*-chromosomes produced by the male being investigated, so that by counting the numbers of daughters having mutant male offspring the number of mutations in the *X*-chromosome could be counted. A recessive lethal was particularly easy to detect, because this resulted in the death of *all* males in the cross of daughter to normal. Crossing-over in the *X*-chromosome would have upset all these calculations, so to eliminate this it was arranged that the *ClB* chromosome carried a device for suppressing it. This was an " inversion "; a portion of the chromosome had been turned round in this manner:

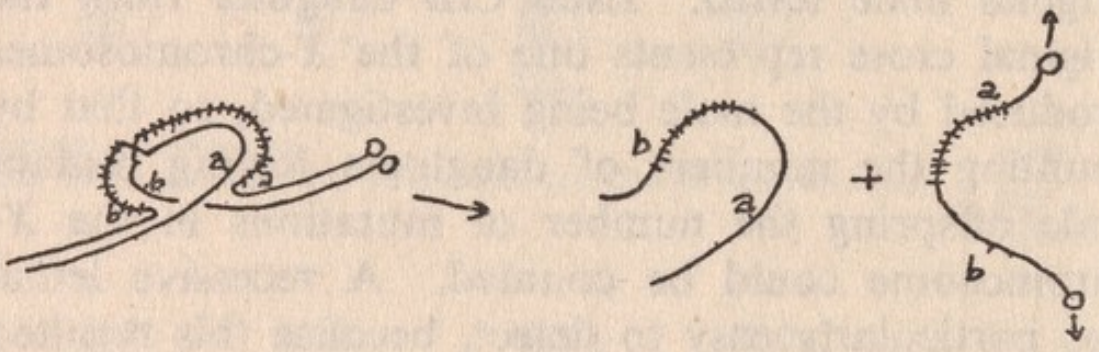


At meiosis this chromosome will pair with a normal one,



Only 2 out of 4 chromatids shown. (Cf. p. 75.)

and if a chiasma forms in the loop the result is one chromosome with two centromeres and one without any.



The two nuclei involved are always lost as polar bodies. Consequently, all the ova which survive are non-cross-overs as far as the *X*-chromosome is concerned. Without this ingenious method the job of tracking down mutations would have been immeasurably harder.

It must be emphasized that it depends for its success on the presence of a considerable number of genes on the *X*-chromosome. These are *sex-linked* genes, of which more will be said when the heredity of man is discussed in the last chapter.

In most of the species which have been examined both *X*- and *Y*-chromosomes appear to carry very few genes, although it does not follow that for this reason

they no longer fulfil any function. In a considerable number of insects more elaborate systems of sex chromosomes are found, particularly those in which several *X*-chromosomes are present. At meiosis these clump together and move to the opposite pole to the *Y*. The males are thus $X_1X_2X_3 \ldots Y$, and the females are $X_1X_1X_2X_2X_3X_3 \ldots$, as far as their sex chromosomes go, and in these species there may be as many as *four* more chromosomes in the female than in the male diploid cells. There are at least two explanations for this state of affairs. In an *XO* : *XX* species, one of the *autosomes* (non-sex-chromosomes), *A*, may have been dragged into the sex-determining system, so that the female was now *XXAA* and the male *XA*; alternatively, the *X*-chromosome might have broken into fragments, or become duplicated, while the *Y* remained whole; this would explain the $X_1X_2X_3 \ldots Y$ or $X_1X_2X_3 \ldots O$ types of male.

In the common earwig the peculiar position exists that males of two types occur in the same localities, and even in the same colony; one is X_1X_2Y and the other *XY*. Proportions of the two types have been found ranging from 50 per cent of each in Switzerland to 100 per cent of *XY* males in South London. In one species of Drosophila there are two *Y*-chromosomes, the males being $X_1X_2Y_1Y_2$, the females $X_1X_1X_2X_2$.

It is true, however, to say that the *XY* : *XX* chromosome system is the commonest type found, and that the various modifications of it all lead to the same result—equal numbers of males and females in the offspring of a male to female mating. There is in some insects, particularly the *Hymenoptera* (wasps, bees, ants, ichneumon flies, etc.), in which it is universal, a

type of sex-determining mechanism of a different character, by which variable ratios of males to females can be produced. This is the condition in which the male is haploid and the female diploid—in other words, their eggs, which on fertilization always give rise to females, are capable, unlike the eggs of most animals, of developing without fertilization, in this case always giving males; hence no male insect of these species has a father! As this condition exists in the social insects, particularly the ants and bees, it is a device for producing a large number of *workers*, which are diploid and therefore potentially female, and a relatively small number of males (all functional) and functional females (queens). The factor which decides whether the fertilized egg shall develop into a worker or a queen is the kind of *food* which is given to the young insect, a very interesting example of the way in which differences in environment can produce different phenotypes from the same genotype. The potential queens are fed on " royal jelly," which, among other things, is said to be very rich in certain vitamins.

The way in which the genotype is adapted to produce females when diploid but males when haploid is not certain, although it has been suggested that the genes which determine sex are carried on several chromosomes and are of such a nature that when homozygous they produce maleness, but when heterozygous, femaleness. On this hypothesis the haploid individuals are male, because they are *effectively* homozygous, each gene having no partner allele; but equally well it should be possible to have diploid males if their two haploid sets are sufficiently alike in the genes concerned. Diploid males have been found in some

species of wasp, and some such explanation is probably the correct one.

A peculiar condition which occasionally arises in organisms having male haploidy, as well as in those with the *XY* mechanism, is *gynandromorphism*. In bees individuals may arise from two cells, one only of which has been fertilized. In this case half the insect will be male, the other half female. Similarly, if an *X*-chromosome is lost during a cell division in the development of an *XX* individual, all the cells will be male in character, the function of the *Y* being so slight that its absence is not harmful. If this occurs at an early stage, when the fertilized egg has divided only once or twice, as much as half the adult may be of a different sex from the rest. In butterflies the effect is particularly striking, because the wings on one side of the body will carry the male pattern, those on the other (which has lost an *X*—the female is *XY* in butterflies) the female. Butterflies like this have been caught occasionally by collectors.

Apart from accidents of this kind, there are other examples of upsets to the sex-determining mechanism. Among these is the action of a gene in Drosophila which leads to the loss of nearly all the *Y*-chromosomes in the males in which it occurs; the *X*, however, divides *twice* at meiosis, so that four female determining sperm are produced. The offspring are thus 90 per cent females.

The apparent virtue of the sexual process in living organisms is that it includes meiosis and hence crossing-over. Where no crossing-over can occur, new genes produced by mutation are destined to remain in the same chromosome indefinitely, and for

that matter, unless there is meiosis and fertilization, in the same diploid set of chromosomes. These processes provide a way in which the genes can be shuffled, both by the shuffling of the chromosomes on which they are carried and by the exchange of material between homologous chromosomes. *In this way the species has the opportunity of trying out (in an unconscious manner, of course) practically all the combinations that are possible with the genes which it possesses.* This does not necessarily mean that it is impossible for a species to struggle successfully with the environment without a sexual process, but that its presence gives it a very powerful advantage.

The alternative to sexual reproduction is *asexual* reproduction, either *vegetative reproduction* or *parthenogenesis ;* the former is the production of new individuals without any process resembling gamete formation, the latter their production from unfertilized eggs. In some plants vegetative reproduction is the usual form, in others it is obligatory, for reasons that will be discussed in the next chapter. Plants are particularly well adapted to this kind of existence, producing runners, bulbs, corms, tubers, and so on, often without prejudice to their ordinary sexual process of seed production. Some plants produce *parthenogenetic seeds ;* these arise by doubling of the chromosomes in the female gamete. The hawkweeds, which Mendel investigated, are of this type and can only rarely be induced to produce fertilized seeds. When he attempted to cross them he got seeds, seeds which were mostly not the result of cross-fertilization but identical genetically with the plants on which they were produced. Consequently, he observed none of the mixing

and separation of characters which he had found in peas and was diverted from the fundamental laws of inheritance which he had unwittingly established with them.

The consequence of continued vegetative reproduction is that no interchange of chromosomal material takes place between separate individuals of a species; in fact, a condition arises in which so-called *clones* are formed consisting of all the individuals having a common ancestor, and therefore genetically identical, apart from the effect of spontaneous mutations. *A possible advantage of habitual asexual reproduction is that a new mutation is, so to speak, "guaranteed a place" and has not to stand its chances of elimination in the usual extravagant wastage of pollen and sperm which takes place at fertilization.*

Another possible advantage of vegetative reproduction is that it is a more efficient way of multiplying the number of individuals in a species than is found in bisexual species, where half the adults (the males) do not *directly* produce offspring. In green-flies, parthenogenesis during the summer months is a regular feature of the life-cycle, and any one who has fought a battle of annihilation against this particular pest will be strongly in favour of its sticking to sexual reproduction throughout the year if that will in any way impair its capacity to multiply. As things are at present the green-fly seems to be particularly successful at having the best of both worlds. In the parthenogenetic females the doubling of the haploid nuclei gives *all* females (*XX*), and the summer generations therefore contain no males. At the end of the season the green-fly extricates itself from this vicious circle by losing

some *X*-chromosomes, and males are once again produced.

Parthenogenesis appears to be a secondary development from a sexual form of reproduction, because with one exception none of the main groups of animals are exclusively parthenogenetic, and in some it never occurs. Where it is an alternative method of reproduction the haploid ovum forms in the usual way, but can develop without fertilization; whereas in those forms in which it is obligatory the egg-cell is usually diploid. Meiosis may or may not take place in the formation of these diploid cells, and hence no crossing-over and no segregation of characters may occur at all. Where there *is* meiotic division the first polar body is lost, as usual, but the second division does not lead in the end to any loss of chromosomes. *It need hardly be emphasized that the existence of these diverse forms of sexual and asexual reproduction makes it essential to acquire an understanding of its life-cycle and mode of reproduction before drawing any conclusions about the genetics of a particular species.* The organisms of greatest interest to man from the genetical point of view include representatives of several of the types mentioned above, while man himself is a simple bisexual species, with an *XY* : *XX* chromosome mechanism of sex-determination.

CHAPTER X

HOW MANY CHROMOSOMES IN A NUCLEUS?

IT might be expected that the process of halving and doubling of chromosome number would occasionally go wrong, and it is interesting to see what are the causes and the results of such accidents.

We can begin by observing that meiosis is possible in cells with a haploid number of chromosomes. In the haploid males of bees it is probable that some at least of the body cells are diploid or tetraploid, but the gametes are formed from haploid cells. Consequently meiosis is of a peculiar type. There can be no pairing of homologues, since each is present only once, and crossing-over cannot occur. If the chromosomes, which split into two chromatids, were distributed between four sperms, each would on the average receive half the haploid number. This does not occur; at the first meiotic division a half-spindle is formed, and it does not lead to the formation of two nuclei, and the second meiotic division leads to the formation of two nuclei by what is essentially mitosis. One of these is lost, and a single haploid sperm is produced. In haploid males of other species two functional sperms are produced.

This indicates that meiosis *can* take place successfully with a haploid number of chromosomes, although in organisms which are abnormally haploid it is usually

abortive. What happens when more than the diploid number is present?

The production of cells with abnormal numbers of haploid sets probably takes place in the following way:

While it is believed that in the majority of organisms all the cells of an individual have the same number of chromosomes, in many insects chromosome-division is known to take place without cell-division (compare the salivary-gland cells of Drosophila), so that the cell nucleus contains a multiple of the diploid number. Cells with as many as eight haploid sets may occur.

If now gametes are produced from (say) a tetraploid (twice diploid) cell, they will be diploid and on fertilization will give a zygote with three times the haploid number of chromosomes (a triploid).

The question arises as to the nature of meiosis in polyploid cells. The simplest example is probably that of the triploid cells we have just mentioned. Here at the beginning of meiosis the chromosomes tend to associate in threes (*trivalents*), and after chiasma formation separate in the usual way at anaphase, one pair of chromatids going to one pole of the spindle and two pairs to the other. After the second division four nuclei are formed, one pair containing this chromosome once, the other pair twice. The same occurs for each chromosome of the haploid set, so that the sperm, or eggs, resulting are a very mixed collection. Thus, if we represent six haploid chromosomes by *A*,*B*,*C*,*D*, *E*,*F*, the triploid mother cell is *AAABBBCCCDDDEEEFFF*, and the sperm or eggs will be *AABBCCDDEEFF* and *ABCDEF* in the most unlikely case, and *ABBCDDEEF* and *AABCCDEFF*, *AABCCDDEF* and *ABBCDEEFF*, and so on. When these are fertilized

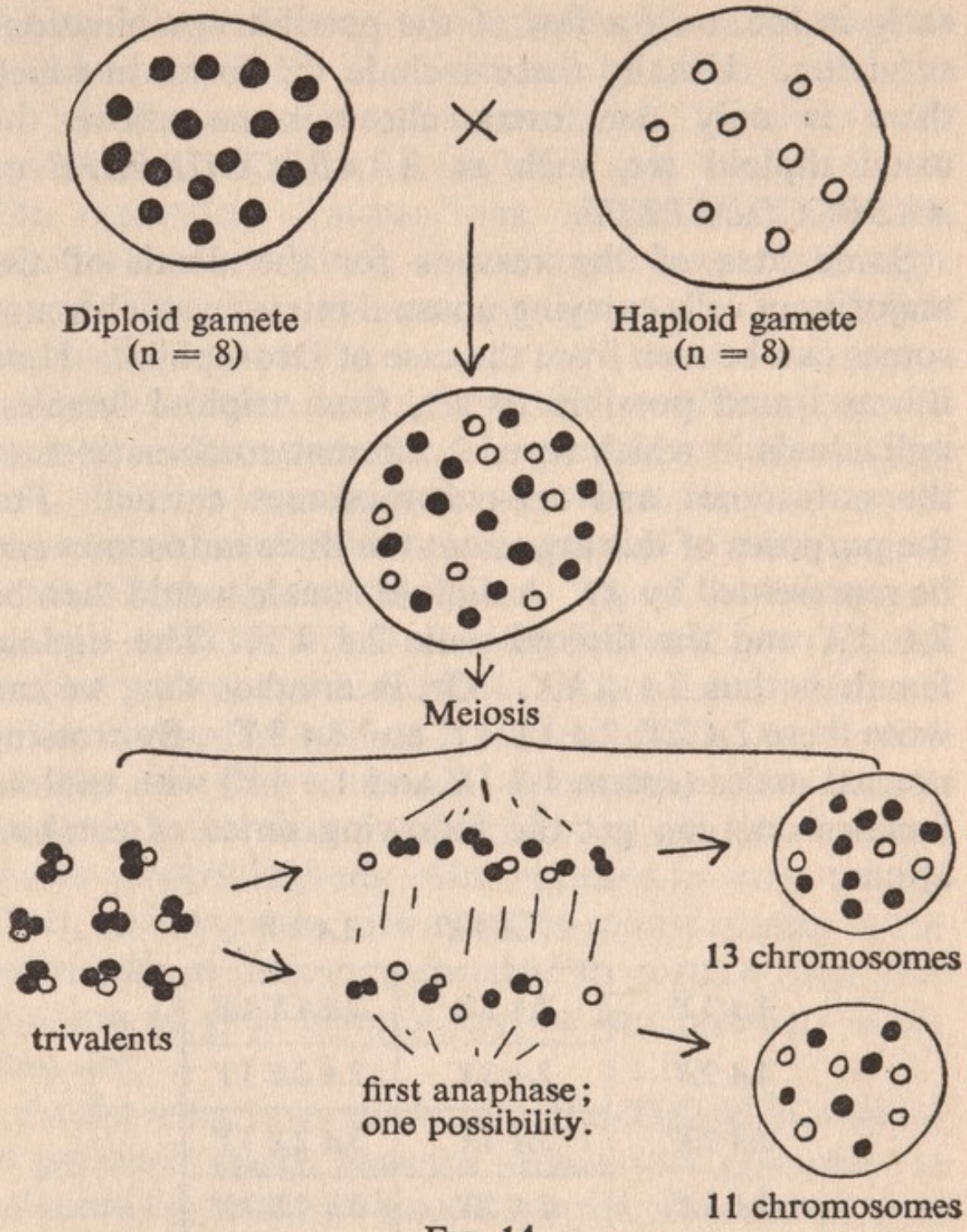


FIG. 14

Meiosis in triploids, and in other *auto*polyploids.

by gametes from a diploid individual they will give rise to a range of zygotes which possess some of their chromosomes in the normal double condition, but others triple. The consequences of such fertilizations are usually a high proportion of embryos which die

early in life, only a few of the possible combinations surviving. Usually these include the forms in which there is only one extra chromosome above the usual diploid set, such as *AAABBCCDDEEFF* or *AABBCCDDEEEFF*.

Some idea of the reasons for the death of the majority of cells carrying unusual mixtures of chromosomes can be seen from the case of Drosophila. Here it was found possible to get, from triploid females, individuals in which several different combinations of the autosomes and sex-chromosomes existed. For the purposes of this argument the three autosomes can be represented by *A*. A diploid female would then be 2*A XX* and the diploid male 2*A XY*. The triploid female is thus 3*A XXX*. Or, in another way, we can write these 2*A* 2*X*, 2*A* 1*X* 1*Y*, and 3*A* 3*X*. By crossing normal males (sperm 1*A* 1*X* and 1*A* 1*Y*) with triploid females one can get the following series of combinations:

	1*A* 1*X*	1*A* 1*Y*
1*A* 1*X*	2*A* 2*X*	2*A* 1*X* 1*Y*
1*A* 2*X*	2*A* 3*X*	2*A* 2*X* 1*Y*
2*A* 2*X*	3*A* 3*X*	3*A* 2*X* 1*Y*
2*A* 1*X*	3*A* 2*X*	3*A* 1*X* 1*Y*

Of these 2*A* 2*X*, 3*A* 3*X*, and 2*A* 2*X* 1*Y* are normal females; 2*A* 1*X* 1*Y* is a normal male. The others are sterile, but show more or less of the characters of one sex. The controlling factor seems to be the ratio between *A* and *X* chromosomes. Thus if *A* : *X* is 1 : 1 the individual is female; where it is 2 : 1, male.

Where it lies in between, the individual is an *intersex*, as $3A\ 2X$ and $3A\ 2X\ 1Y$; where it is less than 1 : 1, as in $2A\ 3X$, the insect is a " super-female "; where it is more than 2 : 1, as in $3A\ 1X\ 1Y$, it is a " super-male." The expression " super "-sex simply indicates the genetical constitution; both super-sexes, although superficially like the sex in question, are feeble physically, and sterile.

The conclusion drawn from these results is that the *balance* of chromosomes is important in determining sex; that it is important that genes on the *X*-chromosome should work with a particular set of other genes, present in the three autosomes. Where the balance of genes is upset the whole carefully adjusted gene system is upset with it, and individuals are produced which are at best imperfect and at worst incapable of survival because of their internal disorganization. If we remember also that a duplication of all the chromosomes in certain body cells appears to have no ill-effect, and may even give a certain robust quality to the individual, it seems reasonable to assume that this question of gene balance applies to characters other than sex.

At the same time, the failure of a triploid individual to produce many gametes which can give rise to balanced or nearly balanced zygotes shows that from the point of view of *sexual reproduction* a " balanced " individual may be hopelessly handicapped. This may apply to tetraploids also, because even if they are able to produce a greater proportion of " balanced " *gametes*, which is not necessarily the case unless they are capable of self-fertilization, their *offspring* from fertilization by a diploid will be triploids. In the

tetraploid mainly quadrivalents will be formed at meiosis, and these may separate, two to each pole; the gametes will all be *diploid*, and hence on fertilization by haploid gametes give triploids. Thus an organism with more than two sets of chromosomes, a *polyploid*, will fare badly in a diploid population in which sexual reproduction including obligatory cross-fertilization is the rule.

Probably for this reason polyploidy is rarely found in animal species, but in plants about half the species examined have chromosome numbers which are multiples of those of related species (see Table I, p. 25). There is an important distinction to be made, however, between two types of polyploids—*autopolyploids* and *allopolyploids*. The first are of the type of the triploid Drosophila, and are presumably produced from diploid gametes, which might arise from a patch of tetraploid tissue in the gonads. They show the characteristic formation of trivalents, quadrivalents, and so on at meiosis, indicating that the haploid sets are all more or less alike. Many wild species of plants are of this type, as many as eight haploid sets being found in the nuclei of one plant.

For the reasons outlined above plants with an *odd* number of haploid sets are sterile (incapable of sexual reproduction). They therefore reproduce by vegetative means; as an example, one may take the tulips, where there are triploid and pentaploid species.

The other group of polyploids differs in that mainly *bivalents* are formed at meiosis, and consequently gamete formation is normal. We infer that they are polyploids because they have chromosome numbers that are multiples of closely related species. Thus in

wheats there are three main types, having haploid numbers of 7, 14, and 21 respectively. The explanation for the formation of bivalents at meiosis is probably that in (for example) the tetraploid plant there are two pairs of similar haploid sets. This is best understood from examination of the artificial production of an allotetraploid. By crossing the radish with the cabbage a vigorous *hybrid* is produced which is almost sterile. Cytological examination shows that the reason for this is almost complete failure of pairing at meiosis. The failure to pair indicates great dissimilarities between the (haploid) nine chromosomes from one parent and the nine from the other. (This might be expected since the plants belong to different *genera*.) Because no pairing takes place the chromosomes are distributed at random to the two poles at the first meiotic division, so that each gamete receives a mixture of radish and cabbage chromosomes. These mixtures are apparently hopelessly unbalanced, and the gametes perish. (It is worth noticing that the cells of the hybrid can tolerate two dissimilar, but *balanced*, chromosome sets.)

Occasionally seed is set, and from it reasonably fertile plants are obtained. These are found to be tetraploids and arise from the fusion of diploid gametes. In the tetraploid cell there is now a complete diploid set of cabbage chromosomes and a diploid set of radish chromosomes; hence at meiosis these can form nine bivalents each, giving gametes, which are balanced diploids, and form fertile seed again. The new plant, which differs from both cabbage and radish, does not give fertile offspring when back-crossed to either parent. However, at meiosis in the (triploid) hybrids

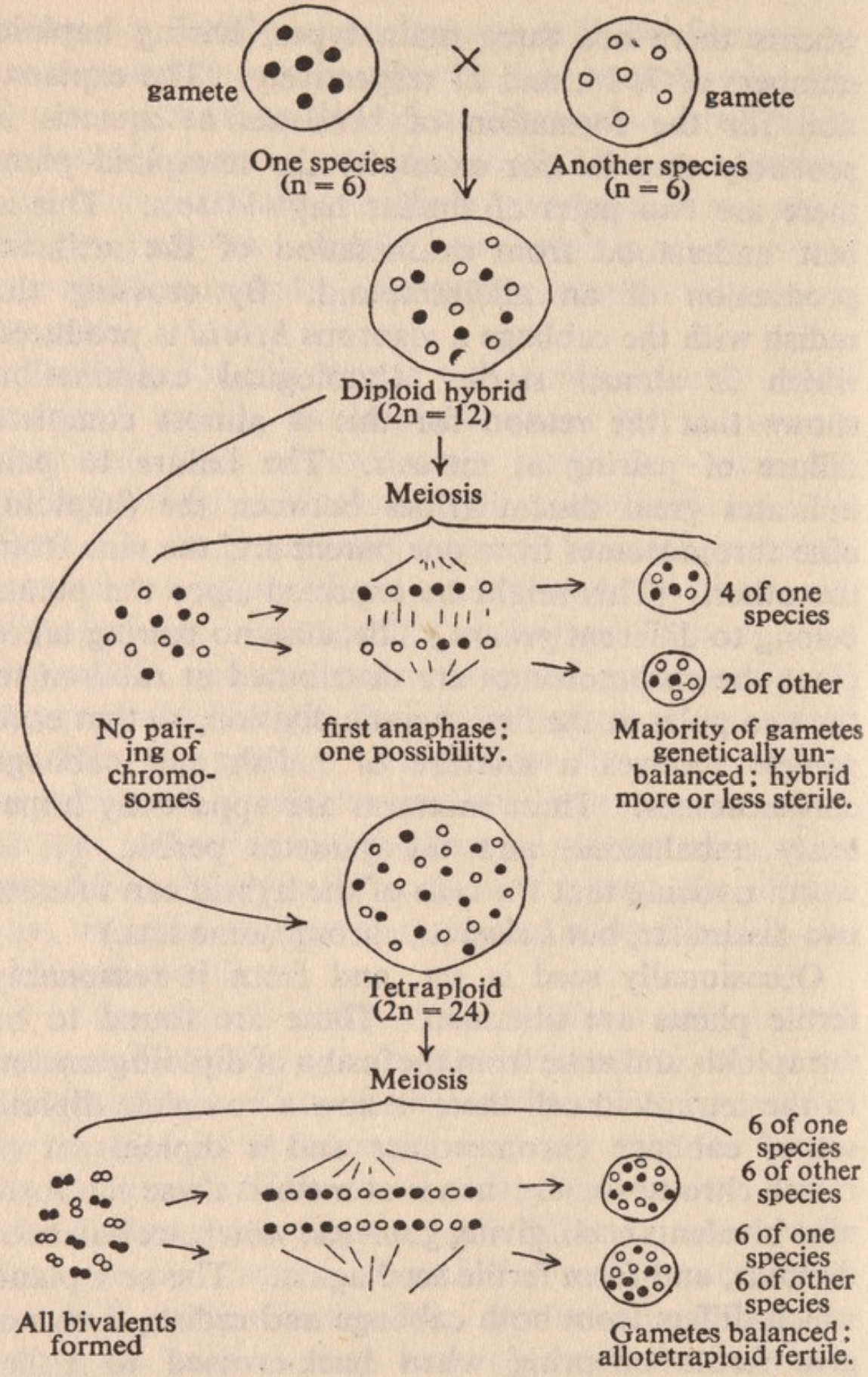


FIG. 15.—Meiosis in species hybrids and allotetraploids.

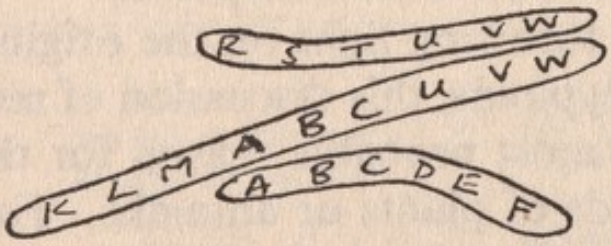
so produced nine univalents and nine bivalents are formed. In other words, it is possible to detect the existence of allopolyploidy by crossing the plant with one of its suspected " parents." If the haploid number of bivalents are formed it is reasonable to assume that these are combinations of the " parental " chromosomes with those chromosomes of the polyploid which came originally from a plant of the type of the " parent."

In this way the cultivated tobacco plant, *Nicotiana tabacum*, has been shown to have a set of 12 chromosomes from a wild species, *N. sylvestris*, and the other 12 from *N. tomentosiformis*. It therefore seems likely that it arose through doubling of the chromosome number in a sterile hybrid between these two wild species. In wheats the *einkorn* types with a *haploid* number of 7 appear to have given rise to the *emmer* types by allopolyploidy, and these to the 21 chromosome bread wheats by yet another hybridization and chromosome doubling. It is not necessary for both parental types to contribute the same number of chromosomes for allopolyploidy to be successful, and *emmer* (gametes—14-chromosomes) type crossed with a 14-chromosome (gametes—7) plant yields a triploid (21-chromosome) plant which by doubling would give a fertile 42-chromosome hexaploid.

As well as throwing light on the origin of naturally occurring polyploids, this discussion of meiotic pairing indicates the most probable reason for the sterility of species hybrids of plants or animals. *For a hybrid to reproduce sexually it has to produce genetically balanced gametes, and this depends on its having a form of pairing at meiosis which ensures that equal numbers of chromosomes pass to each pole, and, more important, that they*

should contain complementary genes. It is unlikely that in two wild species the gene arrangements will be balanced when distributed at random to the two poles, even if pairing is satisfactory. For this reason the F_1 from a cross between species may be quite vigorous and healthy but sterile. The *mule*, the horse–donkey hybrid, is a familiar example of this type of cross. Other hybrids may be so genetically unbalanced that they cannot develop, even in the F_1.

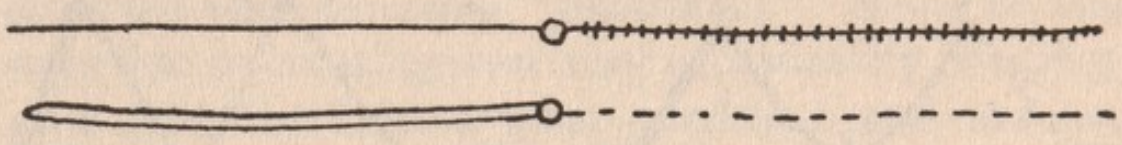
In hybrids from related species it has been found that the difficulties encountered at meiosis are often due not to failure of pairing, but to the formation of groups of more than two chromosomes. In Drosophila the nature of these multivalents can be studied in the salivary-gland chromosomes. They are produced as in the normal meiotic pairing by the attraction between parts of chromosomes having the same band (and hence gene?) structure. However, regions from one chromosome have been transferred to a totally different chromosome, so that if we represent two chromosomes as *ABCDEF* and *RSTUVW*, *one* of the chromosomes of the other species may be *KLMABCDUVW*. Consequently, when related segments of the chromosomes pair a group of three is formed, thus:



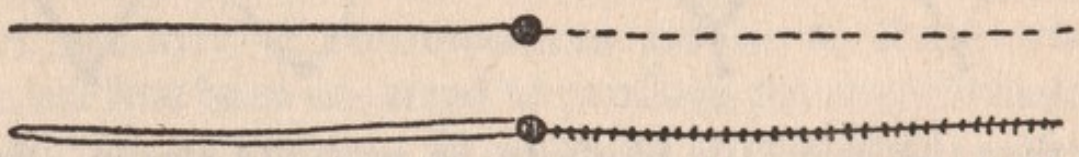
In this way the whole mechanism of meiosis is deranged and sterility of the hybrid results.

In the evening primrose a peculiar condition exists

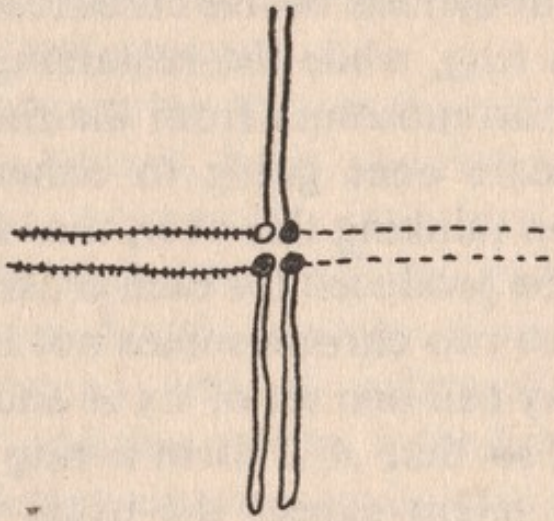
in which this kind of pairing has become normal. Suppose one considers two chromosomes:



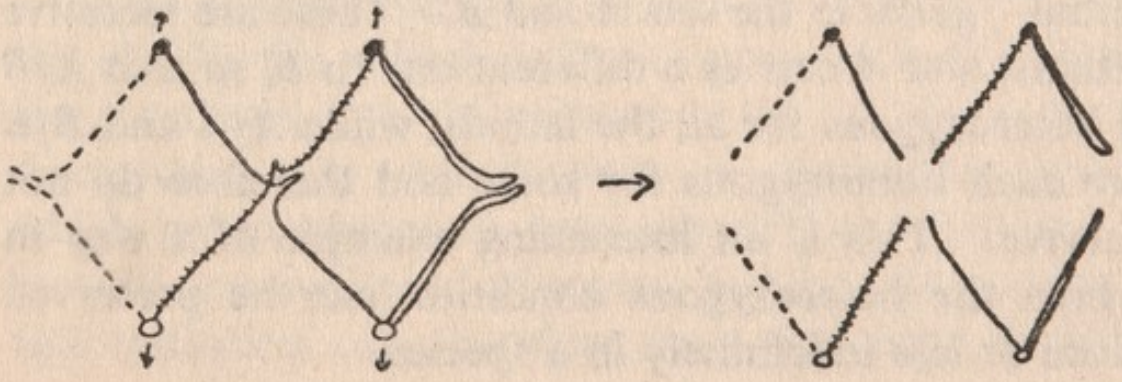
If these exchange arms in one individual to give



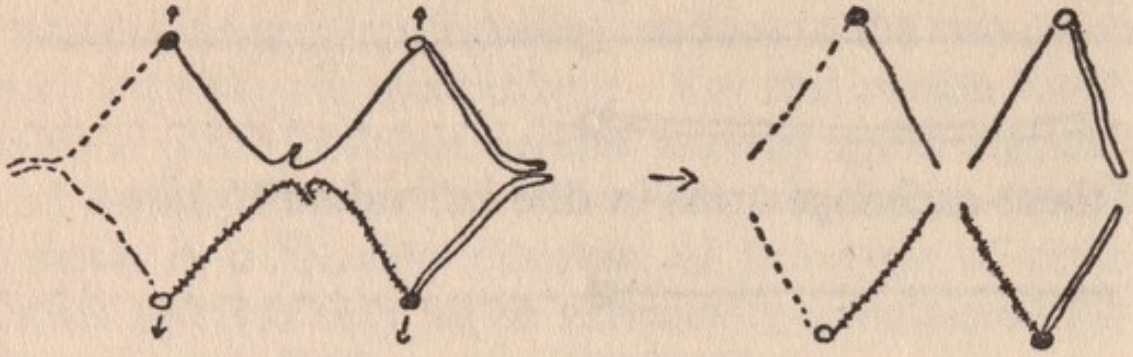
on crossing this plant with a normal one, at meiosis the chromosomes will pair like this:



and after chiasma formation the centromeres will be pulled apart, two going to one pole and two to the other. This may produce sharing of the four different kinds of arms:



or it may lead to unequal sharing:



so that the hybrid is likely to be partially sterile. In the evening primrose this process has become normal and has developed to extremes, so that in the commonest species at meiosis twelve chromosomes arrange themselves in a ring, while the remaining two form a bivalent. Six chromosomes from the ring go to each pole, the alternate ones going to either pole. One might expect, on thinking this over, that three kinds of zygotes would be produced for each cross-fertilization. Disregarding the two chromosomes not taking part in the ring, we may call one set of six *A* and the complementary set *B*, so that *A*/*B* form a ring of twelve at meiosis. One might expect the usual ratio 1 : 2 : 1 of *A*/*A* : *A*/*B* : *B*/*B* on fertilization, but in fact only *A*/*B* appears. This seems to be because although the zygotes *A*/*A*, *B*/*B* are produced they do not survive, and is probably due to the presence of " balanced lethal " genes in the sets *A* and *B*. These are recessive lethals, and *A* carries a different one to *B*, so that *A*/*B* is heterozygous for all the lethals, while *A*/*A* and *B*/*B* are each homozygous for some and therefore do not survive. This is an interesting example of a way in which the heterozygous condition can be preserved more or less indefinitely in a species.

The case of the evening primrose is of historical importance, since it was in this plant that de Vries first observed what he called "mutations." Some of these were due to crossing-over very occasionally bringing a gene into the homozygous condition and are very different from the gene mutations which were mentioned in Chapter VII. Others were due to exchanges of portions of chromosomes similar to those which must first have occurred to produce the ring-formation pairing. This type of mutation in the evening primrose may break the 12-membered ring into two smaller ones and has therefore important effects on the gene combinations possible. (In the normal type there are only two linkage-groups.)

In other organisms this exchange of segments of chromosomes occurs, both spontaneously and as a result of X-ray treatment. In a way it can be compared with normal chiasma formation, but its effects are much more drastic because of the disturbance it causes at meiosis and, if sufficiently extensive, at mitosis. In addition to the interchange of material between different chromosomes, *translocations*, there are the related changes in a single chromosome, *inversion*, by which the gene order is reversed along a segment, and *duplication* and *deletion*, which, as their names imply, result in the gain or loss of segments.

These changes can be produced not only by X-rays but also by the radiations from radio-active substances (e.g., radium, for this reason used in attempts to disorganize the cell-divisions in cancerous tissue), which are produced in great quantities in the manufacture and explosion of atomic bombs. Exposure to this radiation can therefore have the most dreadful

effects on human beings, ranging from direct death, or delayed death from the prevention of the formation of vital cells like the blood corpuscles (which have to be constantly renewed), to effects upon the tissues of rapidly growing unborn children, which are born dead, and on the germ plasm itself, which causes temporary sterility. All these effects were seen in Hiroshima and Nagasaki and make atomic warfare qualitatively more frightful than anything yet seen on this planet.

The effects of deletion have been mentioned in Chapter VII; they are always deleterious, often fatal. *Duplication* has the effect of increasing the phenotypic expression of the genes on the segment duplicated. The dominant *Bar* effect in Drosophila is caused by duplication; and *double Bar* by a double duplication in the same chromosome. It has the effect of reducing the number of facets in the compound eye, a useful quantitative measure of its activity. The wild-type eye has about 750 facets. An interesting comparison has been made of the number of facets when two *Bar* genes are present in the same chromosome (as *double Bar*/ wild-type), or in separate chromosomes (as *Bar*/*Bar*). These numbers, 45 and 68 respectively, indicate that the Bar effect is greater when the two *Bar* segments are side by side. This and experiments with other genes which have been moved by translocation have given rise to the idea of a " position effect "—namely, that the influence of a gene in the phenotype can be modified directly by the genes which lie on either side of it.

Before concluding this brief summary of the variations in chromosome number and structure, we should notice that changes in the chromosomes of the types just

described can cause sterility (i.e., a barrier to successful interbreeding) between the normal and the mutant types. For this reason it has been plausibly suggested that changes of this kind can lead to the formation of new species. This is confirmed by a study of hybrids between species of Drosophila. In the salivary-gland cells of the larva the chromosomes are seen to be paired only in short regions, and it is sometimes possible to show genetically that the same mutant gene occurs in several species.

Although the chromosome *number* of different species may not be the same, it is possible to say that a set of chromosome *arms* is present in all. In *D. virilis* there are six chromosomes (including the *X*), in *D. texana* this has been reduced to five by the fusion of two of them, and in *D. americana* to four by the further fusion of the *X* with one of the autosomes. In addition to these translocations there is a number of inversions in the arms.

Similar relations can be discovered between the numbers of chromosome arms in other groups of animals, and make it possible in a few cases to suggest the evolutionary history of the group from an examination of the chromosomes. In Drosophila the study of translocations and inversions by the salivary-gland technique has made an even more detailed evolutionary study possible—that of the *races* within a species.

In general, one may say that the formation of a new species by chromosome changes is characteristically through translocations and inversions in animals, while in plants the additional process of polyploidy has played an important part. What is even more interesting is that there may exist within a single species

forms differing in their chromosome structure and only detectable by cytological examination. The vagaries of chromosome behaviour may on the one hand prevent breeding between forms which are phenotypically indistinguishable, and on the other hand permit the formation of new species from crosses between forms which are sufficiently distant to be placed in different genera.

CHAPTER XI

ARGUMENTS AGAINST GENETICS

MORE than four-fifths of this book has been devoted to a description of the chromosomes and the genes which they carry. Is this a true reflection of the nature of heredity? Is the nucleus the only means by which characters are transmitted from parents to offspring?

On the answers to these questions turns one of the greatest controversies in biology—the controversy over the inheritance of acquired characters. It will be clear from what has been said about genes that they are not very susceptible to changes in the individual which carries them. Although their phenotypic expression may be modified or suppressed, they emerge unchanged from the majority of generations. Mutation is apparently largely a random change, influenced only by rather drastic physical treatment and not *directed* by it.

Darwin's theory of inheritance postulated "gemmules," which moved from every part of the body into the germ cells and thus were transmitted to the offspring. A change in a muscle, or a leaf, altered the gemmules which it produced, and hence the offspring had altered muscles or leaves. This, crudely, was the basis he suggested for the inheritance of acquired characters; but our present knowledge of biochemistry and cytology provides no sort of confirmation for it.

The modern view was put in its most extreme form by

Weismann, who before the discovery of genes suggested that the germ cells—that is to say, the gametes and the cells which produced them—had immortality, while the somatic cells, which made up the greater part of the body of the individual, had no effect on this germ-line and perished after the adult had reached the end of its reproductive life. This view was a complete rejection of the idea that the environment, by modifying the character of an individual, could produce a change in its germ cells. It also receives no support from modern knowledge of the development of multicellular organisms.

In its place we have the theory that inheritance is due to the transmission of particles having the properties of genes, carried on the chromosomes in every cell nucleus. As we have seen, this theory explains many of the peculiar phenomena encountered in the study of inheritance. It is, in a way, a replacement of Weismann's germ-line by the genes, which are given the same capacity for self-perpetuation (barring mutations) and the same lack of permanent response to changes in its environment. It is also, in a way, the reverse of Darwin's theory of gemmules, the genes *going out* from the zygote (through mitotic division) to determine the structure and functions of all parts of the body. Mutation, occurring more or less independently of the individual in which the gene is located, then appears as the alteration of the offspring, not by forces acting from outside its parent, but *from within.*

The environment, on this view, acts quite differently; it *rejects* the mutations which are harmful to the species by killing, or in some other way incapacitating, the individual carrying them. This apparently means that most mutations are rejected, judging by the number of

recessive lethals which have been detected, both in spontaneous and radiation-induced mutants.

This is Darwin's "natural selection" at work but doing a cleaner job of work than he expected; it weeds out deleterious mutations and preserves the favourable ones.

Once a favourable one has occurred there is no danger of the environment eliminating it by direct action on the germ plasm, nor is there the danger of it being watered down by a blending type of inheritance. On balance, the substitution of the almost immortal gene for the changeable gemmule does not make it more difficult to explain the action of natural selection, but it raises many vital questions for those who are interested in the breeding of better domestic plants and animals.

It is therefore necessary to consider carefully the evidence, if any, *against* the theory that the chromosomes alone transmit hereditary characters.

The most serious objections are naturally those which are based on experimental evidence, and we will take these first.

It is known beyond doubt that in plants the *plastids*, which carry chlorophyll and other pigments, have the capacity of self-reproduction, and that if a particular type of plastid is present in the egg-cell all the offspring will contain this type. If more than one type is present, one may be lost at a particular cell division and variegated tissue will arise; an example of this is the variegation in the Four o'clock, where whole branches may be green or white, and seeds from white branches give rise to seedlings with no chlorophyll, which soon die. It is possible that other characters in plants which

are inherited through the mother alone may be explained by the existence of plastid-like bodies in the cytoplasm.

In animals it has been suggested that the early stages in the development of the fertilized eggs are determined solely by the mother; but unfortunately enough evidence does not exist to prove that this kind of inheritance persists—that is to say, that there are elements in the cytoplasm, or at least outside the chromosomes, which perpetuate themselves. In one instance it is known for certain that the maternal effect is controlled by a genetic mechanism. This is the case of left- or right-handed coiling in the shells of a group of fresh-water snails. Right-handed coiling is dominant over left-handed, but the direction of coiling is determined by the nature of the egg *before* fertilization, so that a gene brought in by the sperm has to wait until the next generation before exerting its influence. Thus, a cross of left-handed coiled females to right-handed males gives *all* left-handed shells, although the F_1 *should* show dominance of right-handedness. This shows up in the F_2 when the genes segregate but the snails are all right-handed. The characteristic 3 : 1 ratio appears on self-fertilization of the F_2 snails (which are hermaphrodite but normally cross-fertilize). All the time the phenotypic expression lags behind the genotype but is nevertheless controlled by the usual genetic process. A similar case can be found in the pollen grains of sweet-peas, where the shape is determined before meiosis is complete, and the effect of a pair of allelomorphs controlling it is delayed until they act in the next (diploid) generation. This can be contrasted with the gene for waxy maize (Chapter VII).

With these objections to the chromosome theory, which do not carry a great deal of weight, it is convenient to take a general one: *that the characters with which the geneticist deals represent the finishing touches put to a basic structure which is determined by some non-genic mechanism.* As an analogy one might take a mass-produced motor-car; the critics would say that genes correspond to the workers who paint it, fit the wind-screen wiper, pump up the tyres, attach the number plates, and so on; while the basic process of inheritance corresponds to the main production line, where a different set of workers make and assemble the chassis and engine and all those parts which are fundamental to the functioning of the car and in which it resembles all other cars of its type. According to this argument the processes by which a fish egg becomes a fish, or a seed a tree, are not the same as those by which one fish becomes a mackerel and another a herring, or by which one seed grows to an oak and the other to a beech-tree.

Beyond a somewhat unsatisfactory challenge to produce evidence for the other type of hereditary mechanism, there is no direct answer to these criticisms. On the other hand, reasons can be suggested for the often superficial nature of the characters with which geneticists deal. In the first place, it is necessary to start with the most easily recognizable characters, and particularly ones which are not subject to a wide and continuous variation. This is true particularly of the genetical work on eye-colours in Drosophila, or on petal colour in plants.

In the second place there is a limit to the alterations of an organism produced by any means, whether

genetical or otherwise, beyond which it fails to develop at all. If it is true, as has been suggested in previous chapters, that the genes control single processes and that many genes may co-operate to produce a single important structure in the organism, the effect of altering the activity of a collection of them taken at random, either by mutation or duplication or deletion, is likely to be catastrophic. If we may return to our motor-car, a gene-mutation which removes the wind-screen wiper will not have a serious effect on the running of the car, but a gene-mutation which removes all the sparking-plugs will stop it at once; it is immaterial at what stage in the making of the *car* the genes operate. The chief difference between a car and a living thing is that the latter has, so to speak, to have its engine running all the time it is being made. For this reason the car will be completed but for the plugs, but the living organism in which such an essential part has failed to develop will die long before maturity.

The job of converting one type of car into another type cannot be achieved by walking into the factory one morning and telling a few of the workers to make differently shaped components; it requires a planned effort by the whole organization. Similarly we cannot expect that by shooting a few ionizing particles into the nucleus of a reptilian germ cell we shall produce an amphibian or a bird.

What *is* known about mutations, of all kinds, *is that they tend to be harmful. This is exactly what one would expect if the genes* DID *control the fundamental processes of development*, and at present this is the best argument which can be used to defend the contention

that genes control most of the inherited characters of living organisms.

Two further criticisms, which have a bearing on the use of genetics for improving cultivated plants and domestic animals, are worth considering here.

The first is that genetic explanations are satisfactory for qualitative characters but not for quantitative ones. It is argued that, for example, the yield of seed or length of straw in cereals do not show abrupt changes from plant to plant, but instead that a graded series exists from those with low seed yield to those with high seed yield, the majority of plants having yields falling somewhere in between. A familiar example of this kind of character is stature in man, where any group chosen at random, as in a company of the Home Guard, will have a few very tall and very short individuals, with a large number near the average height. These differences are not caused solely by such effects of the environment as variations in the fertility of the soil with the wheat plants, differences in income and hence in the standard of nutrition of the men, although this has some effect. In the case of the wheat it is possible to find strains which give a higher average yield than others, despite variations in the soil.

Because these characters varied *continuously* it was thought that Mendel's principles of segregation did not apply, but it now seems probable that the explanation lies in the existence of several gene pairs controlling each character. Some plants will be heterozygous for one pair, some for another. If one crosses plants with different average yields, the F_1 plants usually show an intermediate condition, but when they are self-fertilized a bigger spread of variation occurs in the F_2.

This is indirect evidence for combination and segregation, and for the present is regarded as an indication that a genetic mechanism is responsible.

A second phenomenon which is not very easy to explain is *hybrid vigour*, or *heterosis*. This is connected with the effects of *inbreeding*. If all the plants (or animals, where this is possible) in a population are self-fertilized, there is an increase in *homozygosity*. For example, if one self-fertilizes a plant heterozygous for *g* and *G*, the offspring will be one *G*/*G* to two *G*/*g* to one *g*/*g*, or in other words, half the offspring are homozygous, one quarter for one allele, one quarter for the other. If these plants are again self-fertilized the *G*/*G* and *g*/*g* plants will give more homozygotes, and the *G*/*g* individuals half heterozygotes, half homozygotes. So the number of heterozygotes is halved at each generation, and if all three types have an equal chance of survival the population will become more and more homozygous. The original heterozygous plants will be replaced by a series of homozygous strains. These homozygous strains are often called *pure lines*, and after a few generations of inbreeding they become genetically very uniform. They may of course become homozygous for deleterious genes, so that among the inbred lines some will be feeble and some robust. To what extent this occurs will depend upon the number of deleterious genes in the original population.

In plants like wheat which are habitually self-fertilized these disadvantageous characters will have been eliminated by natural selection, but in plants like maize which are usually cross-fertilized the population will have remained in a state of equilibrium, with a considerable degree of heterozygosity, and harmful

recessives will have survived. Consequently, inbreeding in plants which are habitually cross-fertilized is likely to reveal these harmful genes.

Inbreeding in bisexual species can be achieved by brother–sister matings, or by first-cousin matings, and its effects are ultimately much the same, though a larger number of generations is required to reach the same degree of homozygosity.

Hybrid vigour is capable of a tentative explanation on the following lines. Broadly speaking, it is true that when a cross is made between individuals from different strains of a species, between species, or even between genera, the F_1 generation, though it may be sterile, is extremely vigorous and hardy. The mule is the classical example of this.

The most satisfactory explanation so far produced is that all individuals tend for one reason or another to carry in a homozygous condition recessives which have a harmful, though small, effect on their vitality. Closely related organisms may be homozygous for the same deleterious genes, but widely separated organisms may be homozygous for different ones. When a cross is made, the hybrid is thus heterozygous for both sets of genes, and shows a corresponding gain in vigour over its parents. One plant might have the constitution *AAbbCcDD . . .*, where *b* was a harmful recessive, while a distantly related type might be *aaBBCcDD . . .* where *a* is harmful. The F_1 would then be all *AaBb . . .*

This genetical explanation relates hybrid vigour to the sometimes harmful effects of inbreeding and is the most satisfactory so far produced. Against it stands a comparative lack of specific experimental support.

When this and the preceding criticisms have been voiced there is little more that can be said against the general theory of gene-controlled inheritance. Certainly there is no alternative theory which can find sufficient support to challenge it, and in most countries of the world, although there are differences of opinion about such things as the unchangeable nature of the gene, it is accepted as a working basis for plant and animal breeding. In the Soviet Union, where the scientists have closer connections with the programmes of development of agriculture and industry, a violent controversy has raged for twenty years, and there exists a dominant school of thought (associated with the name of Lysenko) which favours a theory of inheritance similar in some respects to that held by Charles Darwin. While it is true that the " orthodox " geneticists in the U.S.S.R., as elsewhere, have not been able to provide explanations for all the phenomena of inheritance, there is no doubt that their opponents have yet to produce convincing experimental evidence for *their* point of view. The state of the controversy is therefore not very different in the Soviet Union from what it is in other countries, but it has been given much greater importance, and conducted with greater intensity, because on its outcome depends the steps to be taken in improving the quality of crops and livestock. To some extent the plant breeder in all countries has developed his own ideas about inheritance, and has ignored or discounted the work on Drosophila and other " academic " organisms; in the Soviet Union the two groups of workers have been thrown into contact, and the conflict which has developed has been between the practical breeder,

whose ideas, though leading to successful results, may be basically wrong and therefore *in the long run* require modification, and the academic scientist, whose ideas may be sound but who has insufficient experience to apply them in an economically useful way.

In 1948 a conference was held in Moscow at which the views of Lysenko were expounded more fully than hitherto. From the verbatim report it appears that he and his school accept the role of the chromosomes in the transmission of hereditary characters, but do not accept what they call the Weismann theory of an independent hereditary substance. They believe that the chromosomes are not the only particles of a living body which are concerned in heredity, and that under certain conditions the heredity of an organism can be altered by alterations in its environment.

The evidence which they bring forward to support their views is drawn mainly from the study of plants of economic importance, although they have also studied more academically a phenomenon which they call " vegetative hybridism." When one plant is grafted on to another, the one grafted (the *scion*) shows characters which are the direct result of the influence of the other (the *stock*) on it; this is well known to growers of fruit-trees. Lysenko and his school claim that the influence of the stock extends to the *offspring* of the scion, particularly if the latter is grafted at an early stage of its development—in other words, that characters may be inherited without a sexual process being involved. The success of Lysenko's doctrines at the conference was in part due to the much greater practical contributions made by his followers (who call themselves, after a famous Russian plant-breeder,

" Michurinists ") and also to certain philosophical difficulties of the " orthodox " genetical theory (cf. p. 88).

There is no doubt that Lysenko's work, and the theories which he bases on it, have been ignored unjustifiably by most geneticists, both in his own country and abroad. It would seem to the author that there can be no satisfactory development of the science beyond its present stage until his ideas have been considered seriously, particularly from the experimental point of view, and some serious answer made to his criticisms of modern genetics. In the Soviet Union it is evident that the most searching test of the correctness of Lysenko's views has already begun in the field of practice, and whether or not the rest of the world joins in, the next few decades will provide a most decisive answer.

There is a hint in the experiments with micro-organisms described in Chapter VIII that the cytoplasm of the gametes may be capable of carrying substances with a limited power of reproduction, and that the idea of the gene as dwelling in " splendid isolation " in the chromosome may have to be modified in the future. However this may be, further advances in the science of heredity are unlikely to be made by rejecting the genetical theory, but rather by erecting upon it *a theory which takes more account of the interaction between genes and the other cell-constituents, and hence, in the last resort, between the gene and the external environment of the organism which carries it.*

CHAPTER XII

THE IMPACT OF GENETICAL KNOWLEDGE ON THE LIFE OF MAN

WITH some conviction of the essential correctness of the genetical theory of inheritance, we can now examine the manifold problems of man as they are affected by an understanding of heredity. In doing so we must remember that it is only forty years since the word " genetics " was invented and that most of the experimental evidence on which we base our conviction has been accumulated in the last half-century.

Genetics can help man in two ways: by improving his efforts to breed better plants and animals for use in agriculture, and by helping him to understand himself.

The existing species of wild plants and animals have been evolved over hundreds of thousands of years and represent groups of organisms capable of surviving in the intensely competitive world of organic and inorganic nature. Each animal or plant species has had to stand on its feet against the world, and where it has failed to produce a satisfactory answer to new problems raised by its environment has become extinct. Some species have become extinct within the history of civilization; countless others in the long course of evolution.

When man first began to domesticate animals, or to cultivate plants, he provided a certain degree of protection for them, and so enabled them to develop in ways that otherwise would have been fatal to their

existence as a species. He found it possible to obtain organisms which were much more suited to his purposes by increased yield of seed, by increased growth of fleece, and so on.

The raw material from which the cultivated plants were obtained can sometimes be inferred from their present condition. It has already been mentioned that the wheats fall into three main classes by their chromosome numbers, suggesting that polyploidy has played a part in their origin from related grasses. The same is true of the potato, of the tobacco plant, of the cultivated banana, of sugar-cane, and so on. In most cases *allo*polyploidy is inferred, and of course is more likely to produce fertile types.

Another group of cultivated plants, including the cabbages, certain root crops, peas, beans, show little or no evidence of polyploidy when compared with wild species of similar types.

Thirdly, there are such plants as maize, the origin of which is extremely obscure and about which little direct information can be gained from comparison with its nearest wild relatives.

The plants were brought into cultivation and improved largely by empirical methods, and there are references to the *selection* of superior plants in the writings of the ancients. There can be no question that some plants and animals were in this way improved considerably, illustrations from the civilizations of the Middle East showing well-developed breeds of both. Similarly there are representations of maize cobs in the ruins of the great Central American centres of civilization.

Nearer our own times there have been consistent and

determined efforts to improve domesticated plants and animals, particularly in the eighteenth and nineteenth centuries. These and all earlier attempts were, however, based largely on a trial-and-error approach, and though successful were handicapped by the lack of scientifically established fundamental principles. There were also diversions created by the search for organisms which conformed to the desirable outward characteristics of the breed: breeding for the show-ring rather than for the farm.

During the domestication of wild species men have improved their methods of cultivation and have spread them over great tracts of virgin country; some of this expansion of crop areas has taken place in comparatively recent times, as in North America and Australia. As agricultural technique has developed, the aims of breeders have changed. The high-yielding dairy cow would be useless on the small peasant holding, where cattle are beasts of burden and no food-concentrates are available to maintain maximum milk production. The combine harvester, the latest word in arable farming, sets a new task for the plant breeder, requiring a crop which ripens evenly, and preferably one with a strong, short straw. The market gardener (who has reappeared with the rise of the great cities) demands a succession of varieties of vegetables, particularly for salads, which will enable him to grow crops all the year round—the example of lettuce illustrates this well.

It goes without saying that the full potentialities of a wild species are realized only gradually in its process of domestication. At first it is merely shielded from some of the competition which it encountered in the wild state and may for this reason grow rather more

successfully and give a greater yield. Later some attempt is made to eliminate the less productive lines, and later still it becomes possible to extend the season of growth, or in some other way to pass beyond the limits to which the wild species was confined.

This last process includes, of course, the removal of the species from its original home to quite new regions of the earth. The potato is a South American plant, but it has become a staple food crop of the Europeans; maize also, though to a lesser extent, has spread into the Old World. Sometimes this forced transportation has brought together closely related species which had originally been separated geographically. It is believed, for example, that our modern cultivated strawberry arose from the crossing of two species introduced from the Americas. Earlier strawberries cultivated here were derived from one or other of the two wild species found in Europe. In the seventeenth century the Virginian strawberry was brought to Europe from eastern North America, and about a century later came the Chilean strawberry. These two species differed markedly in the size, colour, and flavour of their fruits—that from North America being small, scarlet, and seedless; that from South America large, purple, and resembling pineapple in flavour—but it seems likely that they were crossed and gave rise to hybrids from which British breeders developed the modern varieties with their large, highly flavoured fruits.

In passing, we may notice that man has in at least one case inadvertently created a new *wild* species by bringing together two related wild species of grasses. The grass *Spartina Townsendii* was first seen growing near Southampton in 1870, and it now seems certain

that it arose from a hybrid between a European species *S. stricta* (haploid number, 35) and an American species *S. alterniflora* (haploid number, 28), which reached France about 1800 and was first seen at Southampton in 1829. (Doubling the chromosome number of the hybrid has given a fertile allopolyploid with a haploid number of 63.)

In the last resort the breeder is looking for desirable *genes*. Occasionally these show themselves outwardly, and must, of course, have done so in the wild species which were originally selected by man. In the course of cultivation others may show themselves and be selected, a process which can account for much progress in domestication. In more recent times the search for genes has included both the investigation of wild species closely related to the cultivated plant and the deliberate uncovering of recessive genes by inbreeding. Once desirable genes are discovered and combined in a new variety this tends to oust the older one, and with the development of a seed industry the tendency is for a few varieties of a particular crop plant to be grown almost universally. This means that the older varieties, and the genes they contain, are lost to the plant breeder. For instance, in medieval times wheat was grown from year to year without any very great effort at selection. Consequently, the descendants of these crops contain a useful "reservoir" of genes which have never been fully exploited. With the development of modern varieties the area sown with genetically "impure" seed has been progressively reduced, until there is now a danger that these plants will be lost altogether.

If we were reduced to the state in which all the

reservoirs of genes in cultivated species had dried up we should have to rely on mutation to provide us with new ones or repetitions of old ones. For this reason efforts are made to keep a wide selection of varieties in cultivation on an experimental scale. At the same time expeditions have been sent to what are believed to be the centres of origin of our crop plants—for example, Central Asia for cereals, the Andes for potatoes—to obtain samples of plants closely related to the ancestors of our modern varieties. Vavilov, the Russian geneticist, maintained a large collection of this kind at Leningrad up to the time the Germans besieged the city in 1941–42.

In the first place, then, a supply of genes is needed. Secondly, we require methods for sorting them out. Here the great advance at the beginning of the century was the realization that phenotype and genotype were not identical, that an individual possessing desirable characters might not pass them on to its offspring. The idea of "progeny testing" thus arose. In the progeny test the value of an individual plant or animal is measured *by the performance of its offspring*. This means that the process of selection is slower than it would be if each individual was measured by its own performance, since at least one generation has to elapse before it is accepted or rejected, but in the long run the method has proved its worth.

In this connection the differences between plant and animal breeding show themselves clearly. Most plants reach maturity in a year or two and then produce relatively large numbers of seeds. These can be stored for a season or two if necessary. On the other hand, domestic animals may produce only three or

four offspring in the whole course of their life and may take several years to reach maturity. The cost of producing a single offspring may be considerable unless it can be offset somehow or other. This is the case in cattle, for example, where the herd has almost always to pay its way, and selection may be very slow in producing any economic benefit whatsoever. Consequently, in animal breeding the testing of a particular parent, especially the female, can rarely be at all extensive, while with plants whole generations may be discarded without great loss and a variety of crosses made in any one season. The animal breeder must therefore be cautious and far-sighted, although, as we shall see later, there is at least one way in which his difficulties can be lessened.

Having found the desirable genes, the breeder next tries to " fix " them—that is to say, he attempts to obtain them in the homozygous form and then by close inbreeding to develop a " pure line." Sometimes, as in the case of the Blue Andalusian fowl mentioned earlier, this is impossible, but in most cases the " pure line " is at least theoretically possible.

So, to summarize, the breeder first searches for a supply of genes, next sorts them out, and finally fixes them in the homozygous condition, so that they can be given to the farmer for routine production. Let us next study this process in more detail.

By considering the problems of the plant breeder first we shall be able to see the similarity of general methods, but also, by contrast, the limitations put on animal breeding by the slow rate of reproduction and also by the fact that in most domestic animals the sexes are separate.

Crop and garden plants can be roughly divided into three types for our purpose: those which are habitually self-fertilized, those which are habitually cross-fertilized, and those which are usually propagated vegetatively, by tubers, cuttings, grafts, and so on.

The chief cereal crops of the world (excluding maize) are self-fertilized. This means that recessive genes arising by mutation quickly come to light in the homozygous form; the sowing of a crop of wheat is essentially a process of inbreeding, and by the selection of a single plant it is possible to build up a pure line fairly rapidly, there being no danger that unwanted genes will be brought in by chance cross-pollination with neighbouring fields of the same species. The aim of the breeder of cereals is therefore first to select single plants, and a high degree of skill is needed in assessing their potentialities. Some of the world-famous varieties of wheat have romantic histories. Red Fife is an example of this. A Scots Canadian, by mistake, sowed some winter wheat in the spring and harvested a single plant. This plant became the ancestor of all the Red Fife grown on the North American continent!

Although wheat and related crops are habitually self-fertilized, it is possible to cross-fertilize them. This has been done in an effort to combine the desirable characters of two varieties. Thus, the hard red spring wheat Marquis was produced by crossing Red Fife with a variety called Hard Red Calcutta. At first these crosses were made between different varieties of the same species, but in recent years it has been realized that crosses may be successful when made between plants of different *species*. One of the most notable

advances to the credit of U.S. plant breeders is the production of a hard red spring wheat resistant to the stem-rust fungus. This was the result of crossing the susceptible variety Marquis (a 21-chromosome wheat) with Jaroslav emmer (14 chromosomes), a wheat resistant to the fungus. The value of this discovery may be judged from the fact that stem-rust caused, in North Dakota alone, in 1935, losses estimated at a hundred million dollars' worth.

Even more ambitious attempts are being made in this direction, as for instance the attempt to increase the resistance of wheat to cold by crossing it to rye, or to make it a perennial crop by crossing it to certain perennial grasses. In all cases the fact that plants produced are habitually self-fertilized means that there is no difficulty in " fixing " the new qualities, once they are obtained.

With crops which are usually cross-pollinated two major difficulties arise. The first is that of ensuring that the variety, once obtained, is inbred systematically to preserve its characteristics. This cannot be done with any certainty in ordinary cultivation, and so it is often the case that new seed has to be obtained each year from areas where the varieties are grown sufficiently far apart to prevent cross-fertilization. The cabbage family is one example of this; we have already quoted an extreme example—that of the wide radish–cabbage cross. In allotments and gardens many varieties and species of these plants are grown close together and cross-pollination is more or less inevitable.

The second difficulty arises from the past history of the species of plant in question. In habitually self-

fertilized plants recessive genes are rapidly brought " into the open " by the inbreeding which is normal to the species, and the course of evolution has eliminated most of the harmful ones. In the cross-fertilized plants, on the other hand, considerable latitude was given to such genes, and it is only when the plant breeder begins to inbreed them systematically (in order to reveal desirable recessives) that they appear. Because of their very number they may be very difficult to eliminate economically.

The most important and typical cross-fertilized crop is undoubtedly *maize*, which occurs in several varieties of the same species, as field corn, pop corn, sweet corn, etc., and is one of the characteristic cultivated plants of the New World; in the United States it is grown chiefly as food for livestock. Because it carries separate male and female flowers it has been a particularly convenient subject for genetical study. The haploid chromosome number is 10, and all these have been mapped, upwards of 500 mutant genes being known. Because it is normally cross-fertilized, deliberate self-fertilization leads to the rapid uncovering of recessive genes normally present in the heterozygous state, and with increasing homozygosity the inbred lines show a noticeable loss of vigour. Even the most vigorous inbred lines show an initial decline in yield on continued cultivation, so that inbreeding and selection, although producing some improvement in the qualities, are incapable of exploiting its potentialities to the full. In recent years the whole system of maize growing has been transformed by the introduction of *hybrid corn*, which was designed to overcome the defects of inbred lines without losing the advantages gained by selection.

The earlier practice had been to grow a crop of a particular variety and to select a proportion of it for seed for next year. Under these conditions the plants were heterozygous for many characters, being pollinated at random by the wind, and the genetic constitution varied from year to year and from crop to crop of the "same" variety. Accordingly, to ensure reproducible results in a typical routine of hybrid seed production four inbred lines of corn are used (*A*, *B*, *C*, and *D*). These are maintained by suitable protection from cross-fertilization. In the first year *A* and *B* are grown in alternate rows in large plots and all the male flowers (tassels) removed from the *A* plants before maturity. The cobs harvested from the *A* plants are thus all $A \times B$. Similarly *C* and *D* are crossed. The yields of seeds at this stage are low, since all four inbred strains are relatively feeble in growth and seed production. The seeds from the two crosses are therefore sown next year in alternate rows and give vigorous plants which are again crossed, and give a high yield of $(A \times B) \times (C \times D)$ seed.

Thus in two years a high yield of doubly hybrid seed is produced which is issued to farmers. They are warned that if they save seed from their crops for re-sowing they will get progressively lower yields as the homozygosity of their plants increases, and are advised to buy new hybrid seed each year. In this way the yield of maize may be increased by 10–30 per cent over that got with the best open-pollinated varieties; the total effect of such an increase over 100 million acres planted each year in the U.S.A. is difficult to imagine.

The third type of crop is that reproduced mainly by vegetative means. The obvious example is the potato,

but almost equally important are sugar-cane and most of our native fruits, which are propagated either by cuttings, runners, or grafts. In all these examples the possibility of sexual reproduction still exists, but the technique of cultivation disregards it. However, it is still possible to use sexual reproduction as a means of uncovering recessive genes or to try out new gene combinations. New varieties of potatoes are usually produced in this way; the *true* seeds of the plant, which are borne in the little berries which develop from fertilized flowers, when planted give rise to plants bearing tubers, which can then be used to propagate the chosen variety without further sexual reproduction. The immense advantages of vegetative methods of propagation are, first, that the descendants of a particular plant are more than inbred, they are a *clone*, and, secondly, barring mutations or other accidents to the cell nuclei, they should not alter in genetic constitution at all in the course of many generations. This is " fixing " of characters *par excellence*.

Secondly, the plant can be grown as a crop even when it is sexually sterile. Thus hybrids which would stand no chance of survival if they depended on a sexual process of reproduction can be propagated indefinitely. Good examples of these are the apples, of which some of our best varieties, such as Bramley's Seedling, are triploids. It will be noticed from its name that Bramley's Seedling was obtained initially by planting an apple seed, but it is now propagated exclusively by grafting. In some fruits the failure to set seed may be a positive advantage from the human point of view; in bananas seeds rarely develop, and many varieties of citrous fruits are

practically sterile—i.e., free from pips. All that is required is that the necessary stimulus be given to set fruit. The reader will recall the examples of genetic incompatibility in cherries given in Chapter IX; with them the act of pollination is not sufficient to cause setting, fertilization and the growth of the seed being necessary. Recently it has been shown that unpollinated tomato flowers will set fruit when sprayed with a plant-hormone preparation, suggesting that it may be possible eventually to dispense with pollen in fruit crops which are propagated vegetatively.

Summarizing, we may say that the plant breeder can utilize genetic knowledge to the full, provided always that he takes into account the special features of each crop plant. He begins by selection, with or without inbreeding, and attempts to establish the selected types, either by inbreeding or by vegetative propagation. Where possible he uses crossing, sometimes of distantly related species, and where sterility results he can resort to vegetative reproduction and attempt by the use of certain treatments, as by colchicine, to induce chromosome doubling and the production of allopolyploid varieties.

Many of these techniques are denied to the *animal* breeder, and perhaps for this reason there is less to show for the genetical work on domestic animals, which include mainly birds and mammals. In both these groups the species are bisexual, so that inbreeding cannot be practised as closely as in hermaphrodite plants; the number of offspring from a single cross is very limited; and the time taken between generations may be longer than in plants. The general effect of these three factors is to slow down the speed of

investigation, and for this reason geneticists have attempted to gain information about animal genetics by using small relatively fast-breeding mammals, like mice. Although the use of small " pilot " animals can indicate the most useful lines of approach to the problem, it cannot replace work with the particular species concerned. Hence the application of new scientific methods to the breeding of cattle, sheep, and horses is at present in progress but is not likely to yield spectacular results for many years to come. The introduction of artificial insemination on a large scale in the Soviet Union, and later in other countries, can speed up the present rule-of-thumb methods used to build up our present-day herds, by increasing the number of offspring of a male with desirable qualities.

In poultry breeding there has been some progress, particularly by the use of progeny testing. It is more useful to classify a particular male bird by the egg-laying success of his offspring than by the performance of his mother or sisters. The importance of this principle was recognized in America when attempts to improve the egg-laying capacity of pullets by breeding from the females showing the highest *first year* egg-yield had no success over the course of nine years.

It need hardly be emphasized that in animals attempts to induce polyploidy, or to make wide crosses, with a view to further breeding are very likely to be unsuccessful, since even partial sterility may make it impossible to breed from the resulting animals, and no equivalent of vegetative reproduction can ensure the continuance of a completely sterile genotype. (It can be used, however, if it is not intended as the starting-point of a new breed; the mule is a useful animal,

although it cannot be bred from.) The animal breeder is thus left to search for valuable genes and gene combinations, and to combine them by the slow, and often expensive, method of repeated crosses and back-crosses.

The difficulties of the animal breeder are also the difficulties of the scientist investigating animal genetics, so that the one reflects upon the other; a lack of fundamental knowledge is at once the cause and effect of the relative backwardness in this field. In contrast, with a much studied, convenient biological material such as Drosophila, the advances in detailed knowledge of inheritance make it relatively easy to produce flies of a desired constitution, such as the *ClB* flies used by Muller for the studies of mutation rates.

In man the difficulties presented by the type and speed of animal reproduction are aggravated by the restrictions of social behaviour. These make it impossible to conduct experiments in the breeding of man on any but the smallest scale, and make it necessary for our experimental evidence to be *indirect* in nature. Further, the matings which yield the most enlightening results to the geneticist, the crossing of male and female children of the same parent and the back-cross to one or other parent, are both excluded (it would seem, rightly) by the laws against incest.

Faced by such difficulties the geneticist might have been excused from attempting to apply to man the body of knowledge gained from a study of other organisms. He has, however, pieced together enough evidence to establish the existence of a gene-controlled process in human heredity, and thus confirmed the reasonable hypothesis that man, who is a multicellular

animal with 24 haploid chromosomes and an *XX* : *XY* sex-determining mechanism, does not differ in this respect from his fellow creatures. More genes are, in fact, known in man than in any other mammal, but this is probably because of the backwardness of animal genetics generally.

Much evidence has come from studies of families in which some easily recognizable defect occurred. Some of these are peculiar in that they are *sex-linked.* The most striking example of this is *haemophilia*, a condition in which the blood fails to clot; so that even a small cut or scratch results in a serious loss of blood, and any more severe accident is usually fatal. This is most often encountered in men, but a careful study of many pedigrees shows that a man inherits it from his apparently normal mother. The simplest explanation of the condition is that it is caused by a recessive gene in the *X*-chromosome, which reveals itself in the *XY* sex, the male. On this assumption, female children homozygous for the gene should occur, but if so they would never survive menstruation and reach sexual maturity and would therefore never pass the gene on. This gene is given an added interest by the fact that Queen Victoria was heterozygous for it and passed it on to one son and two of her daughters.

There are reasons for believing that there exists a rarer allelomorph of this gene, causing a less severe condition; both genes are sufficiently common, and yet sufficiently harmful to those carrying them, to make it probable that they arise fairly frequently by mutation, and that a woman who passes it on to her sons may not have received it from her parents.

Another, much more common, sex-linked recessive

gene is that for red–green colour-blindness, men being for this reason more likely to be colour-blind than women.

Recessive genes are also known that are not sex-linked, among them those which control the metabolism of tyrosine (see Chapter VIII) and a peculiar one recently discovered which makes its (homozygous) possessor unable to taste a substance *phenylthiourea*. About 30 per cent of the population are unable to do this; to the remaining 70 per cent it is extremely bitter. Because the gene is so common it is easy to discover the results of " crosses " of tasters to non-tasters and so to confirm the hypothesis that a single recessive is involved.

A more important example of gene-determined characteristics in man is that of the blood groupings. As most readers will have discovered, all blood collected for transfusion purposes is " grouped " before use, because blood from some individuals may kill a particular recipient. Before the reasons for this were known blood transfusion was so risky as to be unusable. Nowadays, thanks to the discoveries of Landsteiner, we know that the blood of all human beings falls into four main *groups AB*, *A*, *B*, and *O*. Blood can be separated into *corpuscles* (minute cells containing the coloured component) and plasma, and the corpuscles from group *A* blood are found to stick together (*agglutinate*) when mixed with a substance called α (an *agglutinin*), present in the plasma of groups *B* and *O*. The corpuscles do this because they contain another substance which we can represent by *A*. Similarly *AB* corpuscles contain *A* and with it another substance *B*, which is found also alone in *B* corpuscles,

and which makes them agglutinate in plasma containing β. So one gets a pattern like this:

Group.	Substance in corpuscles.	Substance in plasma.
AB	*A*, *B*	None
A	*A*	β
B	*B*	α
O	(none)	α, β

In other words, each blood is so composed that its plasma does not agglutinate its corpuscles. If blood *AB* is mixed (by transfusion or in the test-tube) with blood *A*, the *AB* corpuscles will clump together; in the blood vessels of a living human being this would cause death by obstructing the blood flow. However, *A* blood can be transfused safely into a patient of group *A*; and similarly for the other groups. The corpuscles of group *O* (containing neither *A* nor *B*) are not agglutinated by any other blood, and for this reason blood of this kind can be used for *universal* donations, the effect of the plasma α and β on the recipient's corpuscles not having serious consequences, since they are diluted by the recipient's blood.

Genetically, *A*, *B*, and *O* represent multiple alleles, so that *AB* individuals are *A*/*B*, *A* individuals *A*/*A* or *A*/*O*, *B* individuals *B*/*B* or *B*/*O*, and *O* individuals *O*/*O*, the double recessive. Typical percentages of these types, which vary somewhat from population to population, are 5·7, 13·4, 43·7, and 37·3 respectively. The particular interest of these genes is that they help in determining the parentage of children. Thus two *O*/*O* individuals should have all *O*/*O* children (barring mutations) and similarly an *A*/*B* parent cannot have a *O*/*O* child. Where the paternity of a child is in dispute, a

test of the blood groups of mother, child, and the accused man can decide that such a relationship is *not* possible, but not that the man is certainly the father of the child, because many other men are of the same blood group.

Further investigation of human bloods has shown that the red corpuscles may contain other substances inherited like *A* and *B*. If human red cells are injected into rabbits there appears in the blood plasma of the rabbit a substance (an agglutinin) which causes human blood from the same individual to agglutinate. By testing the blood of many persons it was discovered that two substances, *M* and *N*, occurred in human red corpuscles, individuals being *M*/*N*, *M*/*M*, or *N*/*N*. Blood from an *M*/*M* individual injected into a rabbit gives rise to agglutinins which act on the blood of all other *M*/*M* individuals, and those of constitution *M*/*N*, but not the blood of *N*/*N* individuals.

The *M* and *N* factors differ from the *A*,*B*,*O* factors in that there are no naturally occurring agglutinins, like α and β. In order to distinguish individuals of these groups we have to inject blood of a known group into rabbits beforehand, obtain the agglutinin, and use this for testing. It has been found that the bloods of apes and certain monkeys contain one or more of the *A*,*B*,*O*,*M*, and *N* substances, chimpanzees having *A*,*O*,*M*,*N*, but other species probably fewer, *B* being most widely distributed.

In 1940 Landsteiner and one of his colleagues discovered that certain human bloods were agglutinated by an agglutinin prepared by the injection into rabbits of the blood of Rhesus monkeys. For this reason the name of " Rh factor " was given to the substance in the human cells responsible for the effect. It was

further found that when human blood of this (Rh-positive) type was transfused into individuals not possessing the factor (Rh-negative), agglutinins were formed against it.

It is now believed that this factor, which is found in about 80 per cent of human bloods, may be responsible for a blood disease of new-born children. If a woman is " Rh-negative " she carries two recessive genes allelomorphic with the dominant Rh gene, and if she marries a man who is Rh-positive, and who therefore carries at least one Rh gene, she may bear children who are Rh-positive. Thus if the husband was Rh/Rh all her children would be Rh-positive. If during pregnancy small amounts of blood found their way from the unborn child into the mother's blood vessels they might stimulate the production of anti-Rh agglutinins. These, passing back into the child, would cause its blood to be agglutinated and produce an anaemia which might be fatal. A second pregnancy would find the mother already producing agglutinins, and consequently the danger would be even greater. Now that this is known, the blood of the father and mother can be tested to see whether they are Rh-positive or negative, and steps taken to give the infant a complete transfusion of new blood at birth if it should show signs of anaemia.

Certain *dominant* mutant genes are known to exist; Haldane has described one in which the heterozygous condition renders its possessors liable to blistered feet in hot weather. The nature of the effect produced by the homozygous condition is unknown. Inheritance through dominant genes *should* be distinguishable from that through recessives by the fact that the condition is

never passed on by normal individuals, but there appear to be some conditions which are due to dominant genes with low penetrance (see Chapter VII), which show themselves in only a proportion of individuals carrying the gene.

As in other organisms, it can be seen that the genes reveal themselves by their variation from the normal, and that those which attract attention are usually responsible for some defect or other. The total number of such genes in a human population can be calculated from the frequency with which they show themselves, recessive genes being rather like an iceberg in that the greater proportion of them lies submerged in heterozygous combination, much as the greater bulk of the iceberg is under water, and even if the double recessives are constantly removed by deaths before marriage or before many children have been born (as in haemophilia), as the sun might melt the exposed part of the iceberg, there still remains a large reserve to rise above the level of the sea. In contrast to this, dominants are quickly eliminated if they are harmful, and if new ones are constantly appearing by mutation a balance is quickly reached.

Haldane has suggested that the change in Europe from small inbreeding village communities (which still exist even in this country today) to large, freely mixing urban populations has provided a state of affairs in which recessive mutations can accumulate. Previously some were completely eliminated as defective homozygotes in the small inbreeding populations, but now they have a longer run for their money. This is the idea of hybrid corn transferred to human populations, the small inbred communities representing different

homozygous stocks, and the large towns the fields in which the hybrids are produced and the effect of harmful recessives reduced. Whether the phenomenon of hybrid vigour has its parallel in the new industrial civilization is a matter for speculation.

Man is not often content with accumulating knowledge for knowledge's sake, and genetics is no exception to this. Despite the primitive state of our knowledge of human heredity there were soon demands that human breeding should be controlled in the interests of the "race." The supporters of these ideas in their most extreme form found themselves standing shoulder to shoulder with Adolf Hitler and his disciples, who did not hesitate to carry out such measures as compulsory sterilization as part of their general campaign of terror against their political opponents and against the Jews.

The justification for laws or customs which deprive the individual of his rights to beget children must not be sought in the minds of politicians, or even of philosophers, but in evidence accumulated by careful scientific investigation. There already exist certain prohibitions against marriages between closely related individuals, although these are by no means universal in their application nor entirely effective in practice. In general one might say that they are designed to discourage the uncovering of recessive genes by homozygosis, but in small communities they may be relatively ineffective in this although formally observed.

Careful surveys have been made in recent years with the idea of discovering what physical and mental defects are due to inbreeding. By studying hospital records and interviewing patients it is possible to

discover the closeness of relationship of their parents or, at the very least, whether they are related at all. In this way some diseases can be associated with inbreeding, while others appear independent of it, so that it is possible to advise parents who have had one defective child whether this is likely to have been due to their hereditary make-up or not. If the defect were known to be hereditary it might be best for this couple to have no more children. This applies as much to physical as to mental defect.

Study made of mental defectives shows that mental deficiency is not only of many kinds in its outward appearance, but also in its inheritance, some conditions being commoner among children of close marriages, others apparently independent of this factor. The conclusion to be drawn here is not the old and hasty one, " sterilize all mental defectives," but " continue such investigations, particularly of conditions which appear to be hereditary."

It can be calculated that compulsory sterilization of all individuals showing the *effects* of a harmful recessive gene would have little useful effect in reducing the occurrence of the defect. The most effective method would be to find some means of detecting the gene in the *heterozygous* condition and preventing the marriages of two heterozygous individuals. In the meantime, general discouragement of inbreeding can help to a limited extent.

Other eugenists have expressed concern at the fact that the " upper classes " have relatively few children by comparison with their social " inferiors " and have urged measures to combat this tendency. In so doing they have assumed that those with greater wealth or

social standing possess more desirable hereditary characters, an assumption that is quite unjustified without a careful study of the nature of socially desirable characters and of personal qualities which are inheritable. It should also be clear from the distinction between genotype and phenotype that there is no guarantee that a particular character will be best *propagated* by the person exhibiting it in the extreme form; there would seem to be a good case for " progeny testing " if ever restrictions were imposed on the size of families.

A very extensive investigation has been made in America of the ability and personality of human twins. These are of two kinds: those which arise from the fertilization of two eggs by two sperm, and those which are the result of a separation of a single fertilized egg into two halves at some early stage of development. The latter are called *identical twins* and are genetically identical; the others, though sharing pre-natal life and being born at the same time, are as genetically unlike as any two children of the same parents. Consequently, these two kinds of twins provide a useful means of distinguishing between the effects of environment and those of inheritance. Additional information has been gained by studying identical twins who have been separated from birth and brought up in different households. Broadly speaking, these are more alike than non-identical twins brought up together, but less alike than the same individual tested on two separate occasions.

These tests showed that in physical characters identical twins were more alike than ordinary twins, and this extended to such things as scores in intelli-

gence tests. When the question of personality and general level of educational attainment was considered, much larger differences were found, suggesting that in these respects the environment plays a greater part. On the other hand, aptitude and liking for music, and certain other "interests," were found often in both members of an identical twin.

From these and other studies it seems that while heredity plays some part in determining the personality and ability of human beings, there are very large effects of environment which make it impossible to draw general conclusions about the superiority of social classes. Tests of intelligence, which are usually designed to eliminate the effects of environment as much as possible, show that for every child in this country who received secondary education before the war, there were four or more who were equally intelligent yet were denied it. This estimate takes no account of the children whose parents may have done little or nothing to justify their present social position, whether high or low.

While it is reasonable to encourage the reproductive efforts of the more able members of society, we are still far from the time when we shall be able to breed a better nation, even if by then we are agreed on what are the socially desirable qualities.

The family album is, I am afraid, still a bit of a mystery, but we can see the answers to some of our original questions.

Men and women carry in each cell of their bodies 24 pairs of chromosomes, but each parent gives only half of these to each child. These are not chosen entirely at random, one coming from each pair; but even so

there are $2 \times 2 \times 2 \times 2 \times \ldots$ (up to 12 times) ways in which 24 chromosomes can be chosen out of 48. This will not make any difference to the gametes unless the chromosomes of each pair differ in some respect, normally by carrying different alleles. If we assume that each chromosome pair carries a single heterozygous gene-pair, then there will be more than 4,000 different gametes produced by each parent, and 16,000,000 possible zygotes from their combination. If both parents are heterozygous for the same gene loci two in every four of these will be alike, but if they are heterozygous for completely different sets of genes all will be different. Even allowing for the effects of dominance, it is no wonder that the children of a particular marriage are not all exactly alike!

On the other hand, if we consider a particular gene-pair, the number of ways in which the children can differ in this respect is small. If the father is A/A in respect of blood groups, and the mother B/O, then the children will be either A/B or A/O. If the mother carries one recessive gene for haemophilia, on the average half her sons will be sufferers from the disease. We can predict the inheritance of those characters which are readily distinguishable. Others, such as height, eye-colour, and so on, are probably controlled by several genes, and the possible types of offspring correspondingly increased.

A human ovum will develop into a girl if the sperm fertilizing it carries an *X*-chromosome, into a boy if the sperm carries a *Y*; but although these types are produced in equal numbers, other factors intervene, so that more boys than girls are conceived. The determination of the sex of a particular child is thus due to

chance—i.e., we do not know any way of controlling it. The genes carried in that part of the *X*-chromosome which does not cross over with the *Y* will be sex-linked. That is to say, women may carry undetected genes which will show up in their sons, men differing from women mainly in carrying less genes; maleness is probably due to a lower ratio of *X*-chromosome genes to autosome genes.

As for the inheritance of genius, we may hazard the guess that this is often the product of a favourable *gene-combination* rather than the appearance of a single recessive gene in the homozygous condition. If so, the chances of a genius passing on this whole combination to his offspring is remote when one remembers the effect of crossing-over in breaking up gene-combinations, even when they occur in the same chromosome. As yet we have only the most rudimentary knowledge of linkage (except for the *X*-chromosome), and hence of crossing-over, in man.

In conclusion, it is sufficient to point out the youthful characteristics of the science of genetics, its lack of experience, but its undoubted vigour. No one would pretend that these justify its immediate application to the control of human reproduction, although there is no reason to doubt that this will eventually become a possibility. In the meantime we must see that the atomic bomb, which in its cruder aspect is a weapon of destruction, but in a more subtle way can wreak havoc through its effects on the germ plasm, does not reduce the human species to a few scattered populations of genetically defective individuals, which no amount of genetical knowledge (if it is still remembered) can bring back to a healthy and flourishing condition.

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