CHAPTER 2

The Hereditary Mechanism

Das Sein ist ewig; denn Gesetze
Bewahren die lebend'gen Schätze,
Aus welchen sich das All geschmückt.[1] GOETHE

THE CLASSICAL PHYSICIST'S EXPECTATION, FAR FROM BEING TRIVIAL, IS WRONG

Thus we have come to the conclusion that an organism and all the biologically relevant processes that it experiences must have an extremely 'many-atomic' structure and must be safeguarded against haphazard, 'single-atomic' events attaining too great importance. That, the 'naïve physicist' tells us, is essential, so that the organism may, so to speak, have sufficiently accurate physical laws on which to draw for setting up its marvellously regular and well-ordered working. How do these conclusions, reached, biologically speaking, *a priori* (that is, from the purely physical point of view), fit in with actual biological facts?

At first sight one is inclined to think that the conclusions are little more than trivial. A biologist of, say, thirty years ago might have said that, although it was quite suitable for a popular lecturer to emphasize the importance, in the organism as elsewhere, of statistical physics, the point was, in fact, rather a familiar truism. For, naturally, not only the body of an adult individual of any higher species, but every single cell composing it contains a 'cosmical' number of single atoms of

[1]Being is eternal; for laws there are to conserve the treasures of life on which the Universe draws for beauty.

every kind. And every particular physiological process that we observe, either within the cell or in its interaction with the environment, appears – or appeared thirty years ago – to involve such enormous numbers of single atoms and single atomic processes that all the relevant laws of physics and physical chemistry would be safeguarded even under the very exacting demands of statistical physics in respect of 'large numbers'; this demand I illustrated just now by the $\sqrt{n}$ rule.

Today, we know that this opinion would have been a mistake. As we shall presently see, incredibly small groups of atoms, much too small to display exact statistical laws, do play a dominating role in the very orderly and lawful events within a living organism. They have control of the observable large-scale features which the organism acquires in the course of its development, they determine important characteristics of its functioning; and in all this very sharp and very strict biological laws are displayed.

I must begin with giving a brief summary of the situation in biology, more especially in genetics – in other words, I have to summarize the present state of knowledge in a subject of which I am not a master. This cannot be helped and I apologize, particularly to any biologist, for the dilettante character of my summary. On the other hand, I beg leave to put the prevailing ideas before you more or less dogmatically. A poor theoretical physicist could not be expected to produce anything like a competent survey of the experimental evidence, which consists of a large number of long and beautifully interwoven series of breeding experiments of truly unprecedented ingenuity on the one hand and of direct observations of the living cell, conducted with all the refinement of modern microscopy, on the other.

THE HEREDITARY CODE-SCRIPT (CHROMOSOMES)

Let me use the word 'pattern' of an organism in the sense in which the biologist calls it 'the four-dimensional pattern', meaning not only the structure and functioning of that organism in the adult, or in any other particular stage, but the

whole of its ontogenetic development from the fertilized egg cell to the stage of maturity, when the organism begins to reproduce itself. Now, this whole four-dimensional pattern is known to be determined by the structure of that one cell, the fertilized egg. Moreover, we know that it is essentially determined by the structure of only a small part of that cell, its nucleus. This nucleus, in the ordinary 'resting state' of the cell, usually appears as a network of chromatine,[1] distributed over the cell. But in the vitally important processes of cell division (mitosis and meiosis, see below) it is seen to consist of a set of particles, usually fibre-shaped or rod-like, called the chromosomes, which number 8 or 12 or, in man, 48. But I ought really to have written these illustrative numbers as 2×4, 2×6, . . ., 2×24, . . ., and I ought to have spoken of two sets, in order to use the expression in the customary meaning of the biologist. For though the single chromosomes are sometimes clearly distinguished and individualized by shape and size, the two sets are almost entirely alike. As we shall see in a moment, one set comes from the mother (egg cell), one from the father (fertilizing spermatozoon). It is these chromosomes, or probably only an axial skeleton fibre of what we actually see under the microscope as the chromosome, that contain in some kind of code-script the entire pattern of the individual's future development and of its functioning in the mature state. Every complete set of chromosomes contains the full code; so there are, as a rule, two copies of the latter in the fertilized egg cell, which forms the earliest stage of the future individual.

In calling the structure of the chromosome fibres a code-script we mean that the all-penetrating mind, once conceived by Laplace, to which every causal connection lay immediately open, could tell from their structure whether the egg would develop, under suitable conditions, into a black cock or into a speckled hen, into a fly or a maize plant, a rhododendron, a beetle, a mouse or a woman. To which we may add, that the appearances of the egg cells are very often remarkably similar;

[1]The word means 'the substance which takes on colour', viz. in a certain dyeing process used in microscopic technique.

and even when they are not, as in the case of the comparatively gigantic eggs of birds and reptiles, the difference is not so much in the relevant structures as in the nutritive material which in these cases is added for obvious reasons.

But the term code-script is, of course, too narrow. The chromosome structures are at the same time instrumental in bringing about the development they foreshadow. They are law-code and executive power – or, to use another simile, they are architect's plan and builder's craft – in one.

GROWTH OF THE BODY BY CELL DIVISION (MITOSIS)

How do the chromosomes behave in ontogenesis?[1]

The growth of an organism is effected by consecutive cell divisions. Such a cell division is called mitosis. It is, in the life of a cell, not such a very frequent event as one might expect, considering the enormous number of cells of which our body is composed. In the beginning the growth is rapid. The egg divides into two 'daughter cells' which, at the next step, will produce a generation of four, then of 8, 16, 32, 64, . . ., etc. The frequency of division will not remain exactly the same in all parts of the growing body, and that will break the regularity of these numbers. But from their rapid increase we infer by an easy computation that on the average as few as 50 or 60 successive divisions suffice to produce the number of cells[2] in a grown man – or, say, ten times the number,[2] taking into account the exchange of cells during lifetime. Thus, a body cell of mine is, on the average, only the 50th or 60th 'descendant' of the egg that was I.

IN MITOSIS EVERY CHROMOSOME IS DUPLICATED

How do the chromosomes behave on mitosis? They duplicate

[1]Ontogenesis is the development of the individual, during its lifetime, as opposed to phylogenesis, the development of species within geological periods.
[2]Very roughly, a hundred or a thousand (English) billions.

– both sets, both copies of the code, duplicate. The process has been intensively studied under the microscope and is of paramount interest, but much too involved to describe here in detail. The salient point is that each of the two 'daughter cells' gets a dowry of two further complete sets of chromosomes exactly similar to those of the parent cell. So all the body cells are exactly alike as regards their chromosome treasure.[1]

However little we understand the device we cannot but think that it must be in some way very relevant to the functioning of the organism, that every single cell, even a less important one, should be in possession of a complete (double) copy of the code-script. Some time ago we were told in the newspapers that in his African campaign General Montgomery made a point of having every single soldier of his army meticulously informed of all his designs. If that is true (as it conceivably might be, considering the high intelligence and reliability of his troops) it provides an excellent analogy to our case, in which the corresponding fact certainly is literally true. The most surprising fact is the doubleness of the chromosome set, maintained throughout the mitotic divisions. That it is the outstanding feature of the genetic mechanism is most strikingly revealed by the one and only departure from the rule, which we have now to discuss.

REDUCTIVE DIVISION (MEIOSIS) AND FERTILIZATION (SYNGAMY)

Very soon after the development of the individual has set in, a group of cells is reserved for producing at a later stage the so-called gametes, the sperma cells or egg cells, as the case may be, needed for the reproduction of the individual in maturity. 'Reserved' means that they do not serve other purposes in the meantime and suffer many fewer mitotic divisions. The exceptional or reductive division (called meiosis) is the one by which eventually, on maturity, the gametes are produced from these reserved cells, as a rule only a short

[1]The biologist will forgive me for disregarding in this brief summary the exceptional case of mosaics.

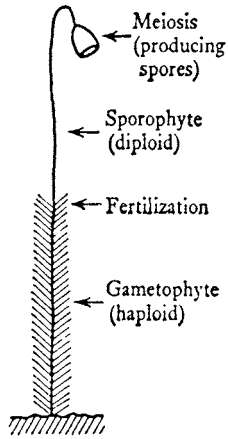

Fig. 5. Alternation of Generations.

time before syngamy is to take place. In meiosis the double chromosome set of the parent cell simply separates into two single sets, one of which goes to each of the two daughter cells, the gametes. In other words, the mitotic doubling of the number of chromosomes does not take place in meiosis, the number remains constant and thus every gamete receives only half – that is, only one complete copy of the code, not two, e.g. in man only 24, not $2 \times 24 = 48$.

Cells with only one chromosome set are called haploid (from Greek ἁπλοῦς, single). Thus the gametes are haploid, the ordinary body cells diploid (from Greek διπλοῦς, double). Individuals with three, four, . . . or generally speaking with many chromosome sets in all their body cells occur occasionally; the latter are then called triploid, tetraploid, . . ., polyploid.

In the act of syngamy the male gamete (spermatozoon) and the female gamete (egg), both haploid cells, coalesce to form the fertilized egg cell, which is thus diploid. One of its chromosome sets comes from the mother, one from the father.

HAPLOID INDIVIDUALS

One other point needs rectification. Though not indispensable for our purpose it is of real interest, since it shows that actually a fairly complete code-script of the 'pattern' is contained in every single set of chromosomes.

There are instances of meiosis not being followed shortly after by fertilization, the haploid cell (the 'gamete') undergoing meanwhile numerous mitotic cell divisions, which result in building up a complete haploid individual. This is the case in the male bee, the drone, which is produced parthenogenetically, that is, from non-fertilized and therefore haploid eggs of the queen. The drone has no father! All its body cells are haploid. If you please, you may call it a grossly exaggerated spermatozoon; and actually, as everybody knows, to function as such happens to be its one and only task in life. However, that is perhaps a ludicrous point of view. For the case is not quite unique. There are families of plants in which the haploid gamete which is produced by meiosis and is called a spore in such cases falls to the ground and, like a seed, develops into a true haploid plant comparable in size with the diploid. Fig. 5 is a rough sketch of a moss, well known in our forests. The leafy lower part is the haploid plant, called the gametophyte, because at its upper end it develops sex organs and gametes, which by mutual fertilization produce in the ordinary way the diploid plant, the bare stem with the capsule at the top. This is called the sporophyte, because it produces, by meiosis, the spores in the capsule at the top. When the capsule opens, the spores fall to the ground and develop into a leafy stem, etc. The course of events is appropriately called alternation of generations. You may, if you choose, look upon the ordinary case, man and the animals, in the same way. But the 'gametophyte' is then as a rule a very short-lived, unicellular generation, spermatozoon or egg cell as the case may be. Our body corresponds to the sporophyte. Our 'spores' are the reserved cells from which, by meiosis, the unicellular generation springs.

THE OUTSTANDING RELEVANCE OF THE REDUCTIVE DIVISION

The important, the really fateful event in the process of reproduction of the individual is not fertilization but meiosis. One set of chromosomes is from the father, one from the mother. Neither chance nor destiny can interfere with that. Every man[1] owes just half of his inheritance to his mother, half of it to his father. That one or the other strain seems often to prevail is due to other reasons which we shall come to later. (Sex itself is, of course, the simplest instance of such prevalence.)

But when you trace the origin of your inheritance back to your grandparents, the case is different. Let me fix attention on my paternal set of chromosomes, in particular on one of them, say No. 5. It is a faithful replica either of the No. 5 my father received from his father or of the No. 5 he had received from his mother. The issue was decided by a 50:50 chance in the meiosis taking place in my father's body in November 1886 and producing the spermatozoon which a few days later was to be effective in begetting me. Exactly the same story could be repeated about chromosomes Nos. 1, 2, 3, . . ., 24 of my paternal set, and *mutatis mutandis* about every one of my maternal chromosomes. Moreover, all the 48 issues are entirely independent. Even if it were known that my paternal chromosome No. 5 came from my grandfather Josef Schrödinger, the No. 7 still stands an equal chance of being either also from him, or from his wife Marie, née Bogner.

CROSSING-OVER. LOCATION OF PROPERTIES

But pure chance has been given even a wider range in mixing the grandparental inheritance in the offspring than would appear from the preceding description, in which it has been

[1] At any rate, every *woman*. To avoid prolixity, I have excluded from this summary the highly interesting sphere of sex determination and sex-linked properties (as, for example, so-called colour blindness).

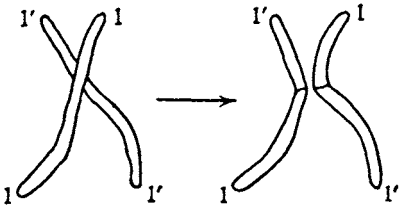

Fig. 6. *Crossing-over.* Left: the two homologous chromosomes in contact. Right: after exchange and separation.

tacitly assumed, or even explicitly stated, that a particular chromosome as a whole was either from the grandfather or from the grandmother; in other words that the single chromosomes are passed on undivided. In actual fact they are not, or not always. Before being separated in the reductive division, say the one in the father's body, any two 'homologous' chromosomes come into close contact with each other, during which they sometimes exchange entire portions in the way illustrated in Fig. 6. By this process, called 'crossing-over', two properties situated in the respective parts of that chromosome will be separated in the grandchild, who will follow the grandfather in one of them, the grandmother in the other one. The act of crossing-over, being neither very rare nor very frequent, has provided us with invaluable information regarding the location of properties in the chromosomes. For a full account we should have to draw on conceptions not introduced before the next chapter (e.g. heterozygosy, dominance, etc.); but as that would take us beyond the range of this little book, let me indicate the salient point right away.

If there were no crossing-over, two properties for which the same chromosome is responsible would always be passed on together, no descendant receiving one of them without receiving the other as well; but two properties, due to different chromosomes, would either stand a 50:50 chance of being separated or they would invariably be separated – the latter when they were situated in homologous chromosomes of the same ancestor, which could never go together.

These rules and chances are interfered with by crossing-over. Hence the probability of this event can be ascertained by registering carefully the percentage composition of the offspring in extended breeding experiments, suitably laid out for the purpose. In analysing the statistics, one accepts the suggestive working hypothesis that the 'linkage' between two properties situated in the same chromosome, is the less frequently broken by crossing-over, the nearer they lie to each other. For then there is less chance of the point of exchange lying between them, whereas properties located near the opposite ends of the chromosomes are separated by every crossing-over. (Much the same applies to the recombination of properties located in homologous chromosomes of the same ancestor.) In this way one may expect to get from the 'statistics of linkage' a sort of 'map of properties' within every chromosome.

These anticipations have been fully confirmed. In the cases to which tests have been thoroughly applied (mainly, but not only, *Drosophila*) the tested properties actually divide into as many separate groups, with no linkage from group to group, as there are different chromosomes (four in *Drosophila*). Within every group a linear map of properties can be drawn up which accounts quantitatively for the degree of linkage between any two out of that group, so that there is little doubt that they actually are located, and located along a line, as the rod-like shape of the chromosome suggests.

Of course, the scheme of the hereditary mechanism, as drawn up here, is still rather empty and colourless, even slightly naïve. For we have not said what exactly we understand by a property. It seems neither adequate nor possible to dissect into discrete 'properties' the pattern of an organism which is essentially a unity, a 'whole'. Now, what we actually state in any particular case is, that a pair of ancestors were different in a certain well-defined respect (say, one had blue eyes, the other brown), and that the offspring follows in this respect either one or the other. What we locate in the chromosome is the seat of this difference. (We call it, in technical language, a 'locus', or, if we think of the hypothetical

material structure underlying it, a 'gene'.) Difference of property, to my view, is really the fundamental concept rather than property itself, notwithstanding the apparent linguistic and logical contradiction of this statement. The differences of properties actually are discrete, as will emerge in the next chapter when we have to speak of mutations and the dry scheme hitherto presented will, as I hope, acquire more life and colour.

MAXIMUM SIZE OF A GENE

We have just introduced the term gene for the hypothetical material carrier of a definite hereditary feature. We must now stress two points which will be highly relevant to our investigation. The first is the size – or, better, the maximum size – of such a carrier; in other words, to how small a volume can we trace the location? The second point will be the permanence of a gene, to be inferred from the durability of the hereditary pattern.

As regards the size, there are two entirely independent estimates, one resting on genetic evidence (breeding experiments), the other on cytological evidence (direct microscopic inspection). The first is, in principle, simple enough. After having, in the way described above, located in the chromosome a considerable number of different (large-scale) features (say of the *Drosophila* fly) within a particular one of its chromosomes, to get the required estimate we need only divide the measured length of that chromosome by the number of features and multiply by the cross-section. For, of course, we count as different only such features as are occasionally separated by crossing-over, so that they cannot be due to the same (microscopic or molecular) structure. On the other hand, it is clear that our estimate can only give a maximum size, because the number of features isolated by genetic analysis is continually increasing as work goes on.

The other estimate, though based on microscopic inspection, is really far less direct. Certain cells of *Drosophila* (namely, those of its salivary glands) are, for some reason,

enormously enlarged, and so are their chromosomes. In them you distinguish a crowded pattern of transverse dark bands across the fibre. C. D. Darlington has remarked that the number of these bands (2,000 in the case he uses) is, though considerably larger, yet roughly of the same order of magnitude as the number of genes located in that chromosome by breeding experiments. He inclines to regard these bands as indicating the actual genes (or separations of genes). Dividing the length of the chromosome, measured in a normal-sized cell by their number (2,000), he finds the volume of a gene equal to a cube of edge 300 Å. Considering the roughness of the estimates, we may regard this to be also the size obtained by the first method.

SMALL NUMBERS

A full discussion of the bearing of statistical physics on all the facts I am recalling – or perhaps, I ought to say, of the bearing of these facts on the use of statistical physics in the living cell – will follow later. But let me draw attention at this point to the fact that 300 Å is only about 100 or 150 atomic distances in a liquid or in a solid, so that a gene contains certainly not more than about a million or a few million atoms. That number is much too small (from the $\sqrt{n}$ point of view) to entail an orderly and lawful behaviour according to statistical physics – and that means according to physics. It is too small, even if all these atoms played the same role, as they do in a gas or in a drop of liquid. And the gene is most certainly not just a homogeneous drop of liquid. It is probably a large protein molecule, in which every atom, every radical, every heterocyclic ring plays an individual role, more or less different from that played by any of the other similar atoms, radicals, or rings. This, at any rate, is the opinion of leading geneticists such as Haldane and Darlington, and we shall soon have to refer to genetic experiments which come very near to proving it.

PERMANENCE

Let us now turn to the second highly relevant question: What degree of permanence do we encounter in hereditary properties and what must we therefore attribute to the material structures which carry them?

The answer to this can really be given without any special investigation. The mere fact that we speak of hereditary properties indicates that we recognize the permanence to be almost absolute. For we must not forget that what is passed on by the parent to the child is not just this or that peculiarity, a hooked nose, short fingers, a tendency to rheumatism, haemophilia, dichromasy, etc. Such features we may conveniently select for studying the laws of heredity. But actually it is the whole (four-dimensional) pattern of the 'phenotype', the visible and manifest nature of the individual, which is reproduced without appreciable change for generations, permanent within centuries – though not within tens of thousands of years – and borne at each transmission by the material structure of the nuclei of the two cells which unite to form the fertilized egg cell. That is a marvel – than which only one is greater; one that, if intimately connected with it, yet lies on a different plane. I mean the fact that we, whose total being is entirely based on a marvellous interplay of this very kind, yet possess the power of acquiring considerable knowledge about it. I think it possible that this knowledge may advance to little short of a complete understanding – of the first marvel. The second may well be beyond human understanding.