# CHAPTER II

## REGENERATION

### 1. Its Cause and Origin in the Idioplasm

It does not follow directly from what has already been said with regard to the structure of the germ-plasm, that lost parts can be more or less completely replaced. The only deduction that can be made so far is, that all the parts of which the entire organism is composed are formed *once* during the development of the organism from the egg: no explanation is given of the fact that individual parts can be produced a *second time*, when they have been lost by the action of external influences. During ontogeny, the determinants of the part in question pass from the ovum into the segmentation-cells, from these into embryonic cells of a later stage, and finally into those cells which constitute the fully formed part. If this part is forcibly removed from the organism to which it belongs, its determinants are removed along with it: this follows from what has already been assumed with regard to the ontogenetic stages of the idioplasm. We must now therefore attempt to explain the fact that a part of the body can nevertheless be reconstructed.

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If the capacity for regeneration were possible at all, it is obvious that it would have to be introduced by Nature, for its physiological importance is apparent. The power of replacing larger or smaller parts of the body must in all cases be useful to the organism, and is often indeed indispensable to its further existence. Arnold Lang * is certainly right in considering the faculty of regeneration in animals to be one of the arrangements for protection which prevent the species from perishing. The capability of completely restoring those parts of the body which have become injured by the bite of an enemy, forms a more

* 'Ueber den Einfluss der festsitzenden Lebensweise auf die Thiere,' &c., Jena, 1888, p. 108.

efficient protection in many of the lower animals — more especially in polypes and worms — than would the possession of shells, stings, poison-organs, and all other kinds of weapons, or even protective coloration. For although all these arrangements certainly serve as a protection from many enemies, and from various dangers, they are not *always* effective, and therefore the capability of restoring losses of substance would certainly be extremely valuable in any case. This fact must not be forgotten in any inquiry with regard to the question of regeneration. If we consider how highly important regeneration is from a physiological point of view, its wide and even general distribution in the animal kingdom need not surprise us, and we shall be able to understand why it has been introduced even into the course of normal life: for the functions of certain organs depend on the fact that their parts continually undergo destruction, and are then correspondingly renewed. In this case it is the process of life itself, and not an external enemy, that destroys the life of a cell. I refer, of course, to the process of *physiological regeneration*.

Our knowledge of histology is not yet sufficient for us to be able to determine what tissue-cells in the higher animals become worn out by use during life, and have therefore to be continually replaced; but it has been proved in many cases that the wearing away of the cells goes on incessantly, and that life could not last if these cells were not constantly replaced. Such a constant loss and renewal of the cells occurs in the cases of the epidermis of the higher Vertebrates, the human finger-nails, blood-corpuscles, hairs and feathers, claws and hoofs, the epithelial lining of the respiratory and other passages, and even in the antlers of stags. In all these cases a continual or periodic wasting away or shedding of groups of cells occurs normally, and a corresponding replacement of these cells is one of the normal functions of the body, and is therefore provided for.

It is not difficult to explain the simplest of these cases of physiological regeneration theoretically. If a tissue such as the human epidermis, for instance, consists of *one* kind of cell only, it is only necessary, in order that regeneration may take place, that all these cells should not be thrown off simultaneously, and that the tissue should be composed of cells of various ages, the youngest of which, under certain influences of nutrition and pressure, always retain the power of reproduction, and so form a stock in which the necessary substitutes for the older cells can constantly be produced. The whole supply of the corresponding determinants is not therefore removed from the body simultaneously by the loss of the worn-out cells, for the young cells which remain contain determinants of the same kind. In the human epidermis, this stock of young cells constitutes the so-called 'rete Malpighii' or 'mucous layer,' in which new cells are constantly being formed by division; these, in proportion as they become older, are gradually pushed upwards mechanically from the deeper into the superficial layers, while the deepest layer of all consists entirely of young cells which are capable of division.

No special theoretical assumption need be made to explain this process. We must only suppose that the first formed epidermic cells are endowed in advance with a capacity for reproduction during many generations. It must be assumed that the reproductive power of a cell is regulated by the idioplasm, because the power and rate of multiplication are essential qualities of a cell, and, as we have seen, are controlled by the nuclear substance. But we cannot at present even form a conjecture as to which qnalities of the idioplasm the degree and rate of the capacity for reproduction are due. We must be satisfied with attributing to the cells which form the epidermis of the embryo an idioplasm possessing a definite reproductive power, which gradually decreases. We can further only suppose that the idioplasm retains its constitution during life, or, in other words, that the determinant of a particular part of the epidermis is always retained in the permanent stock of young cells. Regeneration depends simply on a regular increase of those cells which contain epidermic idioplasm.

The nature of the epidermis is not the same in different parts of the human skin: thus it differs on the volar and on the dorsal surfaces of the fingers; and, again, on the two basal and on the ungual segments. But this fact does not stand in the way of the theoretical explanation of regeneration, for the determinants of different parts must differ somewhat from one another. Even in places where two or more dissimilar parts are situated close together, the retention of the limits between them, during their continual regeneration, may be explained simply by the fact that the different regions of the tissue are regenerated by formative cells possessing different determinants.

Many tissues, even in the highest animals, when they have suffered an *abnormal loss of substance*, are renewed in precisely the same way as in the cases of physiological regeneration already mentioned. Thus in mammals, for instance, portions of muscular tissue, of epithelium covering an organ or lining the duct of a gland, and of bone, can be replaced by cellular elements of a similar kind; and recent researches in pathological anatomy render it almost certain that all these regenerative processes originate in the cells of the tissue which is to be replaced. Hence these tissue-cells retain the power of multiplying by division, but they only begin to exercise this power in response to certain external stimuli, more particularly to that which is produced by a loss of substance in their immediate vicinity. Thus epithelial cells multiply around a defect in the epithelium; and in an injured muscle, the nuclei multiply and cause the surrounding protoplasm to be transformed into cells, which become spindle-shaped, and give rise to muscle-fibres. In both these cases we must merely attribute to the idioplasm the capacity for multiplication: the cells in question only begin to divide when influenced by a stimulus due to the loss of substance, or, as it would be expressed in the language of modern pathology,* 'by the removal of the resistances to growth.' Thus in these very simple cases of the abnormal loss of parts, the rest of the tissue gives rise to a stock of determinants from which replacement of the part can occur.

In more complicated tissues, the process of regeneration is less simple. Thus Fraisse has shown that in the Amphibia *the entire epidermis, together with the slime-glands and the integumentary sense-organs*, is regenerated by the epidermic cells in the vicinity of the defect. In this case also, the new material is furnished by the deeper uncornified layers of the epidermis. But the newly-formed cells do not all develop into the same kind of tissue. The main mass of them gives rise to the stratified epidermis, while others 'unite to form pearl-shaped masses in the deeper part of the epidermis, the cells becoming grouped around an imaginary centre.' 'Connective tissue-cells then migrate from the cutis, and these masses, each consisting of from ten to twenty cells, thus become marked off from the epidermis.' 'At the same time pigment-cells wander into the

* Cf. E. Ziegler, 'Lehrbuch der pathologischen Anatomie,' Jena, 1890.

epidermis, and finally the development of smooth muscle fibres takes place.' * New integumentary sense-organs arise in a similar way. A number of young cells become arranged so as to form a rounded mass in the deeper portion of the newly-formed epidermis: these then become elongated in a direction vertical to the surface of the epidermis, the central element undergoing differentiation into sensory cells, while the peripheral ones form an investment around these.

It is evident that the process is rendered more complicated in this case by the fact that the young epidermic cells, formed by the proliferation of those already present, give rise to cells of various kinds, viz., to ordinary epidermic cells, to gland cells, and to sensory and 'investing' cells; and the complication is further increased by all these cells being arranged and localised in a perfectly definite and more or less prescribed manner. We certainly must not assume that the formative cells which undergo these various differentiations are really identical, although they may appear so. It cannot possibly depend on external influences alone whether one of these subsequently becomes transformed into a horny, glandular, or sensory cell; for we cannot assume the existence of such a regular and localised difference in the external influences. The various differentiations of the formative cells must therefore depend on their own nature — that is to say, on the determinants contained within them, which have hitherto been latent but which have now become ripe, and have impressed a specific character upon each cell. *These formative cells must have contained different sorts of determinants from the first.*

Fraisse compares the processes which can be observed in the regeneration of the skin in Amphibia with those which occur in the embryogeny of this class, and shows that they are essentially similar. We shall therefore be justified in imagining these processes — which are invisible to us even under the highest powers of the microscope — to be homologous with those which take place during the development of the embryo.

We can thus further assume that the stratified cells in the 'mucous layer' of the epidermis, although apparently all alike,

* Cf. Fraisse, 'Die Regeneration von Geweben u. Organen bei den Wirbelthieren, besonders bei Amphibien u. Reptilien.' Cassel and Berlin, 1885.

— as are those cells which form the first rudiment of the embryonic integument, — must nevertheless possess several kinds of determinants. We can hardly venture to say whether the three kinds of determinants with which we are here concerned are all present together in the formative cells, and only become distributed amongst special cells when regeneration sets in, or whether they are distributed amongst special cells *from the first*. *Either* arrangement is possible. Hence we may assume that some of the young formative cells contain determinants for the glands, and others those for horny or sensory cells, and that the proportional numbers and topographical arrangement of these are definitely fixed from the first. A precisely similar assumption is also necessary in the case of embryogeny.

If, for instance, the sensory organs of the lateral line in a fish or amphibian occur only along the lateral lines and their branches, we must suppose that the subdivision of the idioplasm of the ectodermic cells occurs during the development of the epidermis in such a way that the cells containing the determinants of these sensory organs come to be situated only along the lateral lines, and only in definite places on these lines. If now, all the formative cells of the sensory organs do not undergo further development at once, but some of them, on the contrary, remain undeveloped in the immediate neighbourhood — *i.e.*, in the deep layer of young cells — until a necessity for regeneration arises, we can understand in principle why a similar topographical arrangement and numerical relation of the sensory organs to the remaining epidermic elements occurs in the case of regeneration, as well as in that of the primary formation of the epidermis in the embryo.

The idioplasm of the cells does not alone decide what will happen in regenerative processes of this kind. This is shown by the fact that the occurrence of regenerative cell-multiplication depends on a loss of substance, and that the cells cease to proliferate as soon as the defect is made good. The stimulus to the further proliferation of the cells ceases at the same time. These facts, however, only give us a very vague insight into the causes of the limitation of the regenerative process; and we shall presently see that the above explanation is insufficient in more complicated cases of regeneration, and that we must, indeed, assume in addition the existence of other regulating factors, which are situated within the active cells, and not outside them.

It is well known that the limbs of a salamander grow again after they have been cut off, and we owe our accurate knowledge of the regenerative processes concerned mainly to the researches of Götte * and Fraisse.† The investigations of these observers show that the regeneration of the limbs and their formation in embryogeny take place in a similar manner: the individual parts and segments of the extremity become developed in the same order, and are formed of similar cell-material in each instance. Both here and in the case of the epidermis described above, the regeneration is *palingenetic*.

If we take as our basis the law, which holds good at any rate as regards Vertebrates, that in regeneration each specific tissue can only reproduce its own specific cells, we can test the theory of regeneration by taking as an example a single tissue of an extremity. It is certain as regards the bones, for instance, that regeneration always proceeds from the injured bone, or rather from its periosteum. If the extremity is disarticulated from the shoulder-girdle, for example, and the bones are uninjured, these latter do not become re-formed. Although it cannot be denied that the various tissues which are required for the regeneration of the entire limb have an influence upon one another, especially when pressure is exerted by one part on another situated near to it, it is clear that the formation of new bones depends entirely on the bones present in the stump of the amputated limb, which not only determine the quality of the tissue, but also regulate the size and shape of the bone which is to be formed anew. These last-mentioned facts are the most important of all in explaining the phenomenon of regeneration of a limb. From what has already been said, it is evident that the bony tissue, including the periosteum, *can* be formed from the cells of the corresponding pre-existing parts. All that is necessary in order that the process may take place is a supply of cells, capable of proliferation, which contain 'bone-idioplasm,' and which are incited to multiply by the stimulus due to the injury in the tissue surrounding them. The regeneration of the epidermis may be explained in a similar manner. But as regards these bones, it is not merely the production of bony tissue of a definite

* Götte, 'Uber Entwickelung u. Regeneration des Gliedmassen-Skeletts der Molche,' Leipzig, 1879.

† Fraisse, *loc. cit.* on p. 97.

structure which has to be considered, but *the formation of a definite number of bones of a definite shape and size, arranged in a definite series*, must also be taken into account. What assumptions must we make in order to explain such an accurately prescribed and complex mode of construction of these parts? If the fore-limb of a newt (*Triton*) is cut off between the shoulder and elbow, not only does the lost portion of the humerus become formed afresh, but the radius and ulna, and all the bones of the wrist and hand, are regenerated accurately, even as regards the number of segments. It seems hardly possible that so complex a structure could be produced merely by the co-operation of proliferating cells, and it might be supposed that an invisible power — a *spiritus rector* or a *vis formativa* — must be present to direct their mode of increase and arrangement. We are nevertheless probably right in assuming that no such external direction takes place, and that the complex structures in living beings are produced merely by the agency of the forces which are present in the individual cells.

We can understand these processes to some extent in the case of embryogeny if we base our reasoning on the principle of the gradual transformation of the idioplasm, which has already been treated of in connection with ontogeny. This principle may be roughly illustrated with respect to the skeleton of the anterior extremity in the following manner.

When the fore-limb of a Triton begins to arise as a small blunt elevation of the skin, it consists of cells of the external and middle embryonic layers. The whole of the former, and that portion of the latter which forms the cutis, may be left out of consideration; they together give rise to the integument. The rest of the mesoderm now forms a mass of cells which have not yet begun to undergo differentiation, and which individually do not apparently differ essentially from one another. They must, nevertheless, be very different as regards the primary constituents which they contain, for some of them will subsequently give rise, for instance, to muscles, others to connective tissue or to blood-vessels, and others, again, to bones. These cells, which are so differently predisposed, must therefore contain various determinants, which, when they obtain control over them in the course of further cell-divisions, impress on the subsequent generations the character of muscle- or bone-cells.

Each of these kinds of cells must be present from the first in a perfectly definite number, and must occupy a perfectly definite position.

Let us follow out this line of reasoning with regard to one system of organs, namely, the bones, and assume for the sake of simplicity that only a single bone-forming cell is present in the first rudiment of the limb. This cell would virtually contain the entire skeleton of the limb; and we should have to attribute to its idioplasm the power not only of giving the succeeding cells of a certain number of generations the character of bone-forming cells, but also of determining the entire sequence of these cells as regards quantity, quality, and mutual arrangement, as well as the rhythm in which the divisions will follow one another. For the particular point at which an interruption occurs in the continuity of the bone, and consequently also the boundary line between two segments of the bony chain, might essentially depend, indeed, on this rhythm.

We must therefore suppose that the composition of the idioplasm of the first primordial bone-cell of the limb causes all these sequences to take place: in other words, *the idioplasm must contain the determinants of all the succeeding bone-cells.* This may be illustrated by the following diagram (fig. 3), in which the actual processes, which concern hundreds of thousands of cells, are represented as greatly abbreviated, and the different generations of cells are indicated arbitrarily by a genealogical tree, which, however, does not by any means always represent their actual connection.

Each primary cell of the individual bones is represented in the figure by a circle, and is supposed to be so simple that it can be controlled by *one* determinant. Thus the primary cell of the entire series of bones is controlled by determinant 1, but also contains the determinants 2-35 in its ids. In the first cell-division this cell divides into two, — the primary cells of the upper arm (humerus), and of the fore-arm and hand. The former contains determinant 2, and its further division is indicated by the cells containing determinants *2a-2x*. The latter contains the remaining determinants 3-35, which become separated into smaller and smaller groups in each cell-division, until finally each cell only contains a *single* determinant. The diagram only represents the main bones of the extremity, — the individual carpals are omitted.

Let us now return to the question of regeneration. If each cell in the fully-formed bone only contains that kind of idioplasm which controls it, and which is therefore the molecular expression of its own particular nature, it would be impossible to understand how the regeneration of the bone could be effected — when, for instance, it had been cut through longitudinally.

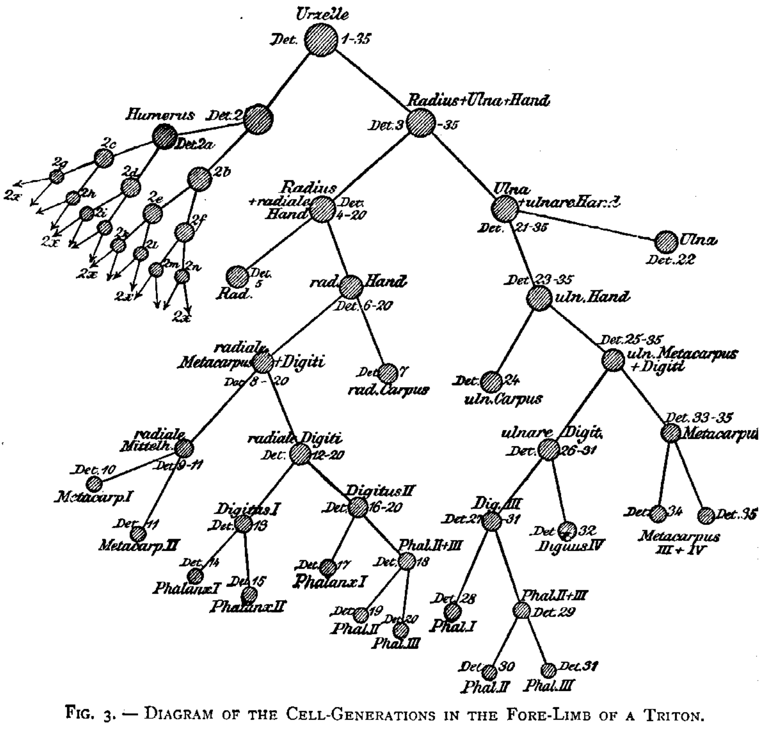


FIG. 3. — DIAGRAM OF THE CELL-GENERATIONS IN THE FORE-LIMB OF A TRITON.

Supposing that a stimulus, produced by the injury, caused the cells of the injured part to undergo multiplication: bony tissue would then, indeed, be developed, but a bone of a definite shape and size would not necessarily be formed. The formation of a definite bone can only take place if the proliferating cells possess, in addition to their active determinants, a supply of determinants which control the missing parts which have to be renewed. If therefore we wish to suppose that Blumenbach's '*nisus formativus*' is situated in the idioplasm of the cell, it appears necessary to assume that each cell capable of regeneration contains an *accessory idioplasm*, consisting of the determinants of the parts which can be regenerated by it, in addition to its primary idioplasm. Thus, for instance, the cells in the bone of the upper-arm must contain, in addition to their controlling determinant 2, the determinants 3-35 as accessory idioplasm, which can cause all the bony parts of the fore-arm to be formed anew; the cells of the radius, again, must contain the determinants 4-20 as accessory idioplasm for the reconstruction of the radial portion of the wrist and hand.

This theoretical illustration may be looked upon, indeed, as representing the phenomena as they occur in reality. It is very possible that the required accessory idioplasm becomes separated from the disintegrating embryonic idioplasm in the earliest stage of development of the entire organ. According to our assumption, the individual determinants are present *singly* in the germ-plasm, and their multiplication increases the further ontogeny advances. As only those determinants which correspond to parts to be formed subsequently are required in the accessory idioplasm, the material for the latter is always present; and we need only assume that in each division of the primary cell of any bone, a portion of the determinants required for the formation of the subsequent parts becomes split off as secondary idioplasm, and remains inactive within the cell until a cause for regeneration arises.

I shall speak of this group of determinants as *accessory idioplasm* ('Neben-Idioplasma'), and its component determinants as *supplementary determinants* ('Ersatz-Determinanten'). We may imagine that these form a special and minute group enclosed within the id in the neighbourhood of the determinants which control the cell in question. A similar assumption may be made as regards the individual bones of the entire limb. The regeneration of the bisected humerus can be explained by supposing that each cell capable of regeneration possesses an accessory idioplasm, containing the determinants of the cells which will subsequently be formed in a distal direction; this formation will be possible because the necessary 'determinant-material' is present. The process only depends on the fact that in each differential cell-division a certain number of determinants, which ripen later on, become split off from the rest, and are retained in the cell as accessory idioplasm. The mechanism for regeneration is certainly a very complicated one, for each separate bone is controlled by a number of different determinants, and not by a single one; and all these special determinants are contained in the accessory idioplasm. As far as we can judge from the investigations made hitherto, the bones are at any rate regenerated in detail fairly exactly. The complexity of the mechanism accounts, in my opinion, for the fact that the fore-limb, which has such a marked power of regeneration in the salamander, has lost this power completely in the higher Vertebrates, for in them the mechanism would have become too complex.

A simpler mechanism than that which we have supposed to exist can only be conceived, if, with Herbert Spencer,* we attribute to each of the units composing the body the power combining to form any necessary organ just when it is wanted. We might then compare the entire animal to a large crystal, in the individual parts of which 'there dwells the intrinsic aptitude to aggregate into the form of that species; just as in the atoms of a salt there dwells the intrinsic aptitude to crystallise in a particular way.' The only difference between the particles of the crystal and those of the organism would be that the former are all permanently alike; and that the latter, in order that regeneration may be possible, are arranged in many different ways, according to whether an entire limb, a tail, a gill, or a single toe, fore-arm, or finger is to be replaced. How are the 'units' shown in each individual case what part is missing, and what form their arrangement is to take in order to produce the part anew? We are thus once more brought back to Blumenbach's '*nisus formativus*.' Spencer himself says:—'If in the case of the crystal we say that the whole aggregate exerts over its parts a force which constrains the newly-integrated atoms to take a certain definite form, we must, in the case of the organism, assume an analogous force.' This force would correspond to what was formerly spoken of as the '*spiritus rector*' or '*nisus formativus*;' and even supposing it to exist, it does not in the least help us in the attempt to explain the mechanism of the phenom-

* Herbert Spencer, 'The Principles of Biology,' Vol. 1, p. 181.

ena. Spencer adds that his view 'in truth is not a hypothesis,' but only 'a generalised expression of facts;' and remarks in another passage, that although it is 'difficult' to imagine regeneration as a sort of process of crystallisation, '*we see that it is so.*' It is just this point that I must object to. We see that it is so, or rather appears to be so, *sometimes*, but we also see that it is often *not* so. If the units of the body were capable of becoming modified at will under the influence of the whole, and of crystallising into the missing part, they must be able to do so in all species and in all organisms. This, however, is not the case. The limb of a salamander can be regenerated, and that of a lizard cannot. In a special section of this chapter I shall be able to show in greater detail that regeneration depends on special adaptation, and not on a *general* capacity of the animal-body.

It will be unnecessary to give a special diagram illustrating the regeneration of a single bone, such as that of the upper arm, and showing the supplementary determinants of each of the cells composing the bone which are necessary in order that regeneration may set in at any point. The diagram given for the entire limb is sufficient to make the general principle clear: an approach to an explanation of the actual details is out of the question, as is evident if we compare the number of cells given in the diagram with that of which the bones actually consist. For this reason I have not attempted to enter into minute histological details, or to define the quality of the cells which are capable of regeneration, — that is, to state whether they belong to the periosteum or to the bone itself, and whether all or only certain cells take part in the process. We only require a diagram which can be adapted to the actual details of the processes when these are known. It is sufficient at present to show that regeneration may be understood by considering the activity of the cells themselves, without having recourse to the assumption of an unknown directive agency. The '*nisus formativus*' descends from its previous position as a single force directing the whole, and breaks up into an unlimited number of material particles which are situated in the individual cells, and each of which prescribes the course of life of the cell. These particles are determined as regards their kind, and are distributed to their proper places so accurately, that by their united effect they give rise to a composite whole, such as, for instance, a series of bones, together with their articular capsules and ligaments, and the muscles, nerves, blood-vessels, connective tissue, and integument which come into relation with them. The diagram I have given to illustrate the regeneration of a bone can obviously be adapted to represent any other part or tissue. We must not look upon the bone as something quite disconnected from the rest of the limb, as we may very likely be inclined to do if we are specialists. The bone is in reality connected most intimately along its entire surface with the surrounding tissues, — the periosteum and loose connective tissue external to the latter, the numerous blood-vessels which penetrate into the substance of the bone, the nerves, and so on. The first rudiment of the limb consists, in fact, of a mass of mesodermic cells, which give no indication of the various structures which will later be developed from them. Nevertheless, their differentiation does not, in my opinion, depend on their accidental position within the limb, or in fact on any other external influences, but is primarily due to their individual nature, that is, *to the constitution of their idioplasm*. The determinants composing the id control the subsequent development of the cell and of its successors. The further changes which the id undergoes in the course of cell-division, and the manner in which the determinants undergo disintegration in the ids of the daughter-cells of all the subsequent generations, is decided by the composition of the id.

We can thus understand, at least to some extent, how it is possible that such a complicated part as a limb, the structure of which is so accurately prescribed, can arise by degrees from a mass of cells which are apparently all similar to one another. The harmony of the whole is primarily brought about by the variation and increase of the cells, the kind and rhythm of which respectively, is prescribed by the idioplasm of each individual cell, rather than by the mutual influence of the cells during their gradual differentiation. A muscle becomes developed at any definite spot, because one particular cell amongst all the apparently similar cells in the first rudiment of the limb contained the determinants which are capable of giving to a large number of the successors of this cell the special character of muscle-cells; and because, again, the id of this particular cell caused a rhythm of multiplication to set in, which, on mechanical grounds, rendered it necessary that certain successors of this cell which contained muscle-determinants should take up their position in the precise region of the limb in which this particular muscle is situated.

We must not, however, imply from what has been said above, that external influences are of no importance whatever in ontogeny, but merely that they certainly only play a secondary part in the process. A limb will certainly grow crooked if a corresponding external pressure is brought to bear upon it. Growing cells do not cease to multiply directly they are subjected to abnormal external influences, for they can accommodate themselves to circumstances. It is such cases as the regeneration of broken bones and the formation of new joints under abnormal external conditions, which prove that the cells continue to perform their functions of growing and of giving rise to organs under circumstances which deviate very markedly from the normal. These false joints also show what a considerable power of adaptation is possessed by the cells, and how efficient may be the parts which these cells are able to produce under abnormal conditions. But although the principle formulated by Roux * of the *struggle of the parts*, or as it might well be called '*intrabiontic selection*,' is certainly a very important one, I think it would be a great mistake to refer the normal process of ontogeny mainly to this principle. The groups and masses of cells must certainly press upon one another during the process of differentiation: in the process of the formation of a joint, for instance, proliferating connective-tissue cells do actually force themselves amongst the cartilage cells in one part of the rudimentary bone, in order to separate them from one another. But this proliferation and pressure are taken account of, just as much as are the processes of dissolution or absorption that occur in those cells in the primordial cartilage which are situated in the region of the joint. It might be supposed that the existence of so-called 'identical' human twins contradict my conception of ontogeny; for although they are undoubtedly derived from a single ovum and sperm-cell, and hence possess the same kind of germ-plasm, they are never really identical, but only very similar to one another. But apart from the fact that the *absolute* identity of the germ-plasm has not been proved in these cases, the very close resemblance between these twins shows

* W. Roux, 'Der Kampf der Theile im Organismus,' Leipzig, 1881.

how slightly the diversity of external influences affects the development of an organism. How wonderfully accurately the course of ontogeny must be prescribed, if it can be kept to so closely, through thousands of generations of cells, that 'identical' twins result! We may compare the process of development of such twins with the course taken by two ships, which, starting from the same place, proceed along the same devious route which has been carefully mapped out beforehand in all its thousands of definite changes in direction, until each finally reaches the same distant shore independently, within a mile of the other.

A careful consideration of such a case as this leaves no doubt that a very exact and definite course is mapped out for the egg-cell by its idioplasm, which, again, directs the special course to be taken by each of the innumerable generations of cells, in the direction of which course external influences can only play a very subordinate part. If this consideration be borne in mind, it will be less likely that the objection may be made that a much too complicated structure has been attributed to the idioplasm. *Its structure must be far more complex than we can possibly imagine*; and in this respect, its construction, as we have represented it theoretically, must certainly be far simpler than is the case in reality. For the same reason, it is less probable that similar objections may be made to the theory of regeneration as here stated. Complicated phenomena cannot possibly depend on a simple mechanism. The machines in a cotton factory cannot be constructed of a few simple levers, nor can a phonograph be manufactured from two lucifer matches.

That form of regeneration which has been considered above may be described as *palingenetic*, for it pursues the course taken by the primary or embryonic development; but as soon as it leaves this course and takes a shorter one, it may be distinguished as *cœnogenetic*.

Cœnogenetic variations of the primary process of development probably always occur in cases of regeneration of complex structures; and even the reconstruction of the extremities, which we have chosen above as an example, will hardly take place in exactly the same way as occurs in the primary development of these parts, although it may resemble the latter in its principal phases.

Even if mere abbreviation of the development of a part can be easily conceived by supposing an aggregation and redistribution of the determinants to occur in the idioplasm, the process of idic division becomes very complicated when the primary and secondary development take place along different lines; for in the latter process the combinations of supplementary determinants in the id of the cell-generations must be different from those which occur in the former. But this difference is evidently due merely to a greater complication of the process, and it does not stand in the way of the theory. In all cases of regeneration, the mode in which the supplementary determinants become split off must be previously arranged for in the id. The assumption of a mere increase in the power of multiplication of certain determinants might seem sufficient in the case of palingenetic regeneration, for this would lead to one portion of a certain group of determinants becoming separated off as accessory idioplasm at a particular ontogenetic stage. In cœnogenetic regeneration, however, we can only assume that a double or still greater number of determinants are present in the germ-plasm, one set of which are destined for embryonic development and the others for regeneration; and these are previously arranged with reference to their internal forces, particularly that of multiplication, so that at a certain stage of development they become split off as 'accessory idioplasm,' either alone or together with the adjacent 'regenerative determinants.'

It seems to me, however, that palingenetic regeneration cannot be satisfactorily accounted for unless we assume the existence of special regenerative determinants, for it would otherwise be impossible to explain the phyletic origin of the cœnogenetic variations in the process of regeneration. These latter must, indeed, depend on variations in a determinant of the germ-plasm. If however the latter contained only the *one* determinant destined for embryogeny, variations must occur in the latter process at the same time. But this is not the case, and consequently a kind of double determinant must be contained in the germ for those hereditary parts (determinants) which are capable of becoming regenerated: — that is to say, two originally identical determinants must be present, one of which becomes functional in embryogeny and the other in regeneration. This will be made apparent if we take some examples.

In most existing amphibians the caudal region of the vertebral column may undergo regeneration, although its embryonic foundation, the notochord, is never formed anew. The cartilaginous sheath of the notochord has an important share in the primary formation of the vertebral column, but it disappears to a greater or less extent at a later stage. If it became possible for the vertebræ to undergo regeneration after a portion of the tail had been lost without a renewal of the notochord taking place, the result would be a useful abbreviation of the process of regeneration. Such an abbreviation has occurred, and everything supports the assumption that *at an earlier stage of phyletic development the notochord was capable of undergoing regeneration*, and that it has only lost this capacity secondarily. In the case of frog-tadpoles, the power has been retained of regenerating the tail when it is cut off *together with the notochord*. We must not assume that the notochord does not become restored in other amphibians because it no longer persists in the full-grown animal; for it is entirely absent only in a few of them (*e.g.*, *Salmandrina*), and the notochord of the larval salamander cannot be regenerated any more than that of the adult. Thus the capacity for regenerating the notochord has been lost by most amphibians in the course of phylogeny. Such a process of degeneration is certainly to be explained most easily by assuming the existence of special regenerative determinants, which may gradually disappear without in the least affecting their embryogenetic partners.

The necessity of this assumption is shown still more conclusively in the case, for instance, of the restoration of the solid axis of the tail in reptiles. The tail of a lizard quickly becomes restored after it has been cut off, but its structure is then different from that of the original tail; for, according to the statements of Leydig and Fraisse, the spinal cord and vertebral column are not renewed. The former is, however, represented by an epithelial tube, but gives off no nerves; and the latter is replaced by an unsegmented cartilaginous tube. As Fraisse points out, this tube does not correspond to the regenerated notochord, but is a new structure which is substituted for it.

A *phyletic development*, tending essentially towards a simplification of the parts, has taken place in this case *as regards the processes of regeneration*. A gradual degeneration has occurred, just as may take place in the tail or any other organ of an animal in the course of phylogeny. The caudal region of the vertebral column has undergone a reduction, which does not influence its primary (embryonic) ontogeny, but only its secondary formation by regeneration. A vertebral column is formed primarily; but if the re-formation of a part of it becomes necessary, in consequence of the loss of the tail, the secondary reduced process for the development of the axis comes into play, and a simple cartilaginous tube is formed. This process recalls the phenomena of 'dichogeny' which take place so frequently in plants, and in which the same group of cells may develop in either of two different ways, according to the nature of the external stimulus which is applied to them. Thus a shoot of ivy will produce roots on a certain side if it is shaded, and leaves if it is exposed to light. The determination of the sex of an animal may perhaps be referred to similar causes, — if, at least, we may assume that the sex is not always universally decided by the act of fertilisation, and that influences exerted upon the organism subsequently may have an effect in this determination. In the case of certain parasitic Crustaceans, the *Cymathoidæ*, the male sexual organs are developed first; and when the animal has fulfilled its function as a male, the female organs become developed, and give the animal the character of a female. The two developmental tendencies here come into operation temporarily, one after the other; just as in the case of the lizard's tail, in which the tendency to form the vertebral column first comes into play, and then that to form the secondary cartilaginous tube. The necessity for the formation of this tube certainly need not arise at all; just as that side of the shoot of ivy from which the roots arise need not necessarily be subsequently exposed to the light, and give rise to leaves; the possibility of such an occurrence is, however, foreseen by Nature. It might be urged that there is an important difference between the regeneration of a lizard's tail and the successive development of the two kinds of sexual organs in the Cymathoids, since in the latter case the rudiments of these organs are present in the embryo, and it is only their final development which takes place successively. This is certainly a difference, but it is just such a one as to indicate to us how these cases of supplementary substitution may be explained theoretically. The cells in the tail of a lizard which give rise to the secondary cartilaginous tube must contain determinants which differ from those of the embryonic formative cells of the caudal vertebræ, just as the idioplasm of the formative cells must contain different determinants for the testes and ovaries. *The supplementary determinants with which the idioplasm of certain cells of the vertebral column was provided for the purposes of regeneration, must have become changed in the course of phylogeny.*

A transmissible variation of this kind must, however, also have had some effect on embryogeny, if only one and the same determinant were present in the germ-plasm for the two modes of development. *Hence each determinant of these caudal vertebræ must be doubled in the germ-plasm.*

It would be premature to go beyond this assumption, and to attempt to decide anything about the manner in which the various supplementary determinants which are required for the restoration of one of the larger parts — such as, for instance, the caudal vertebræ — come together, and how and when they become separated from the primary determinants. The processes of regeneration have not as yet been examined from the point of view which I have here suggested; and in many cases it is not even known for certain from what cells regeneration proceeds.

Hitherto we have not discussed in detail the question as to *the kind of cells which contain the supplementary determinants, and from which regeneration thus takes place.* May these determinants be present in any kind of cell belonging to any tissue, or is their distribution always limited to young and apparently undifferentiated cells of the so-called 'embryonic type'?

If we only consider Man and the higher Vertebrates, we shall be disposed to look upon the latter of these two alternatives as the one which is in general correct. Even recently, in fact, many authors seemed to be in favour of this view: 'embryonic cells' were supposed to be contained in all those tissues which are capable of regeneration, and it was, indeed, believed by many that the leucocytes are cells of this nature. The latest investigations, however, lead us to the conclusion that this is not the case, and that although the white blood corpuscles are extremely important as conveyers of nutriment in the process of regeneration, they do not serve as formative elements in the construction of a tissue. In his text-book on Pathological Anatomy, Ziegler speaks of a formal 'law of the specific character of the tissues,' which he explains as follows: — 'the successors of the various germinal layers which separate from one another at an early embryonic stage, can only give rise to those tissues which belong to the germinal layer from which they were developed.' But this statement can only be true in the case of the highest Vertebrates, for, as the brothers Hertwig have shown, the germinal layers of the Metazoa are not primitive organs in the histological sense; and moreover, in the lower animals, several, if not all of the tissues, can be formed from each of the germinal layers. In lower animals, not only all the varieties of tissue, but under certain circumstances even rows of cells of one primary germinal layer and even indeed the entire animal, may arise from young cells belonging to the other germinal layer. In the chapters on multiplication by fission and gemmation, this process will be traced to its origin in the idioplasm. At present we have only to deal with the question as to whether the determinants of the various kinds of cells which are required for regeneration are contained within young cells only, or whether they are also present in those which have become differentiated histologically.

Although the supplementary determinants are certainly in many cases contained in young cells without any specially marked histological character, their distribution can nevertheless hardly be limited to these cells exclusively. It may happen — as will be shown in greater detail subsequently — that cells, which are fully developed histologically, both in plants and in the lower animals, contain all the determinants of the species; that is to say, they may contain germ-plasm as supplementary idioplasm. Hence there is no reason to assume that smaller groups of determinants may not have been supplied to specific tissue cells wherever they were required, although I am unable to give a definite example of such a case.

Although regeneration may originate in most cases in young, or so-called 'embryonic' cells, it is nevertheless quite a mistake to connect the idea of the undifferentiated state of these cells with this fact, as is so often done. These 'embryonic cells' are not 'capable of giving rise to anything and everything,' for each of them can only develop into that kind of cell the determinant of which it contains. Under certain circumstances such a cell may contain several different determinants at the same time, which are only distributed amongst the individual cells in subsequent cell-generations; but the structure which can and will become developed from it always depends on the cell itself, and its fate is determined by the idioplasm it contains, and can only be affected secondarily by external influences. Cells moreover exist, the idioplasm of which *permanently* retains the possibility of development along one of two lines. 'Dichogeny' in plants, which has already been mentioned, is likewise determined by the idioplasm, inasmuch as the latter must contain two kinds of determinants, one or the other of which either remains inactive owing to the nature of the external influences acting upon the cell, or else becomes active and determines the cell.

There are, however, no such things as 'embryonic cells' in the sense in which this term is used by authors. In the freshwater polype (*Hydra*), for instance, cells which are young and histologically undifferentiated — the so-called 'interstitial cells' — are present in the deeper part of the ectoderm: these can certainly give rise to various structures, viz., to ordinary ectoderm-cells, nettle-cells, muscle-cells, sexual-cells, and in all probability to nerve-cells also. It would nevertheless be absurd to suppose that any particular interstitial cell is capable of developing into any one of these structures. It obviously contains either germ-plasm, *i.e.*, the whole of the determinants, — in which case it can develop into a sexual cell, — or only the determinants of a thread cell or of one of the other kinds of cells, and then it can only give rise to one of the corresponding structures, and can never develop into a sexual cell.

## 2. The Phylogeny of Regeneration

It may, I believe, be deduced with certainty from those phenomena of regeneration with which we are acquainted, that the *capacity for regeneration is not a primary quality of the organism, but that it is a phenomenon of adaptation.*

The power of regeneration has hitherto been practically always regarded as a primary quality of the organism, — that is to say, as a direct result of its organisation: it has been looked upon as a faculty for which no special arrangements are required, but which naturally results as an unintentional secondary effect of the organisation which exists independently of it.

This view is based on the idea, which is in general a correct one, that the regenerative power of an animal is inversely proportional to its degree of organisation.* If this were univer-

* Cf. Herbert Spencer (*loc. cit.*, p. 175), who, however, expresses himself very cautiously with regard to this difficult subject as follows: — 'so

sally true, it would nevertheless not be a convincing argument for the above view, although it would certainly support it. But a closer examination into the facts shows that this statement is not absolutely correct. Although the capacity for regeneration is never so far-reaching in the highest animals as it is in the case of the lower ones,—and this must be due to some cause,—the regenerative power may nevertheless even vary widely in animals of the same degree of organisation, and may in fact be far greater in one of the higher than in one of the lower forms. Thus fishes are unable to regenerate a lost pectoral or pelvic fin, while the much more highly organised salamander has been known to regenerate a limb six times in succession (Spallanzani).

The regenerative power often varies in degree even within the same group of animals. In *Triton* and *Salamandra* the entire limb grows again after amputation, but apparently, so far as I have been able to observe, this does not occur in *Proteus*. The tail, too, is only replaced slowly and imperfectly in the latter animal, whereas it easily becomes restored in the salamander. In the year 1878 I received a living *Siren lacertina*, the fore-limb of which had been torn off, so that only the stump of the upper arm remained, and the entire limb did not grow again in the course of the ten years during which I kept the voracious animal, and gave it abundant food. In this case again the power of regenerating the extremities seems to be less than in that of salamanders, which are much younger phyletically, and much more highly organised.

It is well known also that the limbs of a frog do not grow again when they have been cut off, even when the animal is in the larval condition. The fact that the regenerative power can vary so considerably within the same genus is still more remarkable. Schreiber observed that the power of regeneration in *Triton marmoratus* is relatively very slight as compared with that which is possessed by all other species of Triton which have been examined for this purpose. 'In captivity, at any rate, even slight injuries in such parts as the crest are never re-

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that the power of reproducing lost parts is greatest where the organisation is lowest, and almost disappears where the organisation is highest. And though we cannot say that between these extremes there is a constant inverse relation between reparative power and degree of organisation, yet we may say that there is some approach to such a relation.'

placed while the animal invariably succumbs to greater injuries.' Fraisse gives similar instances. Thus 'an amputated extremity never grew again to its normal size: merely a somewhat deformed protuberance was formed on the stump. The tail also was only reproduced to a very slight extent.' *

With regard to reptiles, Fraisse points out that the regenerative capacity obtains to a much slighter extent in some groups than in others. Chelonians, crocodiles, and snakes are unable to regenerate lost parts to any extent, while lizards and geckos possess this capacity in a high degree.

The dissimilarity, moreover, as regards the power of regeneration which exists in *various members of the same species*, also indicates that adaptation is an important factor in this process. In *Proteus*, which in other respects possesses so slight a capacity for regeneration, the gills grow again rapidly when they have been cut off. In lizards, again, this power is confined to the tail, and the limbs cannot become restored: in these animals, however, the tail is obviously far more likely to become mutilated than are the limbs, which as a matter of fact are seldom lost, although individuals with stumps of limbs are occasionally met with. The physiological importance of the tail of a lizard consists in the fact that it preserves the animal from total destruction; for pursuers will generally aim at the long trailing tail, and thus the animal often escapes, as the tail breaks off when it is firmly seized. It is, in fact, as Leydig was the first to point out, specially adapted for breaking off, the bodies of the caudal vertebræ from the seventh onward being provided with a special plane of fracture, so that they easily break into two transversely. Now if this capability of fracture is provided for by a special arrangement and modification of the parts of the tail, we shall not be making too daring an inference if we regard the regenerative power of the tail as *a special adaptation, produced by selection, of this particular part of the body, the frequent loss of which is in a certain measure provided for*, and not as the outcome of an unknown 'regenerative power' possessed by the entire animal. This arrangement would not have been provided if the part had been of no, or only of slight, physiological importance, as is the case in snakes and chelonians, although these animals are as highly organised as lizards. The reason

* *Loc. cit.*, p. 152.

that the limbs of lizards are not replaced is, I believe, due to the fact that these animals are seldom seized by the leg, owing to their extremely rapid movements. But if a lizard does happen to be caught by one of its limbs, it must fall a prey to its pursuer, and the capacity for regenerating the limb would be useless. The case is very different with regard to such animals as Tritons. Their movements are much less rapid, and their assailants, being too small to swallow the whole animal, frequently bite off a limb. They are often attacked by members of the same species, which gnaw off a gill, limb, or the tail of a weaker comrade, bit by bit. If a considerable power of regeneration were possible at all, it would certainly be provided in this case. This power is possessed in a much smaller degree by Proteus; but these animals are only found in the caves of Carniola, where enemies larger than themselves do not exist, and in which there is no great competition for food, and therefore, at least as far as my observations extend, they do not bite one another.

Spallanzani has stated that nature does not reproduce every part that is cut off; expressed in theoretical terms, this simply means that *the various organs of an animal possess the power of regeneration in different degrees*. If we inquire further into the question, we shall find that those parts which are most frequently exposed to injury or loss must possess the power of regeneration in the highest degree. So far as I can judge from the facts with which we are at present acquainted, this remark appears to me to be a perfectly correct one. Unfortunately Spallanzani gives no instance in support of the above statement, so that we do not know what parts he referred to. I have myself, however, made some investigations in order to ascertain whether the degree of regeneration of a part bears any relation to its liability to injury.

If regeneration is a phenomenon of adaptation, the internal organs — which are not exposed to injury in the natural life of the animal — cannot possess any regenerative power, even in those animals in which the external parts — which are exposed to the attacks of enemies — possess it in a high degree.

The following experiment bears upon this point: — I cut open a large newt (*Triton cristatus*), removed about half of the right lung, and sewed the skin together again. The animal soon recovered from the effects of the chloroform, and its wounds healed: it was then well cared for for fourteen months, and afterwards killed. An examination showed that the right lung had not become restored: it was only half as long as the left one, and its end was blunt, and not pointed as in the normal lung. Four other similar experiments yielded like results: in one of these it was doubtful whether a growth of the lung had not taken place, but even in this case it had not recovered its long, pointed form.

These experiments are still being continued, but we may already deduce from them that a striking disproportion exists between the regenerative power of the external parts of a newt and that of its lungs. This difference seems even more marked if we bear in mind that in the case of a limb the process of regeneration is a very complex one, for complicated parts, consisting of many entirely different portions, have to be reproduced; whereas a lung is a simple hollow sac, which has no joints, and the histological structure of which is relatively simple.

We therefore infer that the internal parts, which are not exposed to injuries of an ordinary kind, do not possess a greater capacity for regeneration in these species than they do in the highest Vertebrates, which are so exceptionally inferior to them as regards the regenerative power of the external parts. Hence *there is no such thing as a general power of regeneration: in each kind of animal this power is graduated according to the need of regeneration in the part under consideration:* that is to say, the degree in which it is present is mainly in proportion to the liability of the part to injury.

This conclusion is closely connected with the fact that the restoration of a part which possesses the power of regeneration in a high degree, can only take place as the result of definite injuries which are in a manner provided for, and not from *any* kind of injury. Philippeaux was the first to discover that the limb of a Triton does not grow again when it has been removed at the joint, and that, in fact, it only does so when it is cut or torn off, so that the bone is injured. This fact has been explained by referring it to the law of the specific nature of the tissues, according to which bone can only be formed from bone, and the bone of the limb must be injured before it can become capable of being formed anew. It seems to me that this explanation is insufficient, although it is founded on a correct principle, according to which the injury to the bone causes the stimulus by which the cells of the stump are incited to proliferate. This is certainly correct, and may be expressed according to our theory by saying that the supplementary determinants which are present in a passive condition in the cells, are prompted to become active by the stimulus. But if an articular cavity is exposed, a stimulus is likewise produced, which must affect the cells of the articular cartilage, and doubtless also those of the underlying bone or periosteum. If, therefore, all the cells in this region were capable of reproducing the missing bones, and if the exposure of the articulation were the ordinary form of injury, these cells would certainly be just as much adapted for and capable of responding to this stimulus, by a formative growth, as would those situated at the broken ends of a bone. *But the disarticulation of a limb, or of a part of a limb, hardly ever takes place in the natural conditions of life, and therefore could not have been provided for by the organism; the respective cells of the exposed articular cavity could not consequently have been supplied with the supplementary determinants necessary for regeneration.* Hence these cells are incapable of reacting in an adequate manner to the stimulus due to the disarticulation.

In spite of all the facts already mentioned, it might still appear doubtful whether regeneration really depends on a special adaptation of the part in question, and whether it does not result from the degree of organisation of the animal, or at any rate from a *general* regenerative force possessed by the entire organism. The following considerations must, however, I think, set aside all doubts on the question. Physiological and pathological regeneration obviously depend on the same causes, and often pass one into the other, so that no real line of demarcation can be drawn between them. We nevertheless find that in those animals in which the power of regeneration is extremely great physiologically, it is very slight pathologically. This proves that a slight power of pathological regeneration cannot possibly depend on a general regenerative force present within the organism, but rather that this power can be provided in those parts of the body which require a continual or periodic regeneration: in other words, *the regenerative power of a part depends on adaptation*. Let us take a few examples. It was mentioned above that fishes are said to possess a very slight 'general regenerative power,' because they are unable to replace lost external parts, especially such structures as fins. Nevertheless many fishes are provided with teeth which are very liable to become worn out, and consequently they possess the power of constantly producing new teeth to replace the old ones. In the mouth of a ray or dog-fish the teeth are arranged in several rows along the edges of the jaws, the outer rows containing those which are worn out, and the inner the younger teeth which take their place. Birds, again, possess a very slight power of repairing defects which have arisen accidentally, and hence they are considered to have a very slight capacity for regeneration. But their power of physiological regeneration with respect to certain parts is nevertheless extraordinarily great: — all the feathers are cast off and renewed once a year. Pathological regeneration occurs to a very slight extent in mammals; defects in the superficial epithelium, the epithelium of the ducts of glands, the various supporting tissues, including bone, and in nerve-fibres, can be repaired from the elements of the respective tissues; but in no mammal does a segment of a finger or an eyelid grow again when once it has been cut off. In certain mammals, however, the power of physiological regeneration with respect to certain parts is unusually marked. Male stags shed their antlers annually, and new ones are formed in four or five months. If we take into consideration the mass of organic tissue which is thus formed in such a short time, this feat outstrips even the regenerative performances of the full-grown salamander. For according to Spallanzani, it takes a salamander more than a year to restore an amputated limb to its normal size and strength. Young individuals can, however, certainly reproduce a limb in a few days; and this gifted experimenter observed in the case of a young Triton that the four limbs and tail when they were cut off grew again six times in the space of three summer months!

In one respect, however, viz., as regards *the complexity of the part replaced*, this remarkable regenerative power in stags and birds is far inferior to that which obtains in the Triton. Although a bird's feather is a very wonderful structure, it is formed merely from epidermic cells, and a stag's antler is only a dermal bone covered over by the epidermis. But the limb of a Triton, on the other hand, consists of every kind of tissue with the exception of endodermal epithelium, — viz., of skin, muscles, a large number of skeletal parts, connective tissue, blood-vessels, nerves, and so forth; and all these have a very definite arrangement, number, and form. There is no doubt therefore that the regeneration of a limb is a greater feat than the renewal of feathers or antlers; and the fact has been long recognised, that *the more complex organs are regenerated less easily than those which have a simpler structure.* A series of carefully performed experiments, made with the view of testing this somewhat vague statement, would be of great value theoretically. We may predict that in one sense it would be confirmed, and that we should find that under similar conditions the simpler organs are on the whole regenerated much more easily than the more complex ones in any particular species. Even in the human race, many simple tissues — such as the connective substances, epithelia and nerves — can be repaired, and it is only the cells of the glands and ganglia, which are the most highly differentiated histologically, which are not replaced at all, or at most only to a very slight extent. We can see from a theoretical point of view that a far less complex apparatus is required in these cases than in those which concern a regeneration of entire parts of the body, such as the tail or limbs; for it is only necessary that the respective tissues should contain cells which are capable of multiplying, in response to the stimulus produced by the loss of substance in their immediate neighbourhood, and which continue to do so until the loss is made good. When, however, several kinds of cells take part in the restoration, and a strict regulation as to their arrangement in groups, their direction of growth, and rate of reproduction is required, it becomes necessary for the individual cells from which the restoration takes place to be accurately provided with supplementary determinants of various kinds; and it is clear that this will gradually become more difficult and complex, the greater the complexity of the part to be regenerated, and the more accurately all the details of its structure have to be preserved.

If, however, we review the facts known to us concerning regeneration in animals of various degrees of organisation, we meet with such marked differences even as regards the regenerative power of homologous parts, that we cannot help receiving the impression, which has affected all writers on this subject, that in general *the regenerative power is greater in less highly organised animals than in those of a more complex structure.* The question thus arises as to how this view is to be interpreted and presented in a scientific form.

Even in Vertebrates, certain facts seem to indicate that the 'lower' forms, as such, always possess the power of replacing lost parts in a greater degree than do the higher ones. It is true that the capacity for regeneration is certainly much slighter in fishes than in the more highly organised amphibians; but although the limb of a Triton becomes restored, and the fin of a fish does not, it must not be forgotten that the physiological importance of the two organs is somewhat unequal. On the other hand, the fore limb of a Triton and the arm of a man are not only homologous structures, but are also of almost equal physiological importance, and yet their power of regeneration is very unequal. We must therefore inquire into the causes of this dissimilarity. The power of regeneration in any particular part cannot depend only on the conditions which exist as regards the species under consideration: it must also be due to arrangements for regeneration which have been transmitted by the series of ancestors of this species. Leaving this question aside, and regarding the power of regeneration as merely depending in each individual case on adaptation, we should arrive at some such conclusion as the following: — the provision of the cells of a certain part with supplementary determinants for the purposes of regeneration, depends primarily on the liability of this part to frequent injury — that is to say, on the degree of *probability of injury*. Precautions are not taken for injuries which seldom occur, even though these may be very disadvantageous to the individual; for the loss thereby resulting to the species as regards the number of individuals would be extremely small and unimportant, and therefore processes of selection would not take place in order to counterbalance this loss.

In the second place, the *physiological or biological importance of the organ* itself must be taken into consideration. A useless or almost useless rudimentary part may often be injured or torn off without causing processes of selection to occur which would produce in it a capacity for regeneration. Thus, so far as is known, the minute limbs of *Siren* and *Proteus*, which are often bitten off, or not replaced; while the gills of these animals and of the Axolotl, which are equally liable to similar injuries, become regenerated: — in the latter case the organs are *physiologically* valuable, while in the former they are not. The tail of a lizard, again, which is very liable to injury, becomes regenerated, because, as we have seen, it is of great importance to the individual, and if lost its owner is placed at a disadvantage.

Finally, *the complexity of the individual parts* constitute the third factor which is concerned in regulating the regenerative power of the part in question; for the more complex the structure is, the longer and more energetically the process of selection must act in order to provide the mechanism for regeneration, which consists in the equipment of a large number of different kinds of cells with supplementary determinants, which are accurately graduated, and regulated as regards their power of multiplication. Thus we can understand, for instance, why the fore-limb of a Triton becomes regenerated, while that of a bird does not, although the wing is of far greater importance and is much more indispensable to its owner than is the fore-limb in the case of the Triton. Although there are fewer bones in a bird's wing than in a Triton's limb, the former is by far the more complicated structure; for it is covered with feathers, and as each quill has a special size, form, and coloration, the wing must contain a large number of special determinants in its formative cells. These determinants must all be contained and arranged in the germ-plasm, so that they can be passed on during embryonic development through a certain series of cells, — first into the outer germinal layers, then into the epidermis of the fore-limb, and finally, by the agency of further series of cells arising in the course of growth, to the region to which they specially belong. It is difficult enough to imagine how the distribution of the determinants can possibly take place in so accurate and certain a manner as must be the case in reality, so that not only the shape of the feather but even every speck of colour on it is accurately repeated in every individual of the species; and it might well, indeed, be considered impossible that the whole of this complex mechanism should also be capable of becoming modified in such a manner, that the entire wing, with all its feathers and patches of colour, could be regenerated from a cut surface in any part. Did this occur, the cells of any section of the wing would, according to our theory, have to contain the whole of the determinants of all the cells required for the construction of the portion of the wing distal to the cut surface as supplementary determinants, in addition to their own special idioplasm; and moreover, these determinants must then be distributed proportionately among the cells of the radial and ulnar, and of the upper and under surfaces of the wing, and the power of multiplication of each cell and its successors would have to be accurately adjusted. Although we cannot easily judge as to what is possible in nature, and are so often impressed by the discouraging conviction that many vital processes are still incomprehensible to us, we may perhaps in this case feel justified in *inferring the impossibility of such an occurrence from the fact that it does not take place*; that is, to infer that the regeneration of a bird's wing is impossible on account of the complexity of the mechanism required for it, because it does not actually occur.

We cannot, however, regard this as a formal proof of the fact that regeneration does not take place in this case. This would be inadmissible, if only because the first of the three factors which, as we have assumed, produces the mechanism of regeneration — that is, the probability of loss — is not present. In the state of nature, at any rate, a bird's wing is seldom injured without loss of life ensuing at the same time. For this reason alone, selective processes in connection with a regenerative mechanism could not be introduced. I have not brought forward the above example for the purpose of proving the case for this instance in particular, but because it seemed to me to be specially fitted to show how extraordinarily the complexity of the regenerative mechanism must increase along with the greater complexity of the part. But this brings us back to the consideration of *the general power of regeneration possessed by the lower, in contrast to the higher, animals.*

The supposition that this power exists, may, I believe, be conceded in a certain sense: that is to say, in consequence of the slighter complexity in structure of *all* the parts in one of the lower groups of animals, any particular part may also become capable of regeneration more easily than in the case of the higher groups. We must, however, always presuppose that the two other factors — the probability of injury, and the physiological importance of the organ — are present in the required degree; so that in speaking of the greater power of regeneration possessed by animals of a lower type, we are only using another expression for the third factor which takes part in the process, viz., the complexity of the organ to be regenerated.

The question, however, arises as to whether the capacity of each part for regeneration results from special processes of adaptation, or whether regeneration occurs as the mere outcome — which is to some extent unforeseen — of the physical nature of an animal. Some statements which have been made on this subject seem hardly to admit of any but the latter explanation. Thus, according to Spallanzani, the jaw of a Triton may become regenerated along with its bones and teeth. Bonnet states that even the eye of this animal is replaced after it has been extirpated. It has never come before my notice that in the natural state Tritons frequently lose the lower jaw in combat; but some of these animals which I had put for a short time in a small vessel attacked each other vigorously, and several times one of them seized another by the lower jaw, and tugged and bit at it so violently that it would have been torn off if I had not separated the animals. The loss of part of the jaw or eye may therefore occur not infrequently in the natural state, and we may thus perhaps assume that these parts are adapted for regeneration. Kennel, moreover, gives an account of a stork, the upper beak of which had accidentally been broken off in the middle, the lower one then being sawn off to the same length, and both were subsequently regenerated. Such cases, the accuracy of which can scarcely be doubted, indicate that the capacity for regeneration does not depend only on the special adaptation of a particular organ, but that a general power also exists which belongs to the whole organism, and to a certain extent affects many, and perhaps even all, parts. By virtue of this power, moreover, simpler organs can be replaced even when they are not specially adapted for regeneration.

From our point of view, such cases are not incomprehensible in principle. We need only assume that in all, or at any rate in many, of the nuclear divisions in the embryo, some of the earlier determinants remain associated with later generations of cells as accessory idioplasm. It only remains to trace this arrangement — which is a more or less universal one, and affects the whole body — to its origin; for no arrangement can be produced which is not useful, especially when it concerns such a complicated mechanism as that for supplying the idioplasm with accessory determinants. We are therefore led to infer that *the general capacity of all parts for regeneration may have been acquired by selection in the lower and simpler forms, and that it gradually decreased in the course of phylogeny in correspondence with the increase in complexity of organisation;* but that it may, on the other hand, *be increased by special selective processes in each stage of its degeneration, in the case of certain parts* *which are physiologically important and are at the same time frequently exposed to loss.* In all probability this view is the correct one.

### 3. Facultative or Polygenetic Regeneration

The tail of a lizard or the limb of a Triton grows again when it has been cut off, but the part amputated does not reproduce the entire animal. In some segmented worms, on the other hand, such as *Nais* and *Lumbriculus*, not only does the amputated tail-end become restored, but this end itself reproduces the anterior part of the body, so that two animals are formed from one.

This fact evidently cannot be deduced merely from the assumption we have made with regard to supplementary determinants; for were this the case, determinants of one kind only — viz., those which are necessary for the construction of the lost part — would be present in the cells. But in the above instances the *same* cells give rise to entirely different parts, according to whether they are situated on the surface which is anterior or posterior to the plane of amputation: in the former case they reproduce the tail-end, and in the latter the head-end. The fact that both parts grow again when the worm is cut into two through any region of the body, proves that regeneration in either direction may proceed from the *same* cells; it therefore follows that the cells situated in any particular transverse plane of the body are not merely provided with the supplementary determinants for the formation of the head- or tail-end only, but every cell can react in either way, according to whether it is situated anteriorly or posteriorly to this plane. In order therefore to explain the twofold action of these cells in accordance with our fundamental view, — which presupposes that the cells taking part in regeneration are arranged and controlled by the forces situated within them, and not by an external agency, — it seems necessary to assume that each cell possesses two different supplementary determinants, one for the construction of the head-end, and one for that of the tail-end; and that the one or the other becomes active according to whether the stimulus, due to the exposure of the cell, is applied to its anterior or to its posterior surface.

Before attempting to verify this assumption, I must mention certain cases in which the regenerative activity of the cells may even be threefold.

It appears to me that the regenerative processes which have been observed in the fresh-water polype Hydra and in the sea-anemones (*Actiniæ*) are instances of this kind of regeneration. If a worm is cut through in the median or any other longitudinal plane, neither part grows again, and each soon dies. The case is different in Hydra. If this animal is cut through longitudinally, the two parts grow again into entire individuals, irrespective of the plane of section. As the transverse section of the animal at any point is likewise followed by the restoration of each part, it follows that Hydra, in every part of the body, must be capable of a threefold regeneration, *i.e.*, of regeneration in the three directions of space. And as the body is differently constructed in these three directions, we are compelled to assume that each cell contains groups of determinants of three different kinds, viz., those which are concerned in the formation of the proximal and distal ends, and in the completion of the body-wall. An individual cell * must therefore be capable of dividing in three different planes, and of giving rise to a part of one of three different regions of the body; and, moreover, the plane in which division actually occurs, and consequently the kind of determinants which become active and control the cell, is decided not by the quality, but by the kind of division resulting from the stimulus produced by the injury.

The processes of regeneration in Hydra can, I think, to a certain extent be understood on this assumption. If, for instance, the group of supplementary determinants of the proximal end of the body becomes active, it will cause the development of linear rows of cells extending in the direction of the axis of the body and united laterally so as to give rise to a tube; these cells, moreover, will have the tendency to close in towards the centre as soon as possible, so as to form the disc or foot, and will also cause the differentiation of the ectoderm cells of the foot into glandular cells which secrete slime: the determinants for the formation of tentacles are wanting in this group. If, again, the group of supplementary determinants of the distal end becomes active, rows of cells arise which will tend to close in to form the oral disc, leaving a large space in the centre for the mouth. Tentacles will then grow out from certain points around

* I shall not refer to the histological details with regard to the process of regeneration in Hydra, as the necessary data appear to be too uncertain and incomplete.

the mouth, and it is certainly not easy to explain why the determinants which cause their formation become active at these points only. It will, however, be shown later on that the cells of Hydra — and probably those of all animal tissues — are in a certain sense polarised; that is to say, they are differently constituted in the three directions of space. The fact that the determinants of the tentacles — which we must suppose to exist in all regions of the body — only become active in certain cells around the margin of the mouth, may be due to the polarisation of the cells as well as to the peculiar conditions of pressure within the cellular dome of the oral disc.

What has just been said can certainly not be looked upon as anything more than the merest provisional explanation of the facts, but it appears to me to be impossible to give a better one at present. It nevertheless, I think, penetrates somewhat further into the problem than does Herbert Spencer's hypothesis, in which regeneration is compared in general to crystallisation, and the capacity of arranging itself on every occasion under the influence of the whole aggregate in the manner required for the renewal of the missing part, is attributed to *every* ultimate particle. If we take the fresh-water polypes alone into consideration, one of these explanations seems just as good as the other; but if other groups of animals are included, it is at once apparent that this capacity is not by any means always possessed by the particles, but that even the cell may give rise by regeneration sometimes to various parts of the whole aggregate, at other times only to one certain part, and at others again only to those similar to itself, and that it must therefore contain something which makes it specially capable of one or of the other kind of regeneration. This something is the group of supplementary determinants.

If a polype or worm is cut through transversely, or if a loss of substance is caused artificially in any organism, the conditions of pressure previously existing in the cell in the region of the injury become changed, the pressure previously exerted by the lost part suddenly ceasing. This induces a change in the vital conditions of the cells thus affected, which must have a definite morphological and physiological result. We are unable at present to state more precisely what this change is; but as we know that such losses of substance are followed by the multiplication of the cells, we may safely assume that it exerts a stimulus on the cell, and more especially on its idioplasm, which forces the latter to undergo multiplication. This view is maintained by those who have the greatest opportunity of investigating the details of such processes, — I refer to the pathological anatomists. The proliferation which ensues in the surrounding tissue after a loss of substance, is not explained by them as being due indeed to a stimulus — in the ordinary sense of the word — exerted on the surrounding cells, but rather to a cessation of the '*resistance to growth*,' and this may in one sense also be described as a 'stimulus,' inasmuch as it is an 'incitement' to growth.

If the cells were constituted alike in the three directions of space, the effect on the idioplasm would be the same whether the stimulus due to the loss of substance acts from before, from behind, or from the side. *One* of the three groups of determinants could not possibly be alone effected by the stimulus and thus rendered active in one case, the second only in another, and the third only in a third instance. We have, however, every reason to suppose that the structure of one of these tissue-cells is not the same in the three directions of space, and that they are, in fact, variously differentiated according to each of these, and consequently respond to stimuli in different ways according to the direction in which the latter act upon them. Vöchting * has proved that at any rate in higher plants, 'a different upper and lower, anterior and posterior, and right and left half, can be distinguished in each living cell in the root and stem.' Portions of the root of the poplar transplanted on to the stem, or portions of the stem transplanted on to the root, only grew and flourished when they were fixed in a certain position; in the reverse position they sometimes indeed grew, but soon showed phenomena of degeneration. Vöchting infers from this observation that the cells are 'polarised,' this term being taken merely in an analogous sense to that in which it is generally used. The root and stem behave in a certain sense like a cylindrical magnet, which is composed of sections equally magnetised in the radial and longitudinal directions. Such a magnet, like the stem and root, may be separated into pieces. If the smooth adjoining surfaces of the portions of the magnet are

* H. Vöchting, 'Uber Transplantation am Planzenkörper,' Tübingen, 1889, p. 400.

placed with their opposite poles as close together as possible, the entire magnet is once more formed. Similarly, if the root of a poplar is cut in half transversely, each half produces buds and roots at the corresponding poles; but if, on the other hand, the two portions are joined together in the same relative position as that which they occupied originally, they become united together, so that a single piece of root, with its two poles, results, quite similar to the original piece.

These important results which Vöchting has obtained by his experiments on transplantation, are mentioned in this place because they can be utilised in considering the phenomena of regeneration in animals, which have just been discussed. We may in this respect compare a fresh-water polype with a poplar root. After a Hydra has been cut in half transversely, the distal portion gives rise to a new foot at its proximal end, and the proximal portion produces an oral region at its distal end. We might therefore in this case speak of pedal- and oral-poles, instead of root- and stem-poles, as in the case of the poplar. And, in fact, if a Hydra is cut transversely into three portions, the distal part or oral pole of the middle piece develops a new oral region, and its proximal part or pedal pole gives rise to a new foot. It might not be impossible for a clever experimenter to cause this middle piece to unite with the two terminal portions of the body before the former had had time to develop into a complete animal, by joining the three portions together with bristles. This would result in a union just as in the case of the poplar.

It would be a mistake to try to deduce that one of the poles of the poplar root must grow shoots and the other roots merely from the fact of its polarisation: one might as well try to deduce it from the fact of the polarisation of a real magnet. Something more is required before this can take place: — *the cells of the poplar root must contain the primary constituents for the formation of shoots and roots*; that state of the cells which Vöchting describes as polarisation only produces the conditions under which one or other of the primary constituents becomes active, and thus undergoes development. The hypothesis of the polarisation of the cells does not, therefore, relieve us in the least from the necessity of making a theoretical assumption to explain how it comes about that the primary constituents of different kinds of structures are present in one and the same cell. According to my view, we must assume in the case of the poplar root that the cells are provided with two different kinds of idioplasm, which remain inactive until the adequate stimulus arises and causes the idioplasm of either the root or of the stem to become active. In both cases the loss of substance must be regarded as the stimulus, and the direction in which it acts must decide the quality of the reaction.

If the idioplasm of the tissue-cells were capable in itself of responding to the effect of this stimulus by causing a regeneration of the missing parts of the body, worms possessing the regenerative power in a high degree, such as *Nais* and *Lumbriculus*, would be capable of regeneration in a lateral as well as in the anterior and posterior directions. This, however, as Bonnet has previously proved, is not the case: when cut in half longitudinally, the missing right or left half is not reproduced, and the cells of these animals must therefore be wanting in that substance — viz., in the *antimeral* supplementary determinants — which renders this kind of reproduction possible.

From our point of view, it is not surprising that these determinants are absent in worms; for in the natural state these animals are never torn in half longitudinally, and there was therefore no need for Nature to provide for such a contingency.

If we consider that the groups of supplementary determinants must become more complicated in proportion as the organism and the part to which they give rise increase in complexity, we can understand why *facultative* regeneration only occurs in relatively simple organisms, and that it apparently takes place in three dimensions in Polypes and Flat-worms only, in two dimensions in Annelids and Starfishes, and merely in one dimension in Arthropods, Molluscs, and Vertebrates.

It must not be supposed that other factors do not also take part in limiting the capacity for regeneration, — such as, in particular, the vulnerability of the higher organisms, and the fact that they are dependent on the circulation and temperature of the blood, even apart from the influence of the nervous system, of which we are practically still very ignorant. The relatively small quantity of substance in the part removed, as compared with that of the rest of the body, would also prevent the amputated limb of a salamander, for instance, from becoming regenerated into an entire animal. All these considerations help to explain why bi-dimensional regeneration —

that is, regeneration in two directions — cannot take place in the higher animals.

If, then, regeneration depends on the distribution of supplementary determinants to certain cells, which occurs whenever it is necessary or possible, the process must be primarily traceable in the case of the Metazoa to the doubling of the ids in a certain *ontogenetic stage. And since a division and doubling of the* idants takes place in every mitotic nuclear division, this hypothesis is supported by actual fact, even although we are still far from being acquainted even with the general details of the processes of growth and doubling of the ids and determinants, not to mention the systematic transference of such inactive determinants to definite cells and series of cells. Here again, however, Nature will have caused an advance from the simple to the more complex; and it therefore follows that, just as complicated organisms could only arise in the course of innumerable series of generations and species, so also the complex apparatus for regeneration in the tail or limb of a newt could not have been developed suddenly, but must have arisen in consequence of similar modifications in innumerable ancestors.

It might be possible to picture to one's self approximately the series of modifications which the apparatus for regeneration has gradually undergone, beginning at the lowest multicellular forms, and passing upwards to those animals in which the power of regeneration is the most highly developed and complex. I shall not, however, attempt to do so. At some future date it may perhaps be found that differences occur as regards the number of ids contained in the cells of those which have, and in those which have not, a marked capacity for regeneration: it will not be worth while to trace in detail the courses which the development of the power of regeneration has taken, until our knowledge of the idioplasm is sufficiently complete to furnish a basis for the theory in fact.

### 4. Regeneration in Plants

The process which may be described as regeneration in the case of the lower plants — the algæ, fungi, and mosses — will be treated of in greater detail subsequently. In this place, I merely wish to point out that true regeneration only occurs in a very slight degree in all the higher plants which are regarded as cormophytes or plant-stocks. If a piece is cut out of a leaf of a tree or of any other Phanerogam, the leaf does not become regenerated. If, again, an anther or a stigma is cut off from a flower, the corresponding filament or style will not give rise to a new anther or stigma. The cells of these organs are therefore not adapted for regeneration, and do not contain 'supplementary determinants.'

Botanists might be inclined to explain this fact by supposing it to be due to the cells having already reached their full size, and having therefore lost their power of multiplication. This is certainly the case, but it does not explain matters in the sense I mean: the question still remains as to why these cells have not been provided with supplementary determinants. The large number of cases in which adult cells of leaves or other parts, which have reached their full size, may under certain circumstances begin to multiply, and form buds from which entire plants arise (*e.g.*, *Begonia*), proves that such a provision is possible.

The solution of the above problem is to be sought for in the fact that it would have been of far too slight importance to the plant to be able to restore such defects in its leaves, as it possesses the power of producing *new* leaves. Buds can be formed and undergo further development in many parts, and thus the plant gains much more than it could possibly do by mere regeneration. *Regeneration can be dispensed with, as the far more important power of budding is possessed by the plant.*

The fact that the higher plants are unable to restore such parts as portions of leaves, furnishes an additional important proof that regeneration is dependent on external circumstances, and that it is a phenomenon of adaptation. True regeneration, however, occurs in those cases in which the losses or injuries would be harmful to the plant, and cannot be made good by the development of buds. Thus a loss of substance in the bark of a tree becomes replaced by the formation of callus, which arises from the edges of the wound, and grows over it, and thus the underlying wood is protected from injury. The cut or broken surface of a branch, even in the case of many herbaceous stems, becomes covered over in a similar manner by a mass of proliferating callus, which may even give rise to new growing points of shoots and roots, and thus become the place of origin of new individuals.* The stimulus to proliferation, as in the case of regeneration in animals, is due to the removal of the opposition to growth; the cells must, however, be adapted for this reaction, otherwise the proliferation cannot take place; the stems as well as the roots and veins of herbaceous plants do not by any means always respond to an injury by the formation of callus. This process is therefore not a primary quality of the plant, but an adaptation, due, in my opinion, to the association of certain supplementary determinants with the active idioplasm of certain kinds of cells.

The formation of callus is probably the only process in plants which can be regarded as an actual regeneration.

### 5. *Regeneration in Animal Embryos, and the* Principles of Ontogeny

The theory of heredity which has now been formulated, — and more especially that portion of it which concerns the composition of the germ-plasm out of determinants, and the gradual disintegration of the mass of determinants in the germ-plasm during the course of ontogeny, — is based on the assumption that the *cells control themselves:* that is to say, the fate of the cells is *determined by forces situated within them, and not by external* influences. The primary cells of the ectoderm and of the endoderm arise by the division of the fertilised egg-cell and its contained germ-plasm, because the determinants of the ectoderm are passed into one cell and those of the endoderm into the other, and not because some external influence, such as the force of gravity, affects the cells in a different manner. Similarly a certain cell in a subsequent embryonic stage does not give rise to a nerve-, a muscle-, or an epithelial-cell because it happens to be so situated as to be influenced by certain other cells in one way or another, but because it contains special determinants for nerve-, muscle-, or epithelial-cells.

This conception of the predestination of the individual cells, the fate of which, together with that of their successors, is determined by the idioplasm they contain, was first imperfectly expressed in the theory formerly propounded by His,† in which he

* J. Sachs, 'Lectures on the Physiology of Plants,' Leipzig, 1882, p. 709. (*English edition, translated by H. Marshall Ward, Oxford, 1887.*)

† Wilhelm His, 'Unsre Körperform u. das physiologische Problem ihrer *Entstehung,' Leipzig, 1874.*

formulated the existence of 'special regions in the germ, which give rise to special organs.' His imagined that the 'primary constituents of the organs of a chick were present in superficial extension in the germinal disc,' *i.e.* in the cell-body of the ovum, and that each organ is therefore represented by a definite part of the body of the egg. As has already been mentioned in the historical introduction, subsequent investigations, made in the course of the following ten years, proved that the 'primary constituents' of the various structures are to be found in the nuclear substance. The special form in which His expressed his views was thus certainly contradicted, although the fundamental principle of his theory was not thereby affected in its general sense, which indicates that the differentiating principle of ontogeny is to be looked for in the cells themselves, and not in external influences. Wilhelm Roux * was the first to prove definitely that the differentiation of the egg into the embryo is certainly not caused by influences existing apart from the egg, but that it is due to causes originating in the egg itself. Pflüger † showed with regard to the ovum of the frog, that whatever position the egg is forced to take up the upper side always gives rise to the animal pole of the embryo, and it was thought that this must be due to the force of gravity. Roux, however, proved that frogs' eggs which are rotated slowly in a vertical direction, develop just as well as those on which the force of gravity is not interfered with. It has further been proved by Born ‡ that, although when an egg undergoes development in a fixed position the substance of the cell-body does not become displaced at first, the nucleus nevertheless changes its position, for it very soon passes to the upper pole of the egg, at which point development then begins. These observations undoubtedly proved that the formative forces are situated in the egg itself; but they still left it undecided whether the differentiation of the ovum is due essentially to the action of the individual cells alone,—that is to say, whether differentiation occurs independently in each individual cell, so that it would, if necessary, be capable of passing through

* Wilhelm Roux, 'Beiträge zur Entwicklungsmechanik des Embryo,' München, 1885.

† Pflüger, 'Ueber den Einfluss der Schwerkraft auf die Thielung der Zellen u. auf die Entwicklung des Embryo,' Arch. f. Physiol., Bd. xxxii., 1883, p. 68.

‡ Born, 'Biologische Untersuchungen,' (I.) Arch. f. mikr. Anat. Bd. 24.

its prescribed course of development apart from the rest of the embryonic cells, — or whether the various cells of the embryo become differentiated by their mutual interaction: or, in other words, whether a determinating influence is to a certain extent exerted by *the whole on its parts* and thus prescribes the fate of the various cells.

The experimental proof of the self-differentiation or predisposition of the individual cells was, I believe, furnished by Roux,* whose ingenious experiments are always accompanied by keen deductions. Roux destroyed a single segmentation-cell in each of a series of frogs' eggs by means of a hot needle, and then observed that eggs treated in this manner developed into 'half or three-quarter embryos,' that part being absent which corresponded to the cell thus destroyed. When one of the first two segmentation-cells was demolished, half of the embryo was formed, and this corresponded either to a lateral or to the anterior or posterior half, according to whether the first segmentation had resulted in a division of the hereditary substance into portions belonging to the right and left, or to the anterior and posterior halves. The process of segmentation in the frog is known to vary in this respect. When one of the first four segmentation-cells was destroyed, three-quarters of the embryo was formed.

These experiments must be regarded as affording a proof of the self-differentiation of the cells. Observations have since been made which seem to contradict this deduction; and although these are still incomplete, and can only be regarded as the preliminaries to more detailed investigations, they must not be passed over in silence, especially as I am convinced that they do not really contradict the hypothesis of the self-determination of the cells.

Chabry's † experiments on the eggs of Ascidians must be mentioned first. By means of a special apparatus, he destroyed one of the first two segmentation-cells, and then observed that the remaining cell continued to develop, and eventually gave rise, not indeed to half an embryo, but to an *entire* one of half the normal size. Such embryos were certainly not quite

* Wilhelm Roux, 'Beiträge zur Entwicklungsmechanik des Embryo,' (V.) Virch. Arch. Bd. 94.

† L. Chabry, 'Embryologie normale et tératologique des Ascidies,' Paris, 1887.

perfect, but only organs of slight importance were wanting in them. Chabry himself has drawn no theoretical conclusions from his observations; Driesch,* however, has made certain deductions from a series of similar experiments on the eggs of Sea-urchins. By continued shaking, Driesch effected a mechanical separation of the two first segmentation-cells, and observed that at first each of them continued to undergo further segmentation just as would occur in the entire egg, but that later on the resulting *hemi*-blastula became completed to form an entire one. In some of these hemi-blastulæ development proceeded still further, the invagination taking place to form the primary digestive cavity of the gastrula, so that eventually a rudimentary pluteus-larva — which, though small, was in other respects normal — could be recognised.

Driesch sums up his results in the following words: — 'These experiments therefore show that under certain circumstances each of the two first segmentation-cells of *Echinus micro-tuberculatus* can give rise to a larva of the normal form, which is *entire* as regards its shape; and that a *partial formation*, and not a *semi-formation*, occurs in this case.' The author concludes that his results 'fundamentally disprove the existence of special regions in the germ which give rise to special organs,' and adopts the following view stated by Hallez †: — 'Il n'est pas dès lors permis de croire que chaque sphère de segmentation doit occuper une place et jouer un rôle, qui lui sont assignés à l'avance.'

Although I am far from wishing to assert that we are at present in a position to give a perfectly reliable and detailed explanation of the extremely interesting and important results of the experiments just described, I nevertheless cannot help thinking that they do not in the least necessitate the giving up of the view which entails a predestination of the individual segmentation-cells, and, in fact, of cells in general. Other than experimental methods may lead us to fundamental views, and an experiment may not always be the safest guide, although it may at first appear perfectly conclusive. Even Driesch himself doubts whether the above-mentioned experiments made by Roux are really conclusive, though, in my opinion, he is wrong

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* H. Driesch, 'Entwicklungsmechanische Studien, Zeitschrift f. wiss. Zoologie,' Bd. 53, 1891.

† Hallez, 'Recherches sur l'embryologie des Nématodes,' Paris, 1885.

in doing so: he asks, in fact, whether the uninjured segmentation-sphere of the frog would not behave exactly in the same manner as that of the sea-urchin if it could be *actually isolated*, instead of remaining in close connection with the other injured sphere. Thus even the apparently incontrovertible result of this experiment may be doubted.

It seems to me that careful conclusions, drawn from the general facts of heredity, are far more reliable in this case than are the results of experiments, which, though extremely valuable and worthy of careful consideration, are never perfectly definite and unquestionable. If what was said in support of the theory of determinants in the first chapter of this book be borne in mind, the conviction that ontogeny can only be explained by evolution, and not by epigenesis, seems to force itself upon us. It would be impossible for any small portion of the skin of a human being to undergo a hereditary and independent change from the germ onwards, unless a small vital element corresponding to this particular part of the skin existed in the germ-substance, a variation in this element causing a corresponding variation in the part concerned. Were this not the case, 'birth-marks' would not exist. If, however, determinants are contained in the germ-plasm, these can only take part in controlling the formation of the body if, in the course of embryogeny, they reach those particular cells which they have to control, — that is to say, if the differentiation of a cell depends primarily *on itself*, and not on any external factor.

If therefore ontogeny is not, as Roux aptly expresses it, a '*new formation*' of multiplicity, or an epigenesis, but is merely the *unfolding* of multiplicity, *i.e.* an evolution, — or, as it might also be called, *the appearance of a previously invisible multiplicity*, — the principle of self-determination is certainly only established with regard to the egg *as a whole:* the self-determination of each cell, and its control of ontogeny, do not necessarily follow from this conclusion. We can only thereby arrive at the very simple assumptions, that the primary constituents of the germ-plasm are distributed by means of the processes which can actually be observed in the nuclear divisions, so that they come to be situated in those regions which correspond to the various parts of the body, and that those primary constituents are present in each cell which correspond to the parts arising from it.

As has just been shown, it is also possible to make the reverse hypothesis, and to suppose that although the whole of the idioplasm is contained in each cell, only that particular primary constituent which properly concerns the individual cell has any effect upon it. The activity of a primary constituent would thus depend not on the idioplasm of the cell, but on the influences arising from all the cells of the organism as a whole. We should thus have to suppose that each region of the body is controlled by all the other regions, and should therefore practically be brought back to Spencer's conception of the organism as a complex crystal. This simply means giving up the attempt to explain the problem at all, for we cannot form any conception of such a controlling influence exerted by the whole on the millions of different parts of which it consists, nor can we bring forward any analogy to support such a view, the acceptance of which would render a great number of observations on the phenomena of heredity totally incomprehensible. What explanation, for instance, could be given of the fact that a certain human birthmark is always inherited on the left side only? According to this hypothesis, the germ-plasm contained in the cells of this region would be present on the right side just as much as on the left: as the two halves of the body are alike in other respects, we cannot suppose that the whole aggregate exerts different influences as regards this region on the left and on the right sides.

It seems to me, therefore, that we must not give up the hypothesis of the self-determination of the cells, in spite of its apparent refutation by the facts described by Chabry and Driesch. Moreover, I think these facts can be explained — in principle at any rate — in another manner, viz., *by attributing the processes observed to regeneration*, the arrangement for which, however, has not been provided for the first stages of segmentation, but for a later period of ontogeny.

It is hardly to be expected that the first stages of segmentation should be in a sense *purposely* arranged for regeneration. Both in Ascidians and sea-urchins the number of eggs produced is so large, that it probably matters very little whether a segmenting ovum perishes or becomes regenerated when one half of it has been eaten by a small enemy. I do not, however, wish to do away entirely with the idea that the eggs of certain animals may conceivably be protected in this manner from numerous enemies, but in this place I must refrain from including such a possible occurrence in the argument.

The following explanation of the phenomena, however, still remains. The first division of the ovum separates the group of determinants into two, viz., that for the right and that for the left half of the body; each of these groups does not constitute a perfect germ-plasm, as each determinant it contains is not doubled; but it is very probable that the ids are capable under certain circumstances of dividing in such a way that each becomes doubled. Such a germ-plasm could not contain *in potentia* a birthmark, or any other asymmetrical peculiarity of the other side of the body, but it would be able to give rise to a complete animal. The destruction or mechanical removal of one segmentation-cell in the first stage of segmentation may be the primary cause of the doubling of the ids in the other cell.

The capability of becoming doubled, which the undivided germ-plasm possesses in certain cases, may be mentioned in support of this view of the regeneration of an isolated cell in the first stage of segmentation. The fact that in each integral division of the cell and nucleus, a longitudinal splitting of the nuclear rods and their contained macrosomes occurs, shows that the ids are as a rule capable of growth and of doubling their number by division. The assumption of a doubling of the ids of germ-plasm must be made in dealing with the origin of *identical* twins, *i.e.* those twins in which we must suppose that the division of the nucleus of the ovum from which they arise occurs *after* and not *before* fertilisation; for otherwise the embryos could not be identical, as two spermatozoa would then take part in the process. In the case of facultative parthenogenesis, a doubling probably also occurs in the ids and idants of the ovum, half of them having previously been removed by the 'reducing divisions.'

The formation of an entire embryo by the regeneration of one of the two first blastomeres admits, however, of another interpretation. Ascidians multiply very freely by budding, and not only by sexual reproduction. It is true that this is not the case with sea-urchins, but the power of regeneration which these animals possess is unusually great. This fact was explained in the present chapter by assuming that certain idic stages of ontogeny are provided with an 'accessory idioplasm,' consisting of the determinants required for regeneration. In a subsequent chapter I shall have occasion to show that we must make a similar assumption in the case of budding. Such assumptions are indispensable if we accept the hypothesis of the germ-plasm and determinants. The accessory idioplasm required for budding causes the reproduction of the entire animal, and must therefore contain all the determinants of the germ-plasm, and must exist in the ovum before segmentation, remaining in a latent condition in a definite series of cells during all the stages of development. If now this accessory idioplasm were capable of becoming active under certain abnormal influences, — such as that produced by the destruction of the other blastomere, — a regeneration of the whole embryo might thus result.

These explanations are, however, only possible ones, and I should not have been sorry to leave them out of consideration altogether, for I am fully aware of their incompleteness and unreliability: I merely wish to show that the observations mentioned above do not render an explanation impossible, even although we are not able at present to state that any particular interpretation of the phenomena is the correct one, because the observations themselves are far too incomplete and deficient. For this reason I shall not attempt to give a more precise explanation of the peculiar development of these embryos.

I must, however, draw attention to the different behaviour of the eggs in the case of the frog and in that of Ascidians and sea-urchins. Leaving aside the question of 'post-generation,' we have seen that only half an embryo arises from *one* blastomere of a frog's ovum, while an *entire* animal becomes developed from one blastomere in the case of either of the other two animals mentioned. However imperfect the explanation I have offered may be, the fundamental assumption on which it is based must in general be a correct one, — viz., that the first blastomeres of the egg of an Ascidian or sea-urchin must possess a capacity which is absent in the case of the frog's egg. As, however, forces are dependent on substances, it is probable that the blastomeres of an Ascidian and of a sea-urchin contain an excess of substance — *the accessory idioplasm* — which gives them the power of regeneration, and that this substance is wanting in the blastomeres of the frog. Driesch, as already mentioned, expresses a doubt as to whether the blastomere of a frog would not behave in a similar manner to that of a sea-urchin, if, like the latter, it could be completely separated and isolated from its injured fellow blastomere. This doubt seems, however, to be hardly justified, as such an isolation was not effected in Chabry's experiments on the ascidian ovum, but nevertheless the development into a complete animal ensued just as in the case of the egg of the sea-urchin.

Although the half of a frog's egg develops into half an embryo only in the first place, the latter may subsequently become completed by a very peculiar regenerative process, which was first observed by Roux in 'half' and 'three-quarter embryos,' and which he designated as 'post-generation.'

Roux observed that a segmentation-cell of a frog's egg may be 're-animated' after it has been deprived of its capacity for development. A considerable number of nuclei pass into the vitellus of the injured part from the normally developed half of the egg, and there increase and give rise to cells. 'The post-generative formation of the germinal layers takes place from the cell-material subsequently formed, while the process of differentiation continues to advance in the quiescent cell-material.' Roux thought he observed that a complete restoration of the embryo may take place in this manner, so that it can continue to live; and, in fact, he actually succeeded in keeping such an embryo alive for some time.

Considerable attention has naturally been drawn to these observations, which are certainly of the greatest interest; but I doubt whether in their present state they are sufficiently complete to form the basis of fundamental theoretical conclusions. With all respect for Roux's accuracy of observation and skill in research, I cannot help thinking that the half embryos which were subsequently 'post-generated' to entire animals, were possibly those in which the thrust with the hot needle had not affected the nucleus of the segmentation-cell.

In any case, it was only possible to observe the actual effect of the operation and its result on the whole series of processes which followed, and which led to the restoration of individuals *other* than those which ultimately became complete. To pierce a segmentation-cell with a hot needle must be a tolerably rough operation, and something different may be destroyed each time it is performed: not only the nuclear matter as a whole, but also the *individual idants*, might possibly remain uninjured. The idants, again, might subsequently increase to the normal number by doubling, and so bring about the development of the half of the egg. Roux certainly states that 'post-generation' does not occur in the same manner as does the normal development of the two primary halves, — that is to say, the germinal layers are not formed independently in each; but the processes which take place in the interior of the ovum can only be followed out by means of sections, the preparation of which necessitates the killing of the embryo.

In such experiments, moreover, no two cases are alike, and it would be necessary to examine a very large amount of material before stating with any degree of certainty that the egg which has been cut into sections, and that in which the development and post-generation have been followed out, have a precisely similar internal structure.

Roux observed a 're-animation' of three different kinds in the halves of the eggs operated upon, one of which consisted in a growth of the cells in the external layer of the living half around the dead half. In this instance, however, post-generation did not result: it only occurred in *certain*, but not *all*, of those cases mentioned above in which nuclei passed from the living half into the part which had been operated upon, *and in which only slight pathological changes had occurred in the yolk.* It is therefore natural to suppose that post-generation only occurred when the injury was a slight one, and when some nuclear matter remained and subsequently caused a formation of cells. This, however, does not imply that living 'nuclei' did not penetrate into the injured half of the egg; the segmentation-cells, even in normal development, have to undergo an enormous increase, and it is therefore not surprising that after the opposition to growth has been removed by the operation on the other half of the egg, they should increase at the expense of the latter. In those cases in which the other half of the embryo was subsequently completed, this completion must have resulted from a kind of infection of the cell, of such a nature that mere contact with ectoderm or mesoderm cells, for example, caused the undifferentiated cells of the injured half of the egg to become correspondingly differentiated into ectoderm and mesoderm cells. But I could only accept such a revolutionary hypothesis as this if it could be proved by incontestable facts.

Roux himself has, however, only looked upon his contributions to this subject as 'a first instalment of a large work,' and has led us to expect a continuation of his experiments. But as long as the processes which he describes admit of more than one interpretation, we cannot reject the hypothesis of the predestination of the cells by means of the distribution of certain determinants and groups of determinants to them, for this view is supported by so large a number of facts, and even by the earlier experiments of Roux himself. It would certainly, however, *have to be rejected if we could prove that the cells of the* germinal layers were really capable of being determined in their nature by the region which they accidentally reach, or by their accidental surroundings.

Further research along the line opened up by Roux will, I am convinced, show us the facts in another light, and will enable us to reconcile them to the rest of our conceptions as to the causes of ontogeny. But I do not consider it worth while at present to enumerate all the possible causes which must be taken into account in an attempt to explain 'post-generation.'