The Problem of Form Regulation [1].

By

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With 3 figures in text.

Eingegangen am 19. Mai 1903.

Introduction.

There are probably few biological problems of more fundamental import than the one I have attempted to discuss in this paper. The investigations which have been devoted to the subject of regeneration and the efforts which have been made to ascertain the factors of the process of development have brought out the inadequacy of the various theories that have been put forward to explain these classes of phenomena. WEISMANN's theory of qualitative nuclear division as a basis of differentiation and the theory of germinal localization of HIS, while they have aroused much discussion and stimulated many lines of investigation, have now mainly ceased to have anything more than a historic interest; yet a consideration of some of the difficulties in the way of accepting these hypotheses will serve to make manifest one of the fundamental requirements which most other theories of development in common with these have failed to fulfil. According to the well known theory of WEISMANN there is a separate kind of preformed element, or determinant, for each independently variable portion of the organism; these determinants are arranged in a particular manner in the chromosomes of the nucleus and, during cell division, different kinds of determinants are sorted out and come to lie in different portions of the embryo which differentiate in a direction controlled by the kind of determinant they receive. This theory, by

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assuming that nuclear division is not merely quantitative but qualitative, lays itself open to very serious objections. The development of normal embryos from isolated cleavage cells, and the pressure experiments performed on the eggs of sea-urchins, annelids, an the *frog showing that the direction of differentiation of a part is independent* of the source of its nuclear material present almost insuperable objections to WEISMANN's view. The various accessory hypotheses which are necessary to make the theory applicable to the facts of development, and especially to the results of experimental embryology render it so complicated and so artificial that it loses all vestiges of probability. If we avoid the difficulties involved in the theory of qualitative nuclear divisions and adopt such a doctrine as DE VRIES' theory of intracellular pangenesis we gain little more insight into the causes of formative changes. Why the right pangens become active at the right time and how the formative processes are correlated so as to work together in a harmonious manner the theory does not make clear. If we admit that the theory is sound as far as it goes it must be confessed that it does not take us very far. We have accomplished very little in explaining any feature of development when we have ascribed it to a particular determinant or pangen. The real problem remains much as before.

The theory of germinal localization of HIS and his followers meets with difficulties in the same facts that overthrow the theory of WEISMANN. It is well known that when the blastomeres of the two-cell stage of the sea-urchin egg are separated each cell develops into a perfect embryo of half the normal size. The theory of HIS assumes that the various organs of the embryo are represented somehow by specialized regions of the egg. Yet when half of this preformed structure is removed a perfect embryo, and not a half embryo is produced. It may be said that the missing part is regenerated and that we cannot deny that the egg possessed a definite structure with all the parts preformed before the first cleavage began. There is no gainsaying the pertinency of this answer. The experiment does not disprove the existence of a complicated egg structure; but it shows, however, that half of this hypothetical organization is not necessary for the formation of the embryo. We may perform all the experiments on the egg we please and it will always be possible for the upholder of this theory to maintain that the egg possesses a complex organization though it cannot be seen; we cannot prove that this organization does not exist, and whoever wishes to espouse the theory of germinal localization may rest in it with a feeling of comfortable security. It may be shown that this organization is not necessary for development and it has been proven that in some forms seven-eighths or even fifteen-sixteenths of it may be dispensed with without destroying the power of forming a normal embryo. If the egg regenerates the missing part of its organization it is just this power of restoration which calls for explanation. Here is a piece of genuine development which is not merely the unfolding of something already preformed. Those factors which produce a perfect embryo notwithstanding the destruction of a large portion of the organization of the egg or the distortion of its parts play so important a part in development that we may as well regard them as the real factors of the normal process. If the egg possesses a considerable degree of organization to begin with we have just so much less development from that stage on to account for. For the development that actually occurs we must still seek an explanation. It is futile therefore to attempt to make a general theory of development out of the theory of germinal localization. It is obvious that the real factors of development cannot lie in anything that can properly be described as a regional differentiation of the ovum. There is indeed evidence that the undivided egg possesses a certain degree of structural organization. The facts of determinate cleavage and partial development point strongly to such a conclusion. We are justified in assuming organization to the extent that there is evidence for it but not in going farther. Peculiarities of cleavage may result from an organized egg structure just as certain features of later development result from the fact that the embryo has passed through a gastrula stage. But there is reason to believe that the ovum has reached its organized state, just as the gastrula stage has been reached, by a process of development. The organized structure of the egg stands for a certain period of embryonic history, — the product of development, not its necessary antecedent.

Neither nuclear nor cytoplasmic preorganization gives us any real explanation of the regulatory processes which must play so important a part in development. We may assume all the preformation that is involved in the most extreme form of the doctrine of emboitement and it will avail us nothing when we grapple with the problem of regulation. Eggs may be divided, distorted, and in many ways thrown widely off the track of normal development and nevertheless finally produce a perfect embryo. Regeneration often follows methods entirely different from those pursued in the formation of organs during ontogeny; in fact, parts arising from one germ layer in the embryo are not infrequently regenerated from tissue in the adult belonging to a different germ layer. We have to do with factors which make for the normal wholeness of the organism, and which operate despite obstacles and interruptions, often by means of new methods, until the final goal is reached. A single false step in development does not throw the subsequent chain of events upon the wrong track. One of the greatest difficulties in the analysis of development by experimental methods lies in the fact that the phenomena cannot easily be separated and kept apart. The regulative factor steps in to nullify the effects of the experiment and events go on much as before. What is this agency which effects the correlation and harmonious combination of developmental changes? In regeneration what guides the differentiation of tissues so that the missing part is restored? Few will be inclined to doubt that development and regeneration are fundamentally akin; we have essentially the same question to deal with in either case. The end result of both processes seems somehow to dominate the means by which it is reached. The *raison d'être* of this remarkable property of organisms is the fundamental problem for which any adequate theory of development or regeneration must afford a solution.

Form Regulation and Natural Selection.

In the changes which occur in the development of an embryo or the restitution of a lost part we meet with numerous remarkable adaptations for bringing about the end result. Our recourse in biology when we have adaptations of any kind to account for is usually to the principle of natural selection. The reactions which make up the instinctive behavior of animals are considered, according to this theory, to owe their adaptive features to the selection of those individuals which happened to react in a favorable manner to the stimuli which affected them. The animals which responded in adaptive ways survived, the other perished. By the gradual summation of favorable variations of behavior complex instincts finally come to be evolved which have all the appearance of actions intelligently directed towards an end. So far as we know, there is nothing in the purely instinctive behavior of animals which obviously refuses to come under this principle of explanation. Now if we regard development and regeneration as resolvable, like the instincts of animals, into reactions to stimuli can we explain the adaptive features of these processes as likewise the outcome of natural selection? Can we explain the behavior of cells, tissues and organs in their relation to each other and to the entire organism as we explain the behavior of the organism as a whole in relation to its surroundings? The development of an organism by the multiplication and differentiation through interaction of its cells bears a suggestive analogy to the development of social groups, such as a community of ants, from a single individual. In some species of ants the queen starts a nest and lays in it a few eggs which produce workers; these workers are provided with instincts which lead them to labor together harmoniously for the good of the colony. As more eggs are laid and hatched the larvae are cared for by the young workers, the nest enlarged, food brought in, and provision made for the growth and protection of the community. By the multiplication of its members, their differentiation into classes, their reaction toward each other and the outer world a social organism is developed whose component members work together for a common good. If natural selection has directed the instinctive activity of these creatures so that the result of their conduct is to produce a harmoniously functioning community, is it not possible to interpret the development of the individual as a series of processes each of which owes its adaptive character to the same principle? Such an interpretation has a certain degree of plausibility and attractiveness, but a little consideration will show that it is beset with serious difficulties. And when we attempt to bring regeneration under the same head the difficulties become even greater. I do not wish to imply that natural selection has had no share in directing the responses which occur in development, but as the sole principle of explanation of the individual adaptive processes which give rise to the normal form of the organism it is, I believe, entirely inadequate. If we accept such a view as the foregoing we are compelled to assume that every act in the process of development which is anything more than incidentally adaptive must have proven of selective value at least several times in the past history of the race. Considering the complexity and number of adjustments occuring in normal development the burden thus thrown of on the shoulders of natural selection is a great one. But what are we to say of the numerous deviations from the normal course of development which are constantly being checked? An organism may be evolved to respond properly to a complex set of outer stimuli; but the stimuli produced through the interaction of the parts of an organism, as the directive stimuli in development very largely are, are dependent upon the previous state of development of the parts. A deviation from the normal path of development would, to a certain extent, produce a new set of stimuli which would naturally cause the departure from the normal to become still greater. This would react to produce still more unusual conditions of stimulation, and so on, throwing the course of development farther and farther from the normal path. Each abnormality naturally tends to produce an ever increasing series of abnormalities. The organism must, therefore, be so perfectly adjusted that it responds to its own imperfections in just the right way to rectify them. In order that the abnormal conditions be provided for, each of them must have appeared several times in the history of the race. This is certainly making the theory of selection bear a great deal, but difficulties come up which make the application of the doctrine not even theoretically possible. If an organism can adjust itself to a condition which has never been presented in its ancestral history we cannot explain this adjustment on the basis of natural selection. We are consequently led to enquire if organisms can adapt themselves to new contingencies, or exhibit new adaptive methods. If one cell of the two-cell stage of the frog's egg be killed, the other cell, after developing for some time as a half embryo, will ultimately give rise to a perfect larva. This process of postgeneration by which the embryonic processes are ultimately brought back upon the right track is one of extreme complexity. It differs in many ways from anything that occurs in normal development. Can we conceive each of the multitudinous steps of this process as especially directed by natural selection? If with Prof. Weismann, we regard regeneration, not as a fundamental property of organisms, but an adaptive acquisition we must take some such view. We must suppose that the death of a blastomere is an accident which has happened very often in the history of the species, and that through a process of selection individuals were developed which responded to the situation by just the proper series of acts to bring about the complete form of the organism. But there are many objections to such an interpretation. First, from what we know of the development of frog's eggs in nature the killing of one blastomere is not of sufficiently frequent occurrence to elicit any special provision by natural selection for meeting the contingency. Second, it is very questionable if it would be of any value to the species for embryos from a single blastomere to develop: they would, at best, give rise only to relatively inferior individuals which natural selection would tend to eliminate rather than preserve. Third, variations in the direction of substituting the missing part would be of no service unless they made this part approximately complete. It would require an enormous number of adaptively directed responses to bring the embryo up to this state, and how are these variations to accumulate before they attain a selective value? Then we know that the egg may produce a complete embryo after injuries of many other kinds, each injury being rectified by a complex series of reparative processes. The theory that all these forms of reparation have been directed in detail by natural selection cannot possibly be upheld. We cannot explain such responses as we explain the instinctive reactions of animals. The tendency towards the normal asserts itself, despite obstacles and injuries, whether they have been frequently met with in the past or not.

In the regeneration of the parts of the adult organism the normal form is reached by methods which certainly cannot have been moulded by ancestral selective processes. It would be futile to attempt to explain the regeneration of internal organs such as the liver and salivary glands of mammals as special adaptations due to natural selection. As MORGAN has pointed out there is no close relation between the liability of an organ to injury and its power of regeneration; the liability to injury may be practically nil, and yet its regenerative capacity be very marked. The case, now well established, of the regeneration of the lens of the eye of a triton from the cells of the margin of the iris has been adduced, with good reason, as one especially difficult to explain by the doctrine of natural selection. Can we conceive that after the loss of the lens (granting that it is a frequent mishap of the species) the first steps towards regeneration would be of selective value? If in some individuals that had lost the lens of the eye the iris happened to respond by the proliferation of a few cells it is difficult to see the value of such a variation. Until a large number of variations had accumulated, bringing the proliferated cells into a form that would be of some service as a lens, natural selection would have no opportunity to act. The attempt to explain the regeneration of the lens as a special adaptation developed by natural selection seems hopeless. The missing organ is restored by a method entirely dissimilar to that by which it is formed in the embryo. The lens, as is well known, develops from cells of the ectoderm on the surface of the body; while the regenerated lens is derived from the cells of the iris which have had a very different embryonic history. In response to a stimulus (or the withdrawal of one) the organism completes its form. by an adaptive process dissimilar to anything which happens in its embryonic development and undirected by the experience of the history of the race. As an explanation of such an occurrence the theory of natural selection is obviously out of court.

If the organism is capable of emending grave injuries by adaptive processes undirected by natural selection there is no necessity of appealing to this principle to explain the correction of minor deviations from the normal which are of frequent occurrence in normal development. The same principle of regulation which accomplishes the one may well take care of the other. Natural selection may increase or diminish the general regenerative capacity of an organism and accelerate or retard the development of any part of an embryo. We may grant that it may perfect the regenerative power of special organs, such as the tail of a lizard, or the cheliped of a crab. But the process of form regulation as such must rest upon a different basis.

If we reject the theory of natural selection as a general explanation of form regulation, how, it may be asked, are we to explain the adaptive character which formative processes exhibit? It is the failure of natural selection to account for such phenomena as are cited above which has driven some writers to ascribe the guidance of formative processes to a special teleological principle. Formative processes work towards an end, the production of the normal form of the organism; this end is often accomplished by new methods as if the normal form exercised some compelling influence upon the processes which lead up to its establishment. Life processes seem to be dominated by an end, much as a man's conduct may be shaped towards the realization of a purpose. Purpose, therefore, has been considered to be the regulative agent in life phenomena, which, on this account, become set apart from the phenomena of the inorganic world to which mechanical explanations are generally admitted to be applicable. The failure of natural selection to account for form regulation does not, I believe, compel us to adopt any of the teleological doctrines of the neovitalists nor to seek for a new theory of the phyletic development of adaptive characters. It will be well, however, before going farther to distinguish two senses of the term adaptation which have ordinarily been confused in the discussion of this subject. We speak of the processes involved in restoring a lost limb as showing adaptation inasmuch as they coöperate to bring about the particular result achieved. We also speak of the adaptation shown in the protecive coloration of an insect, inasmuch as it enables its possessor to escape detection and, therefore, to stand a better chance of survival. An adaptive structure or mode of action in the latter sense is one which aids in the preservation of the individual or the perpetuation of the race. The possession to a remarkable degree of such adaptations is one of the most distinctive features of organic beings. It is undeniable that those processes which bring about the normal wholeness of the organism are adaptive also in the sense that they make for the survival of the individual or the race, but they are not primarily adaptive in this sense; they become so only because the normal form which they complete is an adaptive mechanism. Rudimentary and useless organs are regenerated as well as those which conduce to the survival of the individual; and if we could conceive an organism whose parts show no adaptation to environing conditions there is no reason to doubt that such an organism when injured would possess the power to restore its normal form. What we call an adaptation depends very largely upon our point of view. We may consider the chemical changes occuring in a solution as adapted to the formation of a precipitate, inasmuch as they bring about this result. The properties of common salt are adapted to give rise to a crystal of a certain definite shape. The beautiful outline of a snow flake is the product of activities which show a remarkable adaptation for producing that particular form. The evolution of the solar system from a primitive nebulous condition affords a series of adaptive events exactly regulated so as to bring about the present order. In fact we may take any phenomenon in nature and consider the causes that led up to it as adapted to produce that particular outcome. We do not regard such phenomena as the above as requiring any teleological principle for their explanation. They are explained satisfactorily to all in terms of ordinary physical laws. Certain phenomena in nature more easily and naturally impress us as being the end result of coöperative activities. A little thought will make clear that any other phenomenon such as the occurrence of a mud puddle by the roadside is the outcome of a large number of coöperating causes which we may regard, if we choose, as adapted to produce that particular effect. The processes concerned in form regulation are primarily adaptive in the sense that crystallization is adaptive; they lead to the establishment of a certain form. Were the body of an organism simply a complex aggregate of parts no one would think of appealing to some new principle to explain its production. It is because this complex organization is composed of parts which so arranged that the result of their interaction with each other and with the environment is the maintenance of the life of the whole that we are so greatly exercised to explain how such a phenomenon could have been brought into existence. For all that we know to the contrary the adaptive organization of living beings may have been brought about by the continual selection of favorable variations. If crystals could multiply and compete with each other in a struggle for existence, the power of a crystal to restore its regular form would be an adaptive property in that it would conduce to the survival of that crystal. Natural selection might explain why dominant types of crystal possess certain features on the ground that these features were of value to them in the struggle for existence, but it would not explain the power of the crystals to restore their missing parts. While natural selection does not explain the process of regulation, it may nevertheless suffice to account for the phyletic development of the adaptive characters of the form which is restored. It is the latter problem for which the theory was originally offered as a partial solution. Those who would employ it to explain regeneration and other modes of form regulation extend it to a region beyond its legitimate sphere of application. And then, when the futility of the attempt is shown up, the conclusion is drawn that natural selection has failed to justify its pretensions! The attempt to explain form regulation by natural selection is like employing that theory to explain assimilation or why carbon and oxygen came to be essential elements of living matter.

It may be maintained that form regulation differs from processes occurring in inorganic nature because the final result is often reached by new methods which show an apparently intelligent adaptation of means to ends. In the regeneration of a crystal the perfect form is reached by a regular stereotyped method; in an organism, on the other hand, the process of regeneration seems not to be tied down to a definite routine, but reaches its goal by the most appropriate means. That the normal form may be reached in various ways is indeed a striking peculiarity of organic life; but it does not necessarily imply a teleological explanation any more than does the adjustment of any other self-regulating mechanism. And if it can be shown, as we hope to do, that the tendency to attain the normal form is the outcome of certain physiological laws, as the regulation of a time piece takes place according to a few simple laws of physics, we have done away with the necessity of recourse to a mysterious teleological principle.

The explanation of form regulation is a problem apart from that of the origin of adaptation in the sense that adaptation is a distinctive peculiarity of organisms. Form regulation is shown in the renewal of a tumor, or the regeneration of a useless rudiment as well as in the restoration of useful structures. It does not work primarily for the good of the organism. The regeneration of the tail of an angle-worm in place of a head, or the restoration of supernumerary organs show no regard for the welfare of the individual. The tendency towards normal wholeness is a fundamental feature of organisms as of crystals. The reason why form regulation is of service to the organism is because the structures produced are adapted to perpetuate its life. Why these structures came to be so adapted is a historical problem for which, I believe, the theory of natural selection affords the most satisfactory solution.

The Organism as a Symbiotic Community.

That the parts of the organism stand in a relation of mutual dependence is a familiar fact. The proper functioning of one organ is dependent upon the proper functioning of other organs. If an organ of excretion fails to remove waste products all the other organs suffer; and organs of excretion as well as all others are affected by an inadequate discharge of the functions of digestion, respiration, and circulation. All this is of course trite. But there is an interaction and mutual dependence of parts which is much more intimate than that which is brought about by the division of their obvious functions. Contiguous parts affect each other profoundly. When after the removal of one blastomere of the egg in the two-cell stage the other cell begins to develop in a manner different from its normal course it is evident that the typical mode of development is due to the influence of the missing cell; or to put it in another way, the abnormal course of development is due to the absence of the missing cell. Removal of the lens from the eye of a triton starts the cells of the margin of the iris upon a career of growth and multiplication.

We may fairly conclude that it is the presence of the parts of the eye in their normal relation that prevents the cells of the iris from undergoing further developmont under ordinary conditions. A small transverse slit in the side of a Cerianthus causes the multiplication of the cells below the cut and their differentiation into tentacles. Can it be other than the influence of the cells above them which prevented these cells from forming tentacles before? Each part of the organism is in some way held in place by the others. Removal of a part causes a disturbance in the functioning of other parts. Driesch has recognized that such a disturbance of functional harmony is what he calls the primary stimulus of the process of regulation. And it is evident that if the removal of an organ did not create some functional disturbance in the parts that remain they would not set about the task of repairing the loss. Besides the function of muscle fibers to contract, of gland cells to secrete, and of nerve cells to conduct stimuli we must assume a function which these cells exercise upon their neighbors which has the effect of keeping them in a certain condition of equilibrium. The parts of the eye coöperate to produce distinct images of objects on the retina, but they also influence each other so that the undue development of any part is held in check. The cells of the various parts of the eye are not prevented from further growth and division because they have lost this power. The presence of abnormal stimuli, or the removal of a part may bring about both these processes, as well as differentiation along a line widely different from the original condition. If we suppose that a developing embryo is cut by a plane of infinite thinness but which would act as a barrier to the influences that would otherwise pass between the separated parts, it is reasonably certain that development would no longer go on in a normal way. If development be to a certain extent a mosaic work the pre-established harmony of the parts could not be sufficiently perfect to keep them all developing in the right direction and at the proper relative pace. Whatever theory of development we adopt it is evident that the harmonious development of an organism is due in large measure to the influence of one part upon the other. If the parts of an embryo show, as they do in many cases, a certain independence in their development, the differentiation of these parts may nevertheless be due to the interaction of their smaller constituent elements. Self differentiation, as Roux has pointed out, must always, in the end, be resolvable into development through interaction. We cannot explain the harmonious evolution of an embryo on any other ground than by supposing a thorough-going mutual dependence of its parts which is the result of an intimate functional correlation. This intimate mutual dependence of parts makes for a certain functional harmony, or equilibrium, into which the organism tends to settle. The tendency towards functional equilibration not only maintains in a thousand ways the actions which maintain the normal form, but it is, I believe the guiding principle both of regeneration and embryonic development. All these processes are aspects of form regulation, and form regulation *may be regarded as an expression of the effort to attain a condition* of functional balance. The organism is a sort of a self-regulating mechanism in which deviations from the normal which are constantly occurring are held in check. The parts behave as if they were under the control of an intelligent being intent upon the end of preserving the integrity of the organism. The developing embryo seems to be under the direction of something which, like a shepherd guiding his flock, checks this part, hastens that, directs the other into its proper path, until the desired goal is reached. And as we have seen the normal form may be gained or regained by methods which are largely independent of tradition. This apparently intelligent working towards a definite end, despite all sorts of obstacles, which formative processes manifest seems to stand in marked contrast to the phenomena of the inorganic world which we explain in terms of physical laws. But the problem of form regulation, though one of great complexity, is not one about which we must needs be in despair. We are brought *into somewhat closer touch with it* when we *regard form regulation* as the result of functional equilibration. The harmonious functioning of an organism is mainly secured by a system of automatically acting checks which we may conceive to act in a manner more or less remotely analogous to the governor of a steam engine, or the forces which regulate the motions of the planets. Self-regulating mechanisms are by no means confined to the organic world. Machines which are self-regulating are familiar to all; the solar system is a self-regulating mechanism of a most perfect kind. In these cases deviation from the normal is the cause which automatically sets up activities by which the normal is regained. No one doubts that in a time piece or in the solar system the whole self regulating process is strictly mechanical; and there is consequently some justification for the belief that the regulative processes in organisms may be equally mechanical.

The self regulation of organisms may, I believe, be in a measure understood if we assume that their parts stand in a relation of mutual dependence such that the undue growth or functioning of any part is held in check by the reactions thus brought about by other, and especially the contiguous structures. If we suppose that the various cells constituting the body have each a different kind of metabolism, and that the products of each cell are in some way utilized by the neighboring cells, so that each derives an advantage from the particular association in which it occurs we may understand, in a measure, how this checking may be brought about. This supposed relation is realized in a simple scale by the cases of symbiosis that occur between plants and animals and between the algae and fungi of lichens. The organisms composing these simple communities have markedly different metabolic products; what is eliminated from the one serves as food for the other. In many protozoa there are algae which derive nourishment from their host, and give off oxygen from which their host in turn profits. While both kinds of organisms may compete for certain elements of the food supply, each derives an advantage from its association with the other and would suffer if the other were removed or reduced below a certain degree of functional activity. The undue growth of one kind of organism would result in its being brought into relatively unfavorable conditions, and this would naturally act as a check upon its further increase. If in a community composed of animal cells and symbiotic algae the animal cells came greatly to preponderate they would suffer from a scarcity of oxygen which would tend to retard their growth. If the algae came to exist in undue proportions they would suffer from a scarcity of food and their growth would likewise be checked. The mutual dependence of parts each of which tends to grow and develop on its own account keeps the community in a condition of approximate balance. These symbiotic elements form a self-regulating body, a sort of harmonic system, to use an expression of DRIESCH, like that exemplified by the body of an individual organism, although, of course, much simpler in kind. There is reason to believe that the same fundamental principle which serves to explain the regulation of a simple symbiotic community of animal and plant cells will apply to highly developed organisms as well. We may regard the body of a highly complex organism as a sort of symbiotic community, each part being dependent on the others, and prevented from abnormal development by the very fact of this dependence. By virtue of this dependence it is, to speak figuratively, to the interest of each part to play its normal role in the corporate life. Deviations from the norm bring about their own check.

The supposition that every higher organism is a symbiotic community on a vast scale composed of innumerable different elements, each with a slightly different sort of life, and yet delicately adjusted to and dependent on the others is not so bold as it might at first appear. The delicate adjustment and mutual dependence of parts are indisputable and few will be inclined to doubt that different cells *differ* in the products of their metabolism. The assumption of the particular relation of symbiosis analogous to that subsisting between protozoa and algae receives its justification by affording us a means of explaining how this delicate adjustment and mutual dependence are brought about. What is the nature of the exchange of services which we have supposed to obtain between the component cells of the organism? We may imagine that each cell appropriates some substances that are given off by the neighboring cells and produces some substance upon which the neighboring cells are more or less dependent. Or we may assume that certain products of excretion which would be injurious if allowed to accumulate are removed by the other cells which derive an advantage from this relation. The exchange of services between animal cells and symbiotic algae illustrates, in a way, both of these conditions. Each cell may also be supposed to give off substances which combine with the injurious excreted substances from its neighbors and destroy their noxious properties; or in other words, each cell may produce a sort of antitoxin for the others. Or again, we may suppose that each kind of cell may produce some substance which acts as a specific stimulus to the others, a stimulus upon which the others depend for the maintenance of their normal activity. The importance of internal secretions as a means of affecting correlations in development of parts has been suggested by DELAGE and MATHEWS has worked out somewhat more fully the same idea. We know that contiguous cells do influence each other, and it is most natural to suppose that the effect is brought about by the transfer of substances. But however we may conceive this mutual influence to occur, the assumption of a symbiotic relation between the cells of an organism has much in its favor, especially since by this means we are enabled, I believe, to gain a deeper insight into the causes of form regulation.

The Direction of Differentiation a Function of Social Pressure.

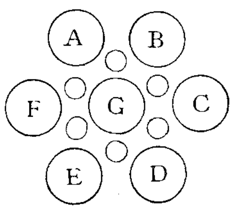
Every one is familiar by this time with the aphorism of DRIESCH *that the fate of a cell is the function of its position*. What a cell becomes depends upon its environment, — the influence of the cells around it. There are limits to this plasticity to be sure; cells may receive a certain specialization early in development which fixes their fate within certain limits, but this does not prove that their fixity is not the result of their previous organic environment. There is little doubt that the environment of a cell tends to mould its course of development, although it may not overcome the specialized and intractable nature which the cell may have acquired. Of course position as such can have nothing to do with directing development. Position means certain social relations and it is these which determine the lines upon which differentiation proceeds. Those influences from surrounding cells which tend to impress upon a part a certain structure and call forth a certain function I have called, for lack of a better term, social pressure. It is analogous to the pressure which an individual is under owing to the particular social condition into which he is born which tends to make him a farmer, a tradesman, a Roman catholic, or a Mohammedan.

We have assumed that the cells of an organism stand in a symbiotic relation to one another, the functioning of each contributing something to the functioning of the rest. When one part is removed there is naturally a disturbance of the balance of functions. This disturbance is the primary stimulus to regeneration. The important question then is: Why does the tissue which regenerates the missing organ produce that particular part and not some other? In the first place we may say that the social pressure upon this tissue is different from that exerted on tissue in any other part of the body, and that this fact somehow determines how it shall develop. But we may again ask: Why does this particular set of stimuli cause development to proceed upon just the right path? If we say that in the past experience of the race organisms whose tissues responded in this way after the loss of the organ in question were preserved, and that the power of reparation was therefore developed by natural selection, we encounter the insuperable objections pointed out in a previous section. The fact that the missing organ supplied a need of the others and in turn depended upon them is one of essential importance. To ascertain how the defects of organic form become the means of their own reparation is the crucial problem in form regulation. And this reparation is, I believe, brought about by the fact that, owing to the symbiotic relation between the constituents of the organism, cells differentiate into the likeness of the missing part because that is the direction which they can most easily and profitably follow. To say that cells develop in a certain way because their social environment renders it easy and profitable may raise a shrug of protest from the critical reader, but there is a sense in which the use of the terms is justified. Cells which develop in the direction of the missing part receive those advantages which the symbiotic relation afforded the cells whose place they take. Differentiation in any other direction deprives them of these advantages and subjects them to other unfavorable conditions. If the parts of an organism are so related that each derives greatest advantage from being situated where it is, it seems probable that, if an organ were removed, the regenerating tissue which supplies its place and which we assume to be totipotent in its regenerative capacity, would differentiate most advantageously to itself in the direction of the missing organ.

To illustrate this conception of regeneration let us recur to our case of a social organism composed of animal cells and symbiotic algae. We may suppose that both animal and plant cells tend to grow and multiply as far as circumstances permit. As these cells depend upon each other to a certain extent, neither kind of cell will tend to preponderate over the other, but they will all adjust themselves to a condition of approximate equilibrium. Now suppose that a considerable number of the algae of this composite organism be removed. There is a functional demand by the rest of the organism for the products of the algae and an excess food supply for those which remain. The algae, therefore, are supplied with exceptionally favorable conditions for growth and multiplication, and will be stimulated to regenerate their missing number. By supplying the functional demand of the animal cells they indirectly benefit themselves, because by producing more oxygen they enable the animal cells to produce more of the substances which they utilize as food. If we suppose that in our hypothetical organism there are, in addition to the two kinds of cells mentioned, indifferent cells which are able to develop into either animal cells or algae, it seems probable that, in the event of the removal of the algae, the indifferent cells would differentiate so as to take the place of the missing members. There would be a sort of premium placed upon development in this direction; there would be less competition and greater advantage in this line of differentiation than in the other. If the indifferent cells began to develop in both directions those which started in the line towards algae would grow and multiply the more rapidly, and would effect a regeneration of the missing cells.

For the sake of a simple illustration we have described an organism consisting of but two kinds of cells, but there is no reason to doubt that in a complex organism consisting of many varieties of cells standing in a symbiotic relation there would be a similar regeneration of any part that is removed. Let us imagine an organism made up of a number of differentiated cells, each of which derives some advantage from some substances produced by the contiguous cells, and giving out some substance upon which the contiguous cells are more or less dependent. We will suppose that, in addition to these differentiated cells, there are scattered through the body numerous indifferent or embryonic cells whose multiplication is held in check by the others, but which upon the removal of any part respond to the functional disturbance by growth and multiplication near the place of mutilation. We may represent our hypothetical organism graphically by the following diagram in which the differentiated cells are represented by the larger circles *A*, *B*, *C*, etc., and the indifferent cells by the smaller circles between them. Each cell such as *A* contributes something utilized by *B*, *G*, and *F*, and derives something in return from each of these sources. Now suppose *A* is removed; the indifferent cell lying near by, no longer held in check by the same stimuli as before, begins to grow and develop. What line of differentiation will it most naturally take? Owing to the symbiotic relation subsisting between the cells differentiation in the direction of *A* will be most favored as this secures it the advantages which *A* received. In other words this will be the direction of development along which social pressure will tend to guide it. And the result will be a regeneration of the missing part.

Fig. 1.



We will now attempt to apply our theory to the regeneration of a more complicated organism such as a planarian. When the head of a planarian is cut off the anterior end of the body, as is well known, begins to regenerate a new head. The process is one of extreme complexity, but may be interpreted according to the same principle that we have just applied. For the sake of illustration we will suppose that regeneration is effected by the development of new tissue in front of the cut end and its transformation into the missing part. New tissue is in fact developed in this case, but it is also true that the tissue that remains is to a certain extent transformed into new structures. But we may for the present exclude the factor

Fig. 2.

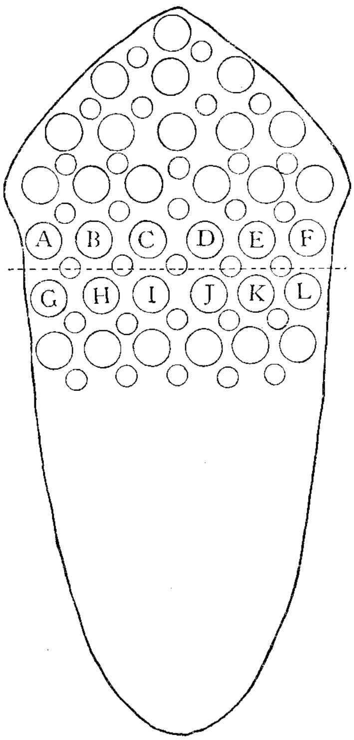
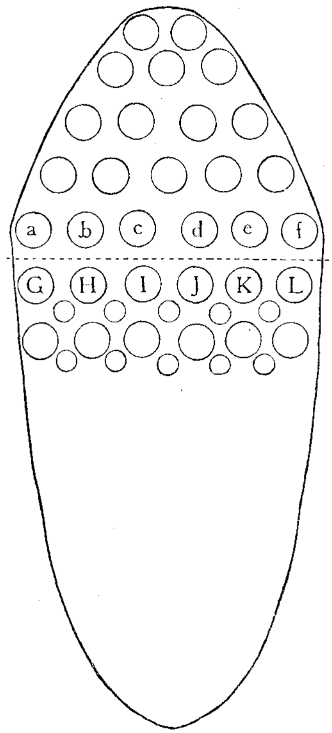


Fig. 3.



of morphallaxis, reserving it for discussion later on. In the diagram the differentiated cells are represented by circles containing letters, the indifferent cells being indicated as before by circles of smaller size. We will suppose the body cut across in the position of the dotted line. The indifferent cells behind the cut being subjected to new conditions of stimulation owing to the functional disturbance set up grow and multiply, producing a mass of tissue at the anterior end of the body as is shown in fig. 3. This mass of cells is differentiated into a new head through the influence of the posterior piece. How is this transformation effected? We may assume that each of these cells is totipotent, — capable of developing into any kind of cell of the body of the animal. The line of development a cell of this mass takes is a function of its social pressure. Let us consider the cell *d* which occupies the same position in relation to the cells *I*, *J*, *K* as was occupied by the cell *D* in the entire animal. The cell *D*, ex hypothesi, was in a position of symbiotic relationship with these cells. It will, therefore, tend to differentiate in the direction of *D*. In the same way the new cell *e* will tend to differentiate by virtue of its social pressure into a cell like *E*, and so on, the row of new cells just in front of the older cells behind the cut end differentiating by virtue of their environment in the same way as their predecessors. The next row in front of these will then be under the same necessity of differentiating into cells like those which occupied the same situation in the entire animal. As soon as the cells are started to develop in a certain way by virtue of the social pressure of the cells behind them they begin to exert a social pressure upon the cells in front, and those in turn will exercise a directive influence upon the next anterior series, and so on. The process will go on until the new cells are worked over into the form of the missing anterior end. When this has been effected there is a functional equilibrium attained which inhibits further development.

If, as we have maintained, new tissue is differentiated under the influence of the old, it would be expected that differentiation of proliferated material would first appear next to the older cells, and proceed outward from this point. Pflüger has advanced the theory that the layer of new cells next to the cut end of a part differentiates under the influence of the old cells; the next layer is then differentiated under the influence of the preceding one, and so on, until the new tissue is modified so as to replace the missing part. Morgan has raised the objection to the general validity of Pflüger's explanation that »the distal end of the new part forms always the distal end of the organ that is to be produced. If enough new material has developed (before the organization of the new part takes place) to produce all of the missing part, the latter is formed, but if the material is insufficient to produce the whole structure, then as much of the distal end as possible is formed. In some cases, as in the planarians, the missing intermediate regions may subsequently develop behind the distal part that is first produced«. The generality of the statement that differentiation begins in the distal end of a new structure may well be questioned. In the development of a tip of an organ there are usually certain noticeable features presented which naturally first strike the eye. Incipient differentiation may have proceeded from the cut end to the periphery of the new part, after which the distal end, having been started in a certain direction by the intermediate region, might differentiate more rapidly and so give rise to the appearance of development independent of the other cells. There may be also a greater functional demand for the development of the organs at the tip of a part which would hasten its development. The anterior end of a worm and the distal extremity of many organs possess specialized parts whose metabolism must be considerably different from that of other regions. If differentiation occurs through the mutual influence of the functional activity of the various parts, the more decided differences of function may be the first to call each other out, and thereby lead to the early appearance of the more pronounced features of structure. The fact that differentiation first appears in the distal end of a part is not, I believe, out of harmony with our interpretation of the regenerative process. Differentiation must proceed quite far before it becomes appearent to our vision. And even if it actually begins at the distal end it may nevertheless be due to the influence of the old tissue. If the removal of the sexual glands of a deer affects the growth of the antlers, the influence of the old part may proceed through the new tissue in front of the cut end of an angle-worm or a planarian.

Form Regulation in Unicellular Organisms.

In the preceding discussion form regulation has been treated of as an essentially social process in which cells play the part of individual units. It is undeniable, I think, that cells actually possess a certain amount of individuality, although their autonomy may be, in many cases, almost completely subordinated to a common life of the organism. But we have described the cell as a sort of individual mainly because it afforded a ready means of illustrating our conception of form regulation as a social process. The cell is not necessarily the unit concerned, or at least the only unit. The cell itself is capable of regenerating missing parts. It is a familiar fact that the protozoa, or unicellular organisms, possess the power of regeneration in the highest degree. If regeneration be the outcome of social relations the cell itself cannot be the individual unit as it takes more than one individual to form a society. We have, therefore, to adopt the view that a protozoan is composed of parts sustaining a symbiotic relation to each other much like that we have assumed to occur in the body of a metazoan. No one doubts that the processes of regeneration and other kinds of form regulation which are so strikingly similar in the protozoa and metazoa are dependent upon the same general factors in both groups. If, therefore, we attempt to interpret them in the same way we must assume that the body of a protozoan is composed of parts that are tied together by bonds of mutual functional dependence. Must we fall back upon the hypothesis of smaller vital units, such as biophors, pangens, micellae, etc., etc. which have so often been appealed to? That living matter is composed of minute, discrete, more or less independent living entities is certainly far from being proven, whatever may be said in favor of this view. But in order to apply our conception of form regulation to the protozoa we are not under the necessity of recourse to this more or less doubtful hypothesis. All that is necessary to be assumed is that the different portions of the protozoan body which we know to be differentiated in various ways stand in the same symbiotic relation to each other as that in which we have supposed the cells to stand in the metazoa. They may be but differently modified areas of a perfectly continuous mass of protoplasm. Mutual dependence of parts does not necessarily imply that the parts are composed of discrete units of different kinds. A portion of protoplasm of a protozoan, if different from surrounding portions, doubtless has its peculiar form of metabolism and gives out substances slightly different from those produced in other regions of the body. It may thus exert a specific influence upon neighboring parts as well as be specifically affected by them. In this way symbiotic relations may be established between different regions and a social pressure brought to bear upon each region which keeps it in its normal condition. Regeneration in the protozoa may therefore be considered to be brought about in essentially the same way, and by the same causes, as in higher forms.

Morphallaxis.

In many cases the restitution of the normal form takes place, not by the production of new tissue which gradually assumes the character of the missing part, but by the transformation of the part that remains into a complete whole of smaller size. This process of morphallaxis, or the working over of old tissue into a new form, is found especially among the lower forms of life. A Stentor cut across the middle develops into two individuals of the same form as the parent but only half its size. The same phenomenon is presented in the regeneration of hydroids. In planarians new tissue is produced, the amount varying according to circumstances, but there is also a considerable amount of remodelling of the tissue that remains. In the higher animals the material for the regenerated organs is mostly derived from new tissue, but it is probable that the factor of morphallaxis is even there to a certain extent operative.

The first stage in morphallaxis seems to be the degeneration oi specialized structures. This is followed and probably to a certain extent accompanied by a constructive phase in which specialization is wrought out in a new direction. How far cells may lose their specialized structure, assume an indifferent or embryonic condition, and then become transformed into specialized cells of another type is somewhat uncertain. This probably does not occur in the case of such highly specialized cells as those of nervous or muscular tissue. It is probable in many cases that the degeneration of old cells is followed by the differentiation of relatively embryonic cells and in some forms it has been found that differentiated cells may degenerate and subsequently give rise to specialized cells of the same kind of tissue. In the regeneration of the limb muscles of Plethodon degeneration of fibers occurs especially near the cut end of the limb and diminishes with increase of distance from the point of injury; multiplication of nuclei then occurs and the new nuclei with their surrounding masses of protoplasm develop into new muscle cells. New muscle cells are thus produced from the old by a process of degeneration, division, and re-specialization. Something analogous to this may take place in the hydroids, although in Tubularia according to Miss Bickford a direct transformation of the cells occurs without previous division. We know, however, very little of the exact histological changes that occur in morphallaxis, and it is very desirable that fuller knowledge in this important field should be obtained.

The alteration of the structure of cells that occurs near the point of injury may be interpreted from our standpoint as the result of a change of social pressure. A cell near the cut end of a part is placed in new functional relations. Certain stimuli that it derived from its neighbors are no longer present and certain draughts upon its functional activity are no longer made. It is these influences which have not only directed the development of the cell into its particular form but which have become necessary in order that its form be maintained. When they are removed the cell lapses into some other condition. Roux has familiarized us with the necessity of functional stimulation for the maintenance as well as the growth of organs. The degeneration phase of morphallaxis may be largely the effect of the lack of certain functional demands, as well as a disturbance of the balance of stimulation. Changes naturally begin in the cells next to the cut end of a part, and thus would disturb the social pressure of the cells behind them; modification of these would affect the cells further back, and so on, the changes becoming less the farther the cells are from the point of injury. Whether or not morphallaxis occurs very probably depends in great measure upon the degree of specialization which a tissue has attained. In some organisms cells may have acquired a certain rigidity or fixity which will not allow their further transformation. And along with this fixity of structure there may go a relative independence of the neighboring cells, so that the removal of a contiguous part will not affect them so profoundly. In proportion to the fixity of structure which cells possess there is less necessity for functional dependence in order to maintain the normal form. In an organism whose tissues are more plastic and in which the cells are more dependent upon mutual support in order to maintain their specific nature the removal of a part would naturally be followed by a more extensive breaking down of the portions that remain.

The constructive phase of morphallaxis may be regarded as taking place much in the same manner as the differentiation of new tissue in front of a missing organ. In a Hydra after the upper end is removed we may assume that a process of disorganization begins at the cut end and proceeds for a certain distance down the stem. Then this material is worked over by a process of differentiation starting with the relatively unmodified portion of the body and extending distally until the disorganized tissue takes on the form of the missing part. After the disorganization phase of morphallaxis we have essentially the same conditions that we have pictured in the case of the planarian with the newly formed tissue in front of the cut end. In both cases we have a relatively unmodified part with organizable material in front of it. In both cases the relatively unmodified part progressively organizes this material through the social pressure which it exerts upon it. Morphallaxis seems to be essentially the same as regeneration in the narrower sense. The material that is organized is in the one case supplied by the disorganization of old tissue, in the other by the proliferation of new tissue.

In morphallaxis the part that remains the least modified by the degenerative process and under whose influence we have assumed the organizable material is worked over into the form of the missing part may be in turn affected by the regenerating part of the organism. The various parts of the body then act and react upon each other until they settle into a condition of functional harmony. The posterior end of a planarian after regenerating the anterior end diminishes in size until it reaches the usual relative proportion to the size of the animal. If the planarian does not receive food during the process of regeneration, the posterior half produces an animal of half the usual size, but of the characteristic form. In this case the part from which the directive influences first sprang must have been reacted upon by the materials undergoing reorganization so as to adapt it to functioning on a smaller scale.

Physiological Regeneration.

It is well known that organisms not only replace parts which have been removed through some unusual circumstance, but that, in many tissues, new cells are continually produced to take the place of the old cells that are no longer capable of playing their alloted part. In some tissues such as striated muscle this process of physiological regeneration does not occur. In others, as in the tissues of many glands, various kinds of epithelium, and the corpuscles of the blood, there is a continual replacement of old cells by new throughout the life of the individual. There are various gradations between replacements of tissue cell by cell such as occurs in the blood and the cases of renewal of organs such as the antlers of deer, the resorbed hydranths of Tubularia, and the cast off peristome of Stentor, which are scarcely to be distinguished from regeneration in the ordinary sense. The kinship between physiological regeneration and the regeneration which follows the accidental loss of an organ has often been commented upon. That both phenomena are the outcome of the same factors few, I believe, will be inclined to deny.

Professor Weismann has attempted to explain one of the simplest cases of physiological regeneration as follows: »If 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. Regeneration depends simply on a regular increase of those cells which contain epidermic idioplasm.« The renewal of tissue consisting of but a single kind of cells is, therefore, apparently a simple matter. Yet there must be a correlation between the rate at which cells die and the rate at which they are renewed. If new cells are produced more rapidly than the older cells die and become cast off there would be a continual thickening of the epidermis. If, on the other hand, cells die a little more rapidly that new cells are formed the whole epidermic layer must soon be dead. Simple as this case is there is a regulative factor which somehow determines an adjustment between the death rate and the rapidity of multiplication of the cells. And an adequate explanation of the phenomenon must show some reason why these two processes are so strictly correlated. There is nothing in Prof. WEISMANN's determinants which helps us in the least in a case like this. In the physiological regeneration of the blood there is a continual production of new red and white corpuscles in bone marrow and lymph glands to take the place of the corpuscles that continually disappear. The death rate and the rate of production of new cells are so adjusted that, under ordinary conditions, an approximately constant number of corpuscles is always maintained. In glands the renewal of new cells keeps pace with the disappearance of the old, the number remaining nearly the same during the life of the gland.

In all these cases we have to do with something more than the multiplication, wearing out, and death of cells. Why are not new cells produced so rapidly that they accumulate to the detriment and final disorganization of the body? Or why does not their multiplication lag far behind the destruction of the cells they replace? It is evident that in physiological regeneration an excess of production of certain cells reacts so as to check their further production, and a deficiency of these cells acts as a stimulus to increase their multiplication. In a symbiotic community of cells the increase of any one kind of cells above the normal number would lead to conditions disadvantageous to these cells and their further increase would be checked. A relative deficiency of this kind of cells would, on the other hand, favor their increase. To recur to our illustration of a community of animal cells and symbiotic algae let us suppose that some of the animal cells become worn out and die. The relatively large supply of oxygen and other favorable conditions thus brought about would act as a stimulus causing an increase of the other animal cells until the normal number is regained. An excess of these cells would, on the other hand, bring them into relatively unfavorable conditions, and would thus bring about its own check. And the same may be said concerning the symbiotic algae. As fast as cells of either kind die conditions become such that other cells of the same kind will step in and take their place. The process of physiological regeneration in all organisms may be conceived to take place in essentially the same way. The symbiotic relation of the parts both checks the undue multiplication of any one kind of cells, and also stimulates their multiplication up to the normal number. The phenomena of physiological regeneration naturally fall under the same principle of explanation which has been applied to the regeneration of parts accidentally removed. Physiological regeneration is but one aspect of form regulation. The fact that it is of normal and regular occurrence does not indicate that it is essentially different from the regeneration of the leg of a salamander or the tail of an earth-worm. The term physiological regeneration is in one respect an unfortunate one. It implies that the other forms of regeneration are not physiological, whereas there is strong reason to believe that all regeneration grows out of and is directed by physiological relations. All forms of regeneration, according to our interpretation, are due to the development of tissue under the guidance of social pressure. To distinguish one kind as physiological is, therefore, to use a term in a false and misleading implication.

Physiological regeneration is met with not only in the normal replacement of organ by organ and cell by cell, but also in the periodic renewal of the parts of the cells themselves. During secretion in the milk glands portions of the cytoplasm of the outer parts of the cells are thrown off. There may be also a multiplication of nuclei in the secreting cell and portions of cytoplasm containing a nucleus separated from the rest of the cell. In other gland cells the cytoplasm seems to be mainly transformed into secreted substance, leaving only a small amount around the nucleus after the cell is discharged. The cytoplasm of the cell in these cases subsequently increases to its usual quantity and the process is repeated time after time.

The same regulative factor that determines the replacement of old cells by new ones and the renewal of the lost parts of the cells themselves also brings about an adjustment of the functional activity of the cells. The cells of an organism tend to grow to a certain size, preserve a particular kind of structure, and maintain a certain degree of functional activity. Under abnormal conditions cells may enlarge beyond, or become reduced below their normal size, their structure may become greatly modified, and their functioning changed both in degree and kind. But under the regime that normally obtains in the body physiological they are held within quite narrow limits. In a symbiotic community of animal cells and algae, if the functioning of the algae should run down so that only a relatively small amount of oxygen were evolved, the activity of the animal cells would consequently become lessened. Sluggish activity of the animal cells would in a similar manner affect the life rate of the algae. The rates at which the two kinds of cells function, since they are to a certain extent mutually dependent, tend to adjust themselves to a certain norm. The maintenance of the functional balance between the various cells of the organism may be brought about in the same way; it is the natural outcome of their symbiotic relations. The process doubtless involves a complicated series of adjustments; but the same fundamental principle of regulation will, I believe, apply to both.

This adjustment of functional relations which is constantly going on throughout the organism is the fundamental regulative process of which physiological regeneration, when it occurs, is the outcome.

Regeneration, physiological or other, is not an isolated biological phenomenon resting on some special property of organic substance; its factors are always present and always operative. Form maintenance and form regulation rest upon the same basis. The tie that binds the parts of an the organism together in functional harmony is also the factor which restores the missing organs of the body. And I believe that we are warranted in holding that the same factor serves as the vis diretrix of their embryonic development.

The Relation of Regeneration to Functional Hypertrophy.

We have interpreted regeneration as the result of the functional equilibration of symbiotically related parts. The way in which cells differentiate is determined by the demands made for certain products which are produced when that line of development is pursued. The meeting of this demand may be regarded as a kind of functional hypertrophy. It is the great merit of Roux to have shown the importance of functional hypertrophy in the development of the embryo, especially in the maintenance of the harmony of the morphogenic processes. But the principle is one of much more fundamental importance, I believe, than even Roux has considered it. The role of functional hypertrophy in the regulation of the functions of the body is well known. Removal of one kidney causes an increased growth in the other kidney in response to the greater demand upon its activity. Ribbert has shown that when some of the mammary glands of the rabbit are removed the other mammary glands increase in size. The same author found that when one testis of a rabbit was removed the other testis developed beyond its ordinary dimensions. Partial removal of the thyroid of the dog has been found to be followed by a hypertrophy of the parathyroids as well as the portion of the gland which was allowed to remain. In many cases of compensatory hypertrophy the cells of the growing organ increase not only in size but also in number. The connection of these cases of functional hypertrophy with regeneration is intimate. Remove one of a pair of organs and its fellow increases in size. Remove a part of one of these organs and the remaining portion grows, forms new tissue, and regenerates the missing part. In both cases the growth that takes place may be regarded as due to the same cause, and the differentiation of new cells in the regenerating organ proceeds upon lines marked out by the demands of the surrounding parts. Regeneration is commonly thought of as belonging in an entirely different category from that of compensatory growth, but the interpretation of regeneration here given enables us to see that there is a fundamental relation between the two processes. In fact regeneration is *nothing* but an elaborate expression of functional hypertrophy, while compensatory growth is a simple manifestation of the same principle.

It must be borne in mind that functional hypertrophy covers a wide field of phenomena which may be due to quite different causes. The increase of a muscle through exercise may have but a remote relation to the hypertrophy of the thyroid or salivary glands. Further analysis of the various cases which come under this head is much to be desired. The presence of certain substances doubtless plays an important part in the regulation of the size of organs, and the fate of certain substances which the organs produce is a factor of perhaps equal or greater importance. We have assumed that a cell of regenerating tissue has the power of developing into any one of several kinds of cells according to the demands of the surrounding parts. The structure which the cell assumes so far as it is not due to pressure or other direct influences of the surrounding cells depends on its peculiar kind of metabolism. It is a matter of considerable importance whether the products of the metabolism of a cell are removed as fast as formed or allowed to accumulate. The growth of yeast cells or cultures of bacteria is checked when certain substances which these organisms produce reach a certain degree of concentration. Removal of these substances permits the multiplication of these organisms to proceed at a more rapid rate. Many cases of compensatory hypertrophy may plausibly be explained in a similar way. If a product of an organ accumulates to a certain degree it seems probable that the activity of the organ would be checked much as the growth of a culture of bacteria is inhibited by the accumulation of excreted substances. When on the other hand the products of an organ are removed so rapidly that they are no longer present in their normal quantity the check which under ordinary conditions acts to inhibit the function of the organ and keep it in its proper state of activity is no longer operative, and a functional hypertrophy will thus be effected. We may conceive that organs tend to increase in size and functioning up to the point at which they become checked by the inhibiting action of their own products. If we remove one of a pair of organs producing some internal secretion the amount of the secreted substance will quickly fall below the normal. The remaining organ, no longer checked by the amount of this substance usually present, will increase in size and functioning until the secreted substance accumulates to the normal amount when the checking again, then, occurs. The occurrence of compensatory hypertrophy is accounted for very naturally according to the theory of symbiosis here set forth. It is an expression of the same tendency to work into a condition of functional equilibrium which we have contended is the guiding principle of the process of regeneration.

Functional Hypertrophy and Chemical Equilibration [1].

The functional hypertrophy which consists in the production in increased amount of substances which are used up in some way bears a suggestive relation to certain well-known features of chemical reactions. The decomposition of compounds in solution proceeds until there is a definite relation established between the amounts of the old compounds and the new. If the chemical equilibration thus established is disturbed by the removal of one of these compounds more of that compound will be produced; and the more rapidly the compound is removed the more rapidly is it formed. Substances which, owing to the fact that they are insoluble or volatile, are removed from the sphere of action nearly as soon as they arise generally continue to be formed as long as the necessary compounds are present. The role of this tendency to chemical equilibrium in the regulatory activities of organisms is one, I believe, of fundamental importance. The inhibition of the growth of a culture of bacteria when certain substances are produced is sufficient quantity suggests

[1] Since the above was written I have found that the influence of mass action as a regulatory agent in vital phenomena has been pointed out by PFEFFER in his masterly work on the Physiology of Plants. Under the heading of Self-regulation PFEFFER says »Self-regulation is attained by the interactions between the different organs both of the plant and of the protoplast and each organ, however minute, has its own specific reactive power. The most obvious example of self-regulation lies in the fact that the course of vital activity is such as to provide for its own continuance, while the absorption and selection of a particular nutrient substance is determined by the needs of the organism and the character of its metabolism. The relations between mass and chemical action are of the utmost importance in the regulation of metabolism, for by the continual removal of the products by diosmosis, metamorphosis, or combination, a feeble chemical action may be carried to completion, and hence by such means the plant is able to stop or continue a given metabolic process according to its needs«.

that this result may have some relation to the stopping of a chemical reaction when the point of equilibrium is reached. If the checking of the growth and functioning of an organ when its products reach a certain degree of concentration is due to the fact that a chemical equilibrium is reached which prevents more of those substances from forming, the self regulation of function which goes on in an organism may to a great extent be the outcome of the tendency towards chemical equilibrium. Suppose that two cells *A* and *B* produce respectively the substances *a* and *b* which when they accumulate to a certain quantity inhibit the further functioning of these cells. As the two cells form parts of the same organism we may suppose that *b* combines with *a* so that the chemical equilibrium that would otherwise tend to be established between each of these substances and other compounds of the same cell is prevented. By the fact that *b* combines with *a* the two cells are able to produce these compounds continuously. *A* and *B* are therefore in a symbiotic relation, the functioning of the one contributing to the functioning of the other. It is tempting to suppose that the symbiotic relation which we have supposed to exist between the component parts of an organism may in the end resolve itself into some such chemical relations as we have supposed to exist between these two cells. The functional hypertrophy of an organ would then be comparable to the increased production of a substance in a chemical reaction when the chemical equilibrium of the compounds concerned in its formation is disturbed by a removal of a part of this substance from the sphere of action. The breaking down of the complex compounds of the living matter of a cell involves the production of a very large number of substances some of which occur only in minute quantities. These substances accumulating in and around the cell would naturally tend to modify the metabolic changes that occur. A new substance diffusing in from a neighboring cell could scarcely fail to disturb the chemical equilibrium that would otherwise tend to establish itself. The relative proportions of the various substances the cell produces would be altered and this might manifest itself as a case of functional hypertrophy. We can thus understand why an organ may produce a substance in increased quantity when there is a greater demand for that substance by the other parts of the organism. If a particular substance is gotten rid of with more than the usual readiness we should expect that substance to be produced in increased amount. We know little about the metabolism of living matter and it is perhaps premature to attempt to speculate very far concerning the chemical basis of functional hypertrophy. It is however worth while to point out the way in which this peculiar property of organisms may be brought into relation with some of the principles manifested in ordinary chemical reactions. As was pointed out above functional hypertrophy may perhaps be brought about in various ways, and the explanation of the class of cases here suggested cannot be made of general application, although it is one that gives us a plausible interpretation of the symbiotic relation of the parts which upon which we have attempted to show form regulation depends.

Development.

As regeneration and development are so closely akin it may be quite safely assumed that the factors involved in the one process play an important role in the ofter. When we say that both are the expression of a tendency towards normal wholeness we of course give no explanation of either process but simply subsume them both under a common category. We have attempted to show that the tendency to normal wholeness, as it is manifested in regeneration, arises out of the symbiotic relation in which the parts of the normal whole stand. In development a very small part, the ovum, completes the whole organism. In regeneration a relatively large portion already organized serves as the starting point and by exerting a social pressure upon adjacent new tissue moulds it into the form of the missing part. Both processes, notwithstanding this difference, grow out of the instability of the incomplete and are brought to a similar goal, the normal whole, by the tendency of the parts to work into a symbiotic harmony as the only satisfactory modus vivendi.

We may assume for the sake of the argument that at a very early stage of development the cells of the embryo have no necessarily predetermined fate before them; all are capable of forming any kind of tissue or organ as their social relations may determine. We do not assume that the fate of a cell is unlimited in its possibilities. Its position may decide which of a limited, although perhaps very large number of forms which it may assume. The nature of the material of which a cell is composed determines its various possibilities of development while the environment decides which of these possibilities is realized. As the egg of a bee may develop into a queen, drone, or worker according to circumstances, but never into a fly or a beetle, so a cell of the early embryo may produce a muscle, gland, or supporting cell, but not a new type of cell, or a kind found only in some other animal. The directive stimuli which determine the fate of embryonic cells are found partly in external agencies, but principally in the inter-relations of the cells themselves. So far as the cells are individually concerned it is perhaps possible for all of them to develop along the same path, but as they are bound up together in an organic relation they show a marked tendency to differentiate along divergent lines. Our assumption of a symbiotic relation between the cells of an organism will aid us in understanding how this tendency to divergent differentiation is brought about. To recur yet once more to our community of animal cells and symbiotic algae, let us suppose this community to arise from a single cell which is so constituted that it may, in response to certain stimuli, develop into cells of either kind. The nature of the first few cells produced by the division of the original cell may be undecided; they are analogous to ova which, according to circumstances, may give rise to an animal of either sex. If for any reason one of these cells should begin to differentiate towards an alga and assume the functions peculiar to that kind of cell it would make differentiation of the other cells in the same direction more difficult and to favor their development into the animal type. If the possible forms into which embryonic cells may develop stand in a symbiotic relation the fact the one cells gets started, perhaps ever so little, to develop into one form will react upon the other cells so as to start them along a divergent line of development. This tendency to divergence will exist whether the possible forms that embryonic cells may assume are two or a great many. Divergence means relief from competition and the securing of the advantages of the symbiotic relation. Circumstances may alter the balance of developmental tendencies of a cell this way or that. Which path is pursued will depend upon the encouragement received (to speak figuratively) from its neighbors.

A community of men founding a colony in a new country will inevitably, under the stress of gaining a livelihood, begin to follow various occupations. The needs of the individual are various and their satisfaction gives rise to different kinds of employment. A crowding of one occupation turns laborers into others in which there is more profit and relief from competition. The fact that some men do one thing tends to make others adopt a different pursuit. A number of civilized men set down in a new region would soon form a society in which each individual would derive an advantage from the exchange of services which would naturally establish itself. The tendency towards divergence of occupations is organically connected with the dependence of the individual upon society. If each man lived entirely unto himself, in independence of his neighbors, this tendency would not arise. The same principle operates, I believe, in the differentiation of embryonic cells. As a man may become a farmer or a mechanic under stress of social conditions, so a cell may develop into this or that form owing to the special social pressure to which it is subjected. On account of the struggle between cells for food and place under conditions of mutual dependence there will inevitably arise a tendency to work into new roles just as there is a tendency for human beings to follow occupations in which there are few competitors. The cells of an early embryo may be said to possess a number of social possibilities. Each cell may for a time be capable of playing any one of many roles in the life of the organism. The role each comes to play depends upon its relation to the others. During development the cells act and react upon each other bringing out differentiations of structure and function. The cells tend, as the result of this interaction to realize all of their various possibilities of development. The line of development which a cell follows is largely determined by the demands of its neighbors, and, as a consequence of this, the cells as they differentiate in various ways grow into a condition of functional equilibrium. This process of adjustment is paralleled in the evolution of human society as we scarcely need to point out. The whole process of embryonic development may be considered as guided by the tendency to settle into a state of harmonious functioning. This goal is reached only when the normal form is attained.

The principle of regulation we have described helps us to understand certain features of development which have been discussed in a previous section. The fact that development is not necessarily tied down to a fixed routine is no longer entirely unintelligible if we bear in mind that the process is guided by the effort towards functional harmony; deviations from this goal bring their own check and approaches towards it are favored by social pressure. The symbiotic relation of the parts affords the basis for the operation of the regulative factor in development to which we found it necessary to make an appeal. It enables us to understand how the end result appears to dominate, in a more or less arbitrary manner, the processes that lead up to it. We are enabled, therefore, to dispense with a teleological factor to guide the course of development since it can be shown that a tendency toward normal wholeness grows out of the symbiotic relation of the parts which we have assumed.

Heteromorphosis.

It sometimes happens that when an organ is removed an organ of another kind is regenerated in its place. This phenomenon which Loeb has called heteromorphosis is of comparatively rare occurrence and seems to be less common in higher animals than among lower forms. It was discovered by Loeb that the cut ends of the stem of the hydroid Antennularia which regenerates a stem bearing polyps if the colony is kept in an upright position will produce roots if the colony is inverted. The cut ends of the stem of Margelis or Pennaria were found to produce roots if they came into contact with some solid object, whereas under ordinary circumstances, they give rise to new polyps. It was found by Morgan that if an earth-worm is cut in two some distance behind the middle, the posterior piece, instead of regenerating a new head at its anterior end, produces a tail. The regeneration of an antenna-like organ in place of an eye which was first found by Herbst in Palæmonetes, and has since been shown to occur in several other decapod crustacea affords a case of heteromorphosis of perhaps even more striking character. The occurrence of heteromorphosis naturally presents a difficulty in the way of any theory of regeneration which attempts to bring all the facts under a common standpoint. One factor which we have thus far left out of account, namely, the influence of external conditions, plays, I believe, an important role in producing this peculiar result. While perhaps the greater number of factors involved in the building up of a complex organ are internal, certain external conditions may alter the balance of developmental tendencies this way or that, and thus determine whether the organ restored is like the one removed or like an entirely different part of the organism. If it is social pressure which guides the differentiation of structures it must be borne in mind that the influence of the external conditions to which a part is exposed is one element in the social pressure by which it is affected. In Margelis contact upon the cut surface of a stem causes the production of a root where otherwise there would be developed a polyp-bearing stem. So far as the general organization of the colony is concerned it probably matters little whether a root or a polyp appears at a certain place; the functional regulation of the colony does not make an imperative demand for the production of a particular structure in the region of the missing part, as is evinced by the fact that as regards details of branching and the distribution of roots and stems there is a large amount of variation in different colonies. The tissue of the stem of Margelis possesses a certain kind of irritability, acquired perhaps through natural selection, causing it to develop roots upon places of contact with solid objects. The material at the cut end of the stem undoubtedly possesses the power of developing into either a stem or a root. When contact stimuli are present functional harmony may be secured only by differentiation in the direction of a root. Both the development of root and stem may be guided by social pressure, but as the external conditions are different in the two cases, so the social pressure is different and leads to unlike results. It is not an improbable supposition that the tissue of Margelis is endowed with specific forms of irritability to certain external agents which may determine which of two developmental tendencies gain the upper hand, and that these forms of irritability have been modified by natural selection so as to lead to responses adapting the organism to the external stimuli that affect it. Of course external conditions can be said to cause the development of this or that structure only in the sense that they form one element in the process without which the structure would not be formed. Many other elements in the form of internal factors are equally necessary to produce the result. In the case of heteromorphosis the external conditions form the occasion which turns the scale in one or the other direction. When the stem of a hydroid is cut off the question arises: Why does not the old material progressively organize the new, as we have supposed it to do in the case of regeneration in the planarian, and always produce a structure like the one removed? There may be a tendency to do so, but in the loose organisation of a hydroid colony this tendency cannot be much stronger than the tendency to produce a root. And the influence of contact upon the exposed tissue would accelerate the differentiation of that part into a root as the social pressure would be different upon this portion of tissue; and this tendency might be considered to outweigh the predilection to develop into a stem derived from the social pressure of the old material. The fact that polyps which come into contact with solid objects are sometimes resorbed and roots developed in their stead may perhaps be interpreted in the same way. The regeneration of roots instead of a stem in Antennularia when the cut end of the hydroid is pointed downward may also be brought under the same explanation, gravity here acting instead of contact to alter the social pressure on the organizable material at the cut surface. In the regeneration of a tail instead of an anterior end of an earth-worm the heteromorphosis cannot be explained in the same way, as the external factors acting upon the exposed end of the worm are the same whether the animal is cut in two near the anterior or near the posterior extremity. We might suppose that the readiness with which the cells of the earth-worm begin to regenerate a new tail increases the nearer they lie to the posterior end of the body. Such a condition may have been established by natural selection as a means of enabling the animal to repair more or less frequent injuries to which the tail is exposed. The capacity of regeneration is a variable property, and it lies, I believe, within the power of natural selection to increase or diminish this property in certain regions of the body, although it cannot explain the power of regeneration itself. When the tail of an earth-worm is cut off cells are proliferated at the anterior end of the part removed. We may regard these cells as at first unorganized and consequently in a condition of unstable equilibrium. Even if they were cut off from the influence of the older cells an organization would tend to arise, and this organization, so far as we know, might set in at any point and from there work over the other cells into a condition of symbiotic harmony. It seems not improbable that since the organisation of the new cells through the social pressure of the older tissue proceeds slowly, organisation might set in from another point, say at the tip of the mass of new tissue, and proceed towards the proximal end. The kind of organisation which would start in here, if we consider it to arise independently of the older cells, is not necessarily the same as that which would tend to extend itself from the other end. And as the tissue lying near the posterior end of the worm has a predilection for differentiating into a tail rather that into a head, the organisation which would arise independently from the tip of the mass of new cells would produce a new tail at the anterior end of the old one. In general we may say that heteromorphosis may arise when, for any reason, organisation of new material gets a start independently of the social pressure of the older part. If this organisation is the same as that which would extend itself from the older tissue we have of course a case of simple regeneration. If another kind of organisation sets in the result, if sustained, will be heteromorphosis. An organisation similar to that of the missing part might begin at the tip of a proliferated mass of cells and proceed back to the older part, but the steps by which this organisation extends, and the formation of a congruous union with the rest of the organism would necessarily be under the guidance of social pressure. As organisation, according to our theory would be developed in a separated mass of indifferent cells it would be quite possible for differentiation to arise in some part of an indifferent mass of cells connected with the rest of the body, before that part was affected by the organisation extending gradually from the older tissue. That the new organisation generally reproduces the missing part is rather against this view, but the fact may be accounted for by supposing that the proliferated material has a predilection owing to the region from which it is derived for restoring the lost part rather than some other. It may be for this reason that cells derived from near the anterior end of an angle-worm reproduce the anterior segments, while those from the tail region produce a new tail at the anterior end of the cut piece. Wherever the differentiation of regenerating tissue may be found to begin the result will not affect the general validity of the explanation of regeneration here given. The fact that our theory may be applied to such diverse phenomena as regeneration and heteromorphosis may rightly be considered I believe a strong point in its favor.

Conclusion.

The general principle of regulation set forth in this paper might be illustrated at much greater length and applied to many other classes of vital phenomena, but I trust that enough has been said to render the main point of view sufficiently plain. In attributing a very important role to functional hypertrophy our theory is in accordance with the views which Roux has expressed in his work on »Der Kampf der Theile im Organismus«. The doctrine of the struggle of the parts which Roux has elaborated in that suggestive treatise, we have adopted only in a modified form. Except in so far as each part is supposed to increase until checked in some way we have assumed nothing like an actual process of selection going on among vital units of any order as a necessary part of our theory of regulation. The process of intra-selection described by Roux probably plays a certain role in development, and in many form changes, such as physiological regeneration, which occur in the adult. The resorbtion of parts, such as the tail of a salamander may perhaps be considered as due in part to a process of selection which results in the elimination of certain cells. The application of the doctrine of the struggle of the parts to the parts of an organism is a plausible and consistent extension of the Darwinian theory, but the extent to which the factor of intra-selection is operative is a vexed question into which I do not wish to enter. The process of form regulation does not necessarily involve the preservation of favorable variations among the vital units, although it may involve one factor of that process, namely, the tendency of parts to increase as fast as circumstances permit. We have conceived that the checking process by which regulation is effected is brought about, not by the selection of certain vital units, but through the symbiotic relation in which we have supposed the parts of an organism to stand. The whole process of development, so far as it does not involve the tearing down of structures previously formed, may occur, according to our theory, without the elimination of vital units of any kind, whether they be biophors, determinants, or individualities of a higher order, such as cells or organs. We have conceived the parts of an organism to be engaged in a struggle for existence, but, as the parts are mutually dependent, the struggle leads to an adjustment to a norm instead of the elimination of some parts and the survival of others. Only through the assumption that the parts are symbiotically related can we understand how the struggle in which they take part leads to unification and harmonious coöperation instead of the disruption and death of the organism.

Zusammenfassung.

Das in dieser Arbeit aus einander gesetzte Regulationsprincip im Allgemeinen könnte in viel größerer Ausführlichkeit behandelt und auf manche anderen Klassen von Lebenserscheinungen angewendet werden. Ich wollte indess den Gegenstand so kurz behandeln, als es sich mit der nöthigen Klarheit verträgt und hoffe, ausführlich genug gewesen zu sein, um den Hauptpunkt einleuchtend genug gemacht zu haben. Unsere Theorie ist dadurch, dass sie der funktionellen Hypertrophie eine ganz wesentliche Rolle zutheilt, in Übereinstimmung mit den Gesichtspunkten, welche Roux in seinem Werke »Der Kampf der Theile im Organismus« gewählt hat. Die Lehre vom Kampf der Theile, welche Roux

in dieser wichtigen Abhandlung ausgearbeitet hat, haben wir nur in einer modificirten Form zur unserigen gemacht. Abgesehen von der Annahme, dass jeder Theil so lange wächst, bis er irgendwie auf Hindernisse stößt, haben wir nichts als einen nothwendigen Bestandtheil unserer Regulationstheorie vorausgesetzt, was einem wirklichen Selektionsprocess gliche, der zwischen den vitalen Einheiten irgend welcher Ordnung vor sich ginge. Der von Roux beschriebene Process der Intraselektion spielt möglicher Weise bei der Entwickelung eine gewisse Rolle und bei manchen das erwachsene Individuum treffenden Formveränderungen, z. B. bei der physiologischen Regeneration. Die Resorption gewisser Theile, z. B. eines Salamanderschwanzes, kann vielleicht theilweise auf einen Selektionsprocess geschoben werden, dessen Ergebnis die Elimination gewisser Zellen ist. Die Anwendung der Lehre von dem Kampf der Theile auf die Theile eines Organismus ist eine plausible und gerechtfertigte Erweiterung der Darwin'schen Theorie, aber die Frage nach der Ausdehnung der Wirksamkeit des Intraselektionsfaktors ist eine sehr schwierige, so dass ich in ihre Behandlung nicht eintreten möchte. Der Process der Formregulation involvirt nicht mit Nothwendigkeit die Erhaltung günstiger Variationen unter den vitalen Einheiten, wenn er auch vielleicht einen Faktor dieses Processes bedingt, nämlich die Tendenz der Theile zu so raschem Wachsthum, als die Umstände erlauben. Wir haben gesehen, dass der Hemmungsprocess, durch welchen die Regulation bewirkt wird, zu Stande kommt nicht durch die Selektion gewisser Lebenseinheiten, sondern durch die Beziehungen der Symbiose, in welchen, nach unserer Annahme, die Theile eines Organismus zu einander stehen. Der ganze Entwickelungsprocess, so weit er nicht den Abbau vorgebildeter Strukturen bedingt, kann nach unserer Theorie ohne die Elimination von Lebenseinheiten irgend welcher Art vor sich gehen, seien es nun Biophoren, Determinanten oder Individualitäten höherer Ordnung, wie Zellen oder Organe. Wir haben die Theile des Organismus im Kampfe um ihre Existenz gesehen, da aber die Theile gegenseitig von einander abhängig sind, so führt der Kampf zu einer Einstellung auf eine Norm, statt zur Elimination einiger Theile und zum Überleben anderer. Allein durch unsere Annahme symbiotischer Beziehungen zwischen den Theilen können wir verstehen, wie der Kampf, an dem sie theilnehmen, zur Bildung eines Ganzen und zu harmonischem Zusammenwirken führt, statt zum Zerfall und Tod des Organismus.