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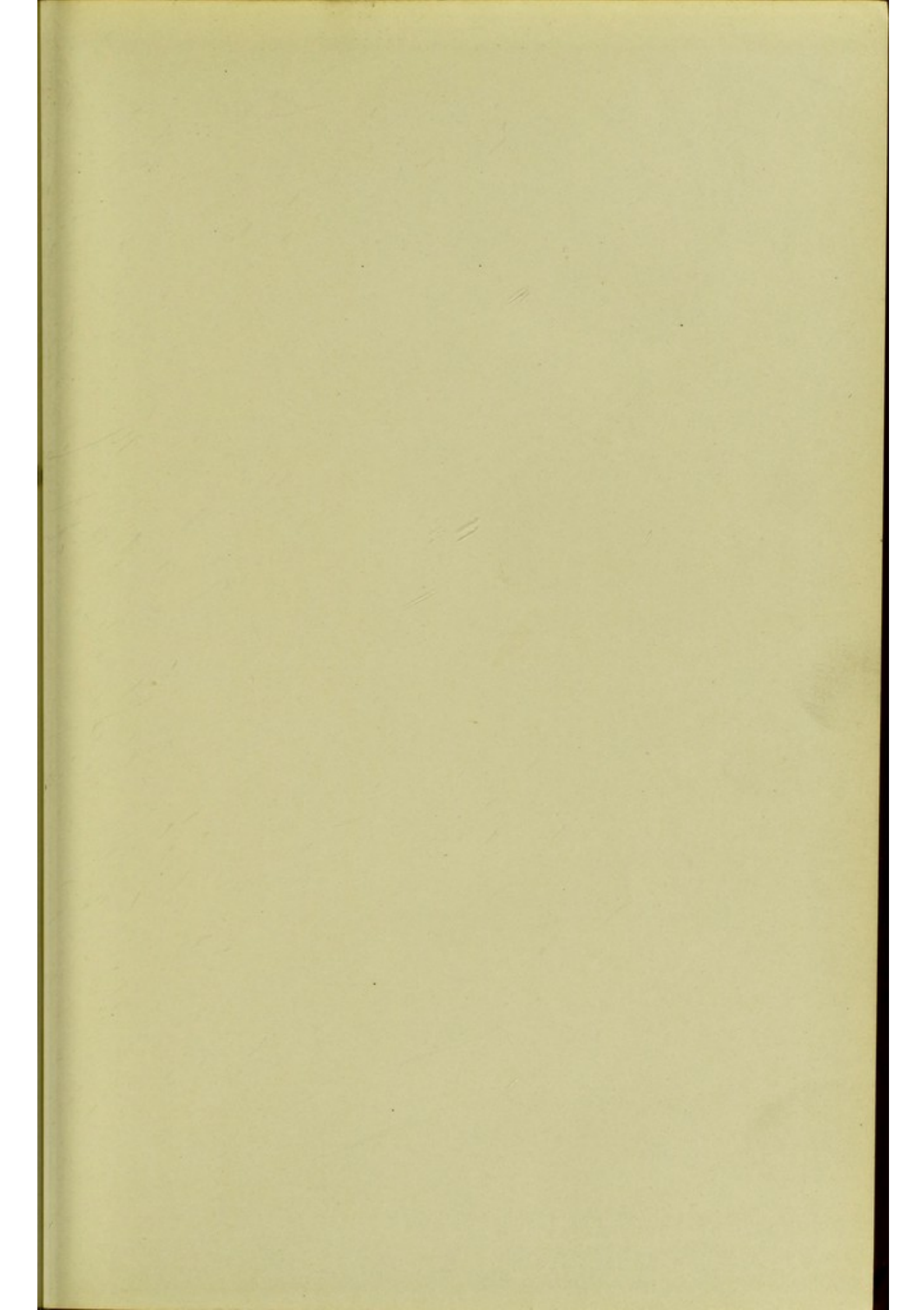


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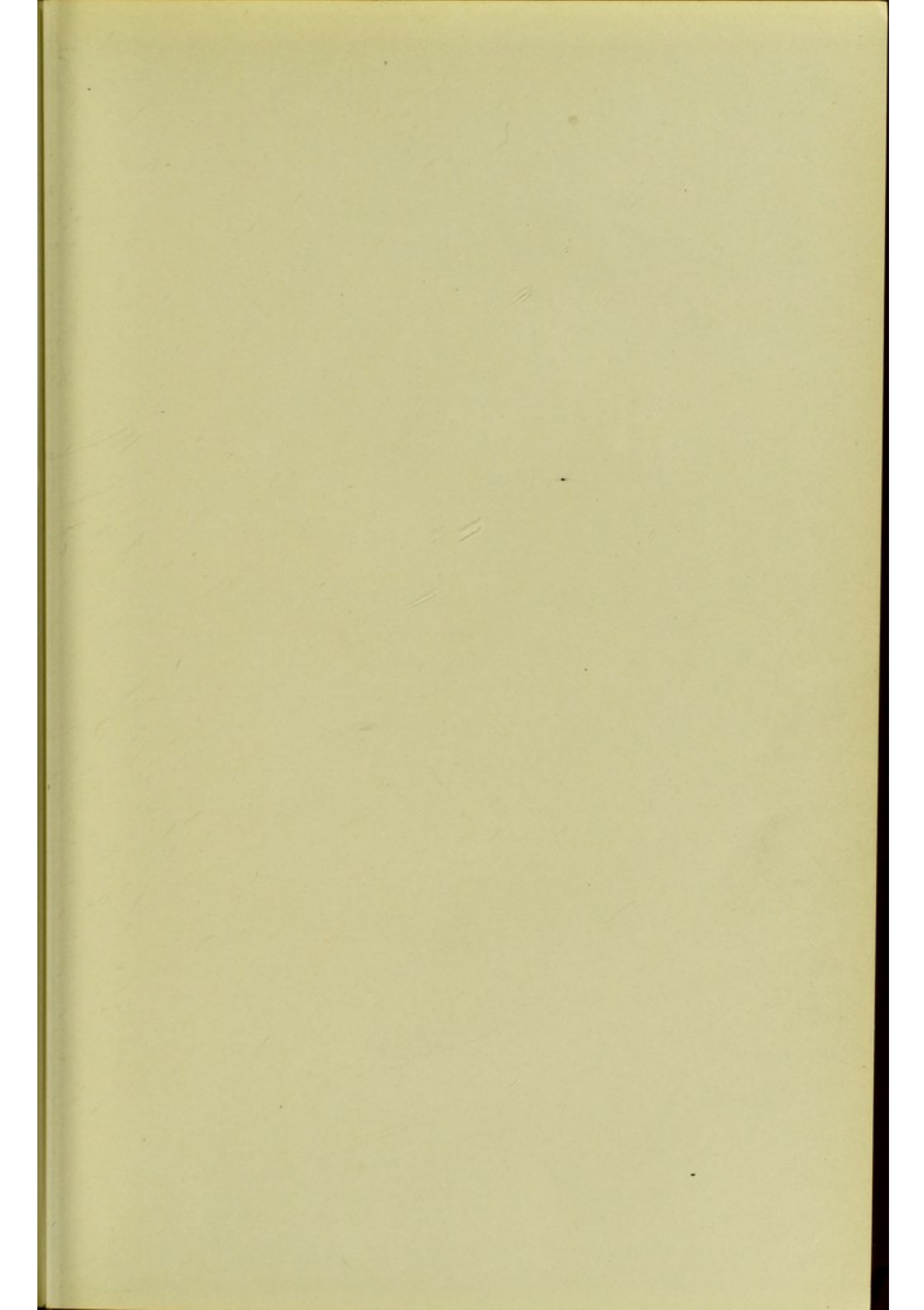
















MODERN PROBLEMS OF BIOLOGY

MINOT

BY THE SAME AUTHOR

Embryology. A Laboratory Text-book of Embryology. By CHARLES S. MINOT, S.D., LL.D., *Professor of Comparative Anatomy, Harvard University Medical School.* Second Edition, Revised. With 262 Illus. xii+402 pages. Cloth, 3.50.

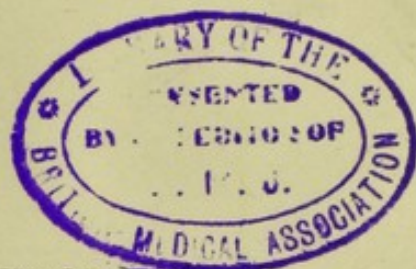
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MODERN PROBLEMS OF BIOLOGY



LECTURES DELIVERED AT THE UNIVERSITY OF JENA,
DECEMBER, 1912

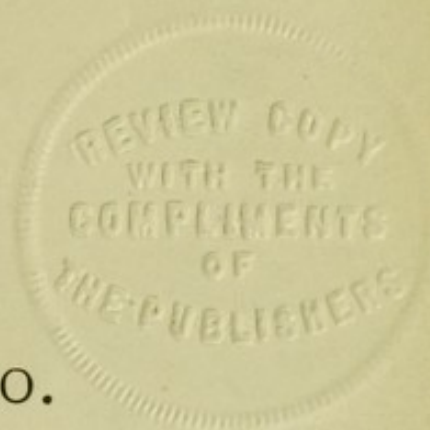
BY

CHARLES SEDGWICK MINOT

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OF THE ANATOMICAL LABORATORIES, HARVARD MEDICAL
SCHOOL; EXCHANGE PROFESSOR AT THE UNIVERS-
SITIES OF BERLIN AND JENA, 1912-13.

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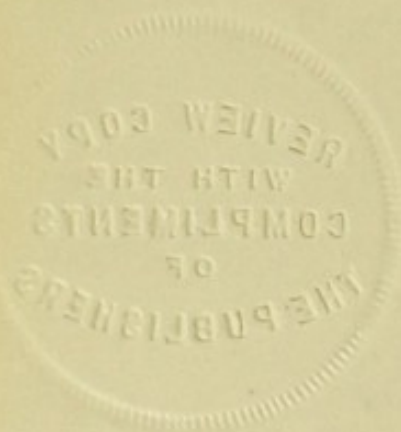


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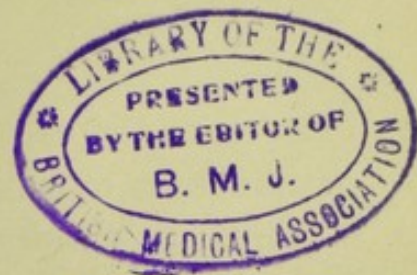
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TO THE
UNIVERSITY OF JENA





PREFACE

His Royal Highness, the Grand-Duke of Saxe-Weimar, the Rector Magnificentissimus of the University, has graciously pleased, after Professor Eucken of Jena had been called to Harvard University as Exchange Professor, to express the wish that the Harvard Exchange Professor at Berlin this year should lecture also in Jena. This wish was communicated to Harvard University by the Prussian Ministry of Education. After further correspondence the formal invitation was sent me to deliver in Jena the six lectures which appear in printed form in the following pages.

It is always a difficult problem to so present new biological discoveries that they will be comprehensible to a mixed public, and yet lose nothing of their scientific value. The reader therefore is requested to exercise a lenient judgment, when he finds that the performance leaves much to be desired. It seemed desirable to consider the first lecture as an introduction which might render it easier for non-biologists to understand the following lectures. The researches quoted are chiefly American. This plan was adopted partly because the author was the American Exchange Professor and partly because he was informed that his audience in Jena would like to hear especially about American discoveries. In the short time at command it was impossible to present the evidence for all that was said, and the reader must be begged to pardon the author if many assertions sound like *obiter dicta*.

To their Royal Highnesses, the Grand-duke and the Grand-duchess of Saxony, the author expresses his thanks for their interest and for the great honor of their presence at one of the lectures. He has pleasure in thanking also their Excellencies, the Ministers of Education of Saxe-Weimar-Eisenach, Altenburg and Meiningen, his Magnificency the Prorektor, the Curator of the University and his Colleagues for their encouragement and hospitality, by which the visit to Jena was made very delightful.

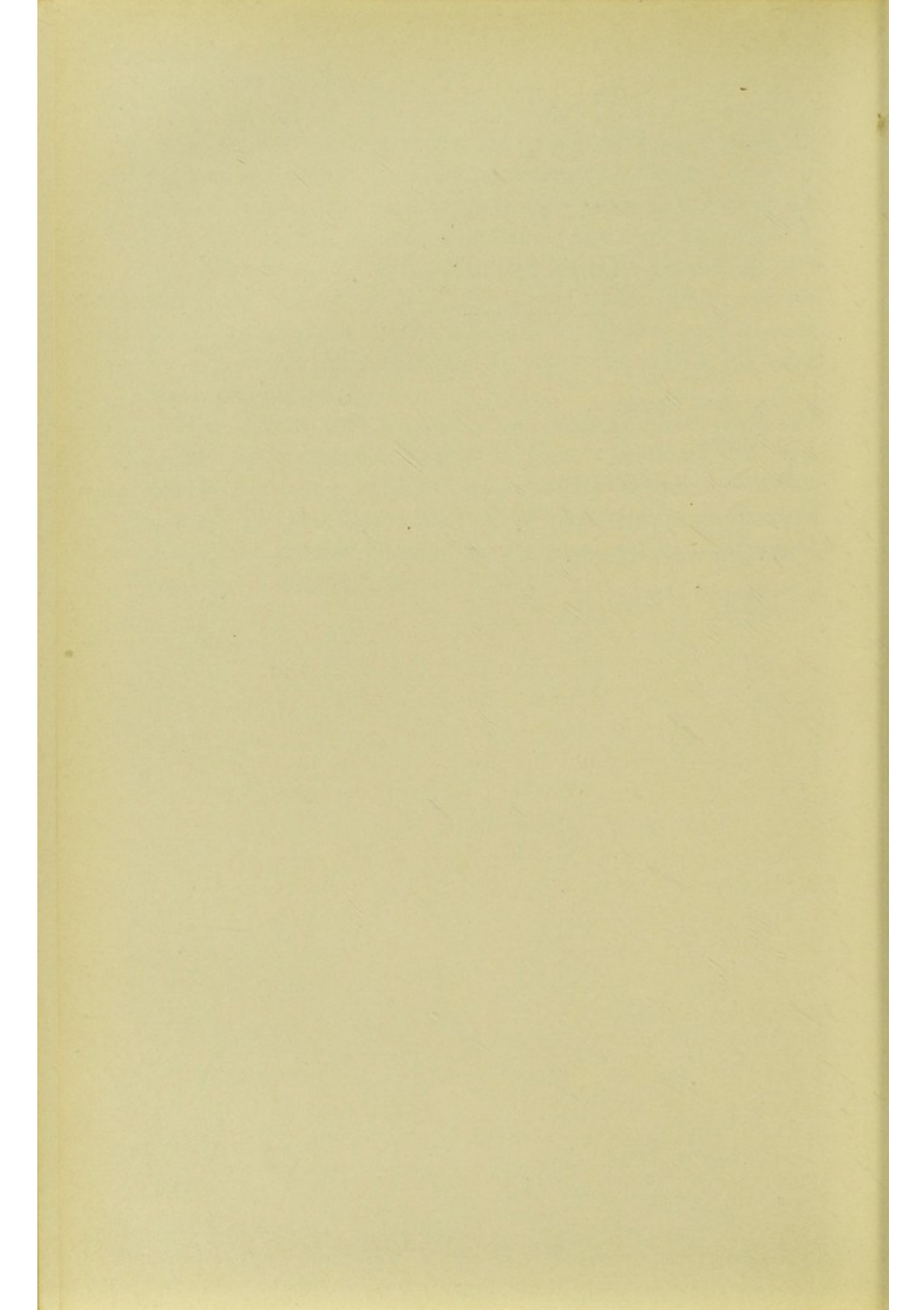
The lectures were written and have already been published in German by Gustav Fischer in Jena. Professor von Bardeleben had the great kindness to revise the original manuscript. The translation has been prepared by the author and follows the original closely, though now and then a phrase has been rendered freely.

CHARLES S. MINOT.

BOSTON.

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PROBLEMS IN BIOLOGY

THE NEW CELL DOCTRINE

Your Magnificence!
Gentlemen!

To his Royal Highness, the Grand Duke of Saxe-Weimar, I wish to express with the highest respect my sincere thanks for the interest which his Royal Highness has shown in the exchange of professors with America. It is a great honor to be the first Harvard professor to come to you, as the official representative of the American academical world. The University of Jena is as famous and as highly esteemed in America as in Germany. When I consider the reputation of the Jena professors I cannot venture to hope that the lectures I am to deliver will attain that degree of perfection to which you are accustomed. Therefore I request you to consider my lectures as an expression of my sense of obligation. Not merely Harvard University, but the whole United States are grateful to you that you have permitted Professor Eucken to come to us as exchange professor. I owe your Ministry of Education special thanks for the invitation sent me to appear here as the guest of your University.

It is always a difficult task so to present scientific conclusions that they shall be comprehensible to the public and, at the same time, keep their precision and their scientific value; but when a branch of science has progressed so far that

conclusions of wide bearing can be drawn, it becomes desirable to communicate the results to wider circles. The new achievements of biology are significant and claim the interest of all thinkers, and therefore I have decided to attempt to make clear to you some of our fundamental conclusions. My fellow biologists are requested to excuse the mention of much already known to them.

The general conclusions of biology are formed slowly. The phenomena of life are so complicated that they can be analyzed only by the most many-sided investigations. If one wishes completely to master the science one would have to be not only a biologist in the stricter sense, but also a chemist, a physicist and a geologist. It has become impossible for a single investigator of our time to acquire special knowledge in the whole field of biology, and you will certainly not expect from me that I attempt to make clear to you all the fundamental conclusions of modern biology. Indeed for this, the time at our disposal would not suffice. Therefore I shall permit myself to treat only such questions as I have found occasion to consider often in the course of my special work. We may arrange the subjects to be discussed in the following order:

1. The New Cell Doctrine.
2. Cytomorphosis.
3. The Doctrine of Immortality.
4. The Development of Death.
5. The Determination of Sex.
6. The Notion of Life.

You all know something of cells, which have been described often as the units of life. They are small masses of living substance, in each of which lies a smaller body, which is desig-

nated as nucleus. The living substance is commonly termed protoplasm. Unfortunately with the progress of investigation we have become more and more uncertain what we can properly designate as protoplasm. The nucleus is also a living substance, but it is commonly not reckoned as protoplasm. Many authors apply the term protoplasm to the body of the cell, which often has a very complicated structure. Thus we see spaces which we name vacuoles, and which contain only fluid. Such a fluid is usually not considered part of the protoplasm. More frequently we find special enclosures, granules, etc., which reveal

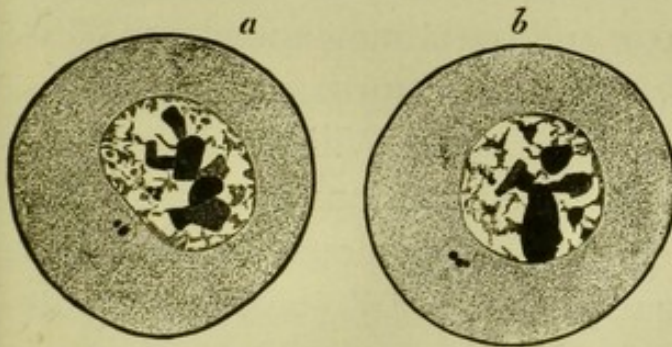


FIG. 1.—Two blood cells from an embryo duck. The protoplasm has a uniform constitution and contains the centrosome. In the rounded nucleus the material is irregularly distributed and forms a larger mass of chromatine. The cells have been artificially colored.—*After M. Heidenhain.*

an entirely different constitution from the rest of the mass, which one is inclined to name protoplasm in the stricter

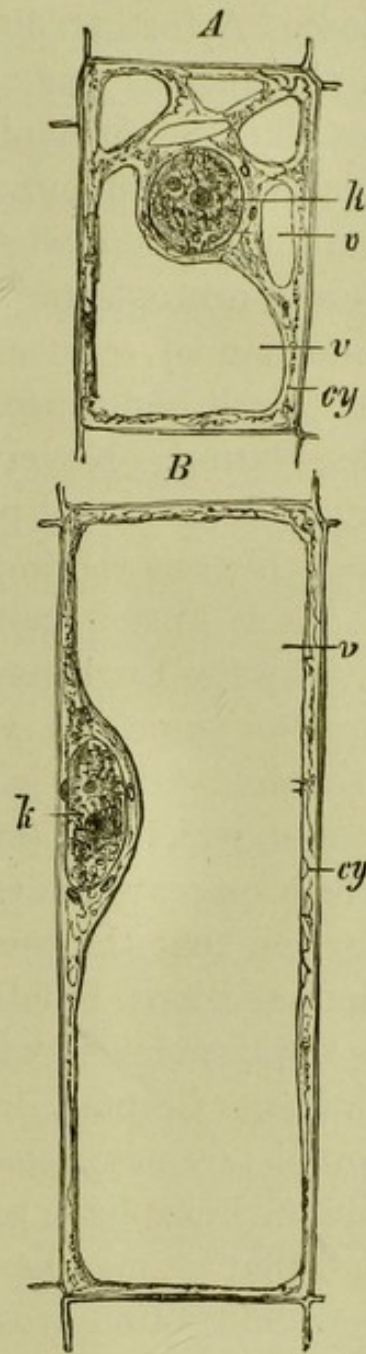


FIG. 2.—Two plant cells from the vegetative point of a Phanerogam. *a*, younger; *b*, older stage; *k*, nucleus; *v*, sap space; *cy*, protoplasm.—*After Strassburger.*

sense. A further difficulty arises from the observation that in the nucleus also a substance can be found with peculiarities like the protoplasm. Thus it happens that with the enlargement of our knowledge we have become more and more uncertain what we can properly designate with this word "protoplasm." It corresponds better to the present condition of science if we say that a cell consists of nucleus and a cell body, because we thus restate clearly our direct observation. Nevertheless a biologist would hardly like to lay aside the word protoplasm, in part because it has such a great historic significance.

As is known, cells were discovered by the botanists, and first by the Englishman Hook, and they received from botanists the name cell, which is completely suitable for the form first observed, for in many plants one sees the cells as small spaces, which are separated from one another by partitions. These spaces were designated simply as cells. Later it was recognized that the essential thing was not the arrangement of the partitions, but the content of each cell. This content is protoplasm mixed with water and containing a nucleus. Two eminent German investigators have furnished us with a completely new conception of the cell. Wilhelm Kühne and Max Schulze have proven that the partitions are unessential and that we may have a complete cell without them. Thus a new conception arose, namely, that a cell consists of protoplasm and nucleus. The great English biologist, Huxley, who appreciated the importance of the new views of Kühne and Schulze, has presented them in a lecture to which he gave the title, "The Physical Basis of Life." Huxley's presentation is so clear and comprehensible that his readers cannot fail to appreciate the full significance of the views presented. Huxley's lecture occasioned great excitement among thinkers in Eng-

land and America, and also on the European Continent. Everybody discussed at that time the question whether protoplasm was really the physical basis of life or not. The solution of this problem we have not fully reached even yet. The description of the cell which we owe to Max Schulze dominates everywhere and yet with the progress of science it has become insufficient.

The size of the cell is of the greatest significance to biologists. Cells for the most part are rather small, and the size is extremely variable. The cells of the human body, according to an estimate I have made, have an average diameter of perhaps 0.014 mm. Variations, however, are considerable; some cells, like the blood-corpuscles, are very small; certain nerve cells, on the other hand, attain a considerable size. The largest cells of all, known to us at present, are eggs. Those of certain animals appear as true giants in comparison with other cells. The largest eggs occur in birds. The entire yolk of the bird's egg corresponds to but a single cell. The albumen which surrounds the yolk and the shell do not belong to this cell, but are simply layers which are added by the oviduct to the egg proper, and which are secretions of the glands of the oviduct. Of all the animals now living the ostrich has the largest egg and the yolk of the ostrich egg is certainly the largest living cell known to us. These enormously enlarged eggs might be described as the monsters of the cellular world. They are exceptions. By far the majority of cells are of such dimensions that they are visible with the microscope alone. The smallest organisms which we know are the vegetable germs, which may have a diameter of not more than one-tenth of a millimeter. As is well known to all, certain of these smallest organisms cause diseases which may be extremely dangerous to man. The investigators of infectious diseases have made the inter-

esting discovery that there are disease causers which are invisible even with the microscope. In recent years we hear more and more of the so-called invisible organisms. In regard to this we must express our opinion with reservation, for it is by no means demonstrated that we have to deal in this case with actually living organisms. It is possible that we have to do only with chemical ferments. We have not time, how-

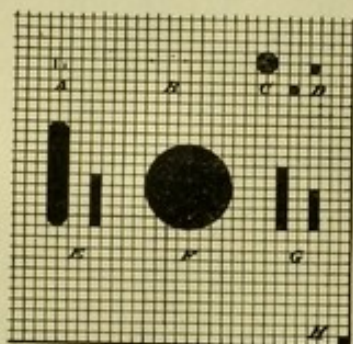


FIG. 3.—Drawing to show the size of bacteria. Magnification 1000 (1 mm. of the picture = 0.001). A, smallest bacilli (influenza); B, streptococcus gracilis (round); C, largest cocci; D, pus cocci; E, bacillus megatherium; F, red blood corpuscle; G, splenic fever bacillus.—After H. Jaeger.

ever, to enter upon this discussion. For the present at least we must hold to the opinion that vital phenomena can appear only when the amount of living substance is so great that it can be seen with the microscope. In other words, the minimum quantity of chemical substance which can serve as the basis of life is many times greater than the minimum quantity of substance which suffices for a chemical reaction. Here we encounter a fundamental characteristic of life. To permit the activities which are characteristic for life to go on we must bring together many substances which stand in very special relations to one another. Hence the

assertion that life is only possible when these conditions are fulfilled, and this requires that the total amount should be so much that we can see it with the microscope.

Cells have been considered for a long time as independent bodies. Quite slowly this view has been changing. Many years ago botanists made the observation that vegetable cells may be united by fine threads of living substance. Similar relations have been observed in animals. In the sev-

enties of the last century J. Heitzmann, a Viennese physician who had emigrated to New York, affirmed that cells are not definitely separated from one another. He advanced the statement that protoplasm is continuous and has scattered nuclei. The opinions expressed by Heitzmann¹ remained in their time almost without notice. Very gradually his view met with wider acceptance. The botanist Sachs has contributed much to develop our interpretation. For the zoologists the writings of the American Whitman² have been of the greatest importance. Whit-

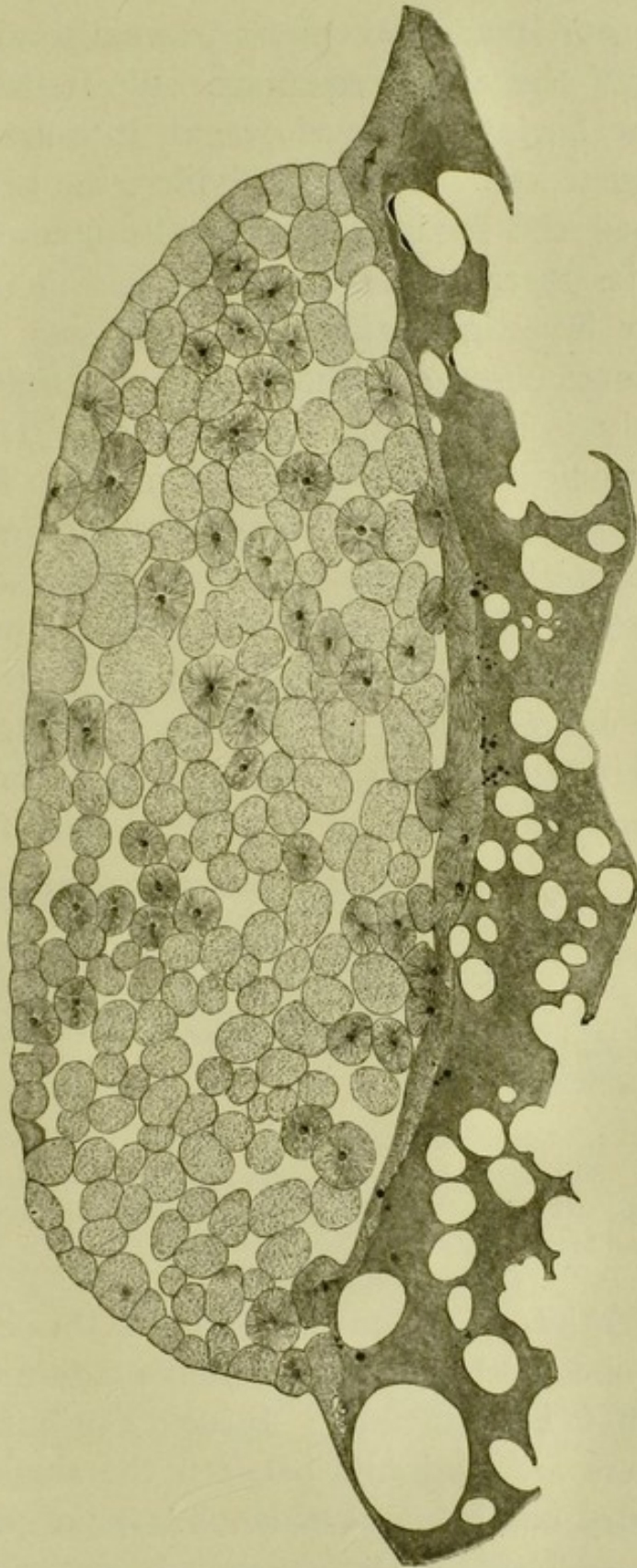


FIG. 4.—Germinal disc of a brook trout, consisting of numerous isolated cells. The differentiation of the embryo has not yet begun.—After Fr. Kopsch.

man and many others have greatly advanced the recognition of the actual relations. We know now that when an ovum begins its development it must be regarded as a complete cell. This cell divides, the process being usually termed the segmentation of the ovum. When the ovum divides there arise two new cells which then divide again. If we investigate the relations of such cells in vertebrates we may observe without difficulty that the cells are completely isolated from one another. They have no direct communication between themselves. They live alongside one another, but the living substance of one cell is nowise united with the living substances of the neighbor cell. In the course of the further development, however, the relation changes because the cells begin to unite with one another. This occurs chiefly in two ways. Consequently we obtain two kinds of tissues which we regard as the primitive tissues of the body, since from them all the tissues of the adult are slowly

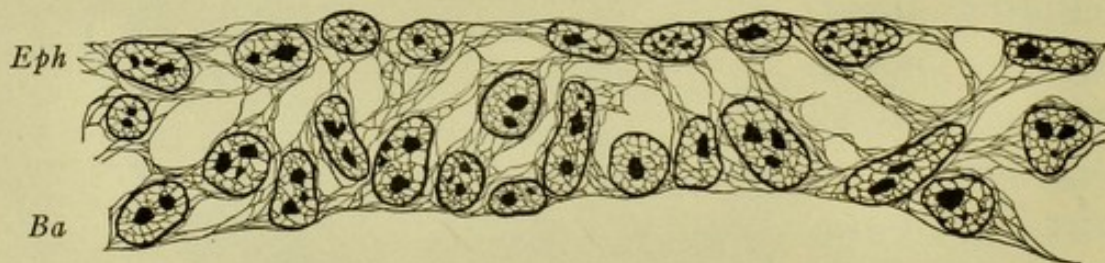


FIG. 5.—Epithelium (epidermis) of a chicken embryo of the second day of incubation. The nuclei are mostly oval and lie scattered. The protoplasm forms a network. There are no intercellular partitions present. *Eph*, epitrichial layer; *Ba*, basal layer.

differentiated. In one form we find the cells completely fused with one another and they build a continuous layer which we designate as epithelium. In such a primitive epithelium, Fig. 5, there are no limits between the single cells, but on the contrary one has a continuous layer of protoplasm in which the nuclei are scattered, though generally rather close to-

gether. When such an epithelium grows the nuclei multiply by division which is in itself a complicated process. The pro-

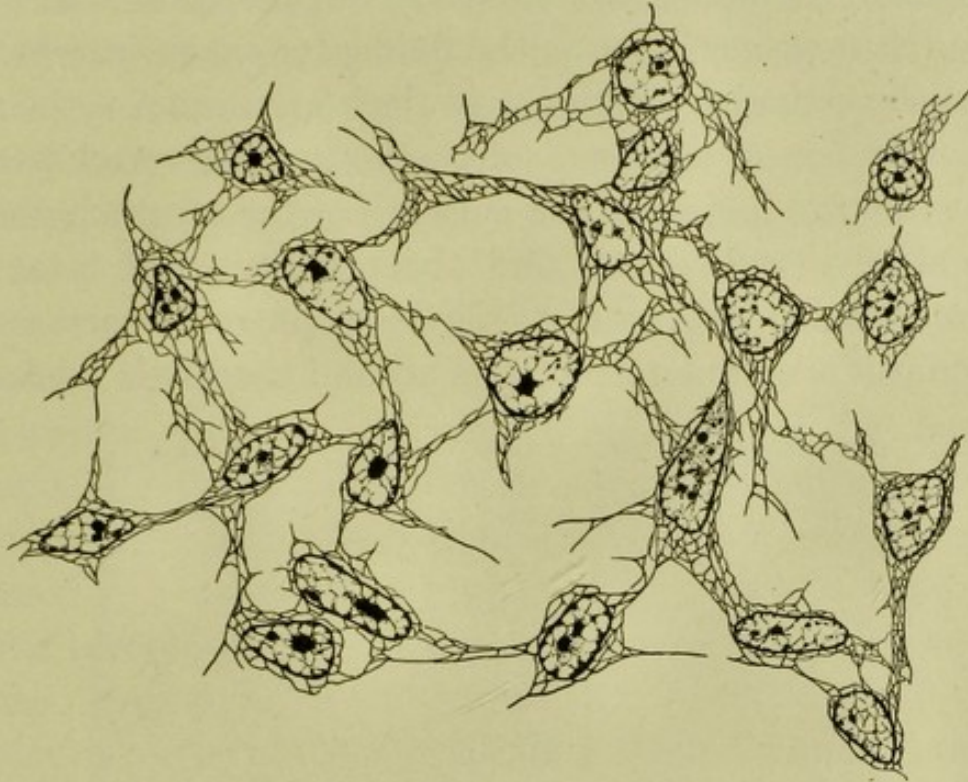


FIG. 6.—Mesenchyma of a chicken embryo of the third day of incubation. Every nucleus is surrounded by a thin layer of protoplasm from which run out the strands that form the intercellular network. Cell boundaries are not present.

toplasm also grows. We have in this case, therefore, a substance which, though living, does not, strictly speaking, con-



FIG. 7.—Adult epithelium. Epidermis of *Lumbricus venetra*. *schl. z.*, mucous cells; *Cu*, cuticula; *d. z.*, cylinder cells; *m. f.*, muscle fibers—below the epithelium. The single cells are separated by partition walls from one another.—After *M. Heidenhain*.

sist of cells. The second form of tissue is called mesenchyma. In mesenchyma, Fig. 6, one observes nuclei which are found

at more or less regular distances from one another, and also protoplasm which forms an open network. The meshes of this net contain a fluid, which is usually not interpreted as a part of the tissue proper, just as the fluids, for example, which we find in the articular cavities or in the body cavity of the adult are not reckoned as tissues of the body. In vertebrates, in which the protoplasm of the network of the mesenchyma has been chiefly studied, we find that the network is at first extremely irregular; but early, as development progresses, the protoplasm accumulates in parts around the single nuclei and



FIG. 8.—Hyaline cartilage of a human embryo. Between the cells the firm basal substance of the cartilage is developed in large quantities.—After J. Sabotta. $\times 280$.

forms, so to speak, a court of protoplasm around every nucleus. From each court radiate the threads of protoplasm, which establish the connection with the neighboring courts, and thus the mesenchyma remains a network still. These two forms of tissue, which are characteristic for the connection or fusion of cells, we call syncytium. On tracing the development

further we learn that alterations occur so that we can observe the progressive separation of the single cells; thus, for example, in epithelium there arise partition walls, Fig. 7, separating the cells finally and completely from one another. In mesenchyma the connections may become interrupted by which the protoplasmic masses around the single nuclei are joined together, Fig. 8. In this way the cells become completely isolated. When we encounter cells which have been separated in this way we have to do not with a primitive but with a secondary condition.

The descriptions just given lead us to one of the chief conclusions of the new cell doctrine. We have learned that the relations are much more complicated than was previously assumed.

We turn to the discussion of protoplasm, or, as we have termed it before, of the cell body. It is necessary to direct attention to the fact that in the living world we know two chief types of cells; first, such cells as exist alone, the so-called unicellular organisms. Of such cells there are very many species which have been grouped into numerous genera. Each genus and each species has its special peculiarities which we learn chiefly through the microscope. When a cell of any of the just-mentioned species is observed for a longer period few alterations in its structure can be observed. The chief changes we can observe are, first, an enlargement of the cell, and second, the inner alterations which are usually specially noticeable in the nucleus, which lead gradually to the division of the cell. The two new daughter cells remain extremely similar to the original mother cell in all peculiarities. Such an organism propagates itself in this manner endlessly and without essentially changing its structure.

Very different are the conditions in the second type of

cells, which we find only in the multicellular organisms, that is, in the higher plants and animals. In them we observe different cells which take over the function of propagation. In the case of animals such cells are called ova and spermatozoa. A spermatozoon unites with an ovum, which we then designate as fertilized. A fertilized ovum is a complete cell which divides and continues dividing until the number of cells for the construction of an animal body has been produced. This number may be enormous. The ovum, or egg-cell, proliferates by division precisely as does the cell of a unicellular organism. The cells of the latter do not change, but the cells which arise from the ovum do change. The cells of the multicellular organisms through several or many early generations retain a relatively similar structure, but later there follows a transformation which with the succeeding generations progresses, and at the same time becomes multifarious. In this manner the tissues of the adult arise gradually and in accordance with fixed laws.

In consequence of these conditions it has come about that we have derived our conception of protoplasm and in part also of the nucleus chiefly from studies which investigators have made on the developing ova, for in the early generations of these cells we have relatively simple relations. Fortunately, however, there occur among the unicellular organisms species which are comparatively simple in structure, and which are therefore favorable for the study of protoplasm. If we wish to summarize the result of numerous investigations in brief form we may say that we have learned to recognize three conditions of protoplasm; that is, one condition of which we know as yet little, but which is of the greatest significance and which is characterized by the fact that the protoplasm appears to us under the microscope absolutely homogeneous.

Homogeneous protoplasm is of the greatest rarity and as yet has been studied chiefly by the American, E. B. Wilson.³ It claims our highest interest because it represents apparently the simplest condition of the living substance which we know. In the second state we find the protoplasm consists of two fluids which exhibit a foam structure, that is to say, the two fluids are so mixed together that one, apparently the more fluid, forms droplets and the other holds these droplets apart and separates them from one another completely. As is well known, Professor Butschli has specially studied protoplasm in this condition, and has founded the theory, which he has further defended, that we encounter in

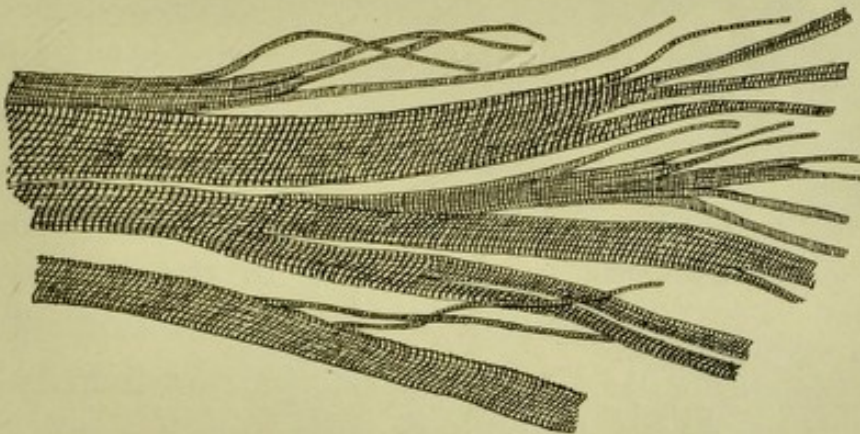


FIG. 9.—Striated muscle fibers of a rabbit, colored by Bielschowski's method and then teased so as to demonstrate the single muscle fibrillæ.—*After a preparation of Prof. Poll's.*

this foam structure the essential true fundamental structure of living substance. For this view much may be said. Whether, however, we may assume that protoplasm, which is apparently homogeneous, also really possesses a foam structure, although it escapes our present observation, must remain undecided. In its third condition protoplasm is no longer simple because new structures have arisen in it which are probably also living, but which differ from protoplasm

in appearance and behavior; thus, for example, if we study the development of muscles, we find at first cells with the usual so-called undifferentiated protoplasm. In this appear fine fibers which we name fibrillæ, and which are no longer simple protoplasm, but really something new, Fig. 9. These fibrils effect the contraction of the muscle. They develop themselves, clearly in order to take over this special function

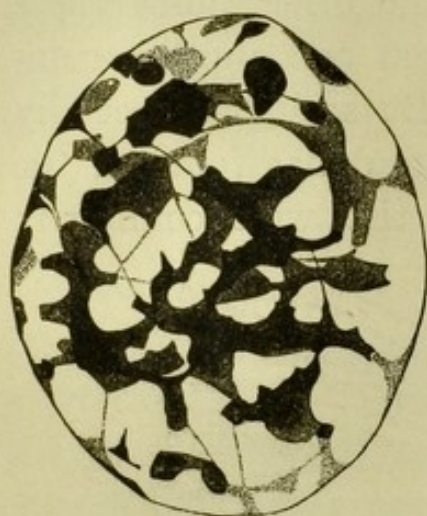


FIG. 10.—A vesting nucleus after ordinary preservation and staining with iron hæmatoxyline. From a cell of the intestinal epithelium of a salamander.—After M. Heidenhain. Magnified 2300.

of the muscle cells. Accordingly we designate the third condition of protoplasm as the differentiated.

We must now turn to a consideration of the nucleus. It appears in the majority of cases as a body with definite limits, completely surrounded by protoplasm and with special substances in its interior. Usually one can distinguish without difficulty a network, and in the meshes of this network the nuclear sap. The network varies extraordinarily in the single nucleus, but has one striking peculiarity, namely, that it may be easily artificially colored. On account

of this peculiarity the substance has been named chromatin. Nucleus differs in one respect very noticeably from protoplasm, for the nuclei develop no new structures comparable to those which we may observe in protoplasm. A nucleus, to be sure, changes during the development of tissues more or less, but we cannot observe new structures in the nuclei. This fact is of special significance for the considerations which are to be presented in the next following lecture. For this reason attention is now directed to this peculiarity of the nucleus.

Although the nucleus changes comparatively little during the progressive division of the cell, yet during the division of the cell matters are very different, for during every cell division the nucleus passes through wonderful transformations.*

During these transformations the sharp limits of the nucleus disappear, and the nuclear substance gathers together in small masses to which we apply the name chromosomes. Each chromosome divides, and one piece of each chromosome contributes to the formation of one of the new nuclei; the

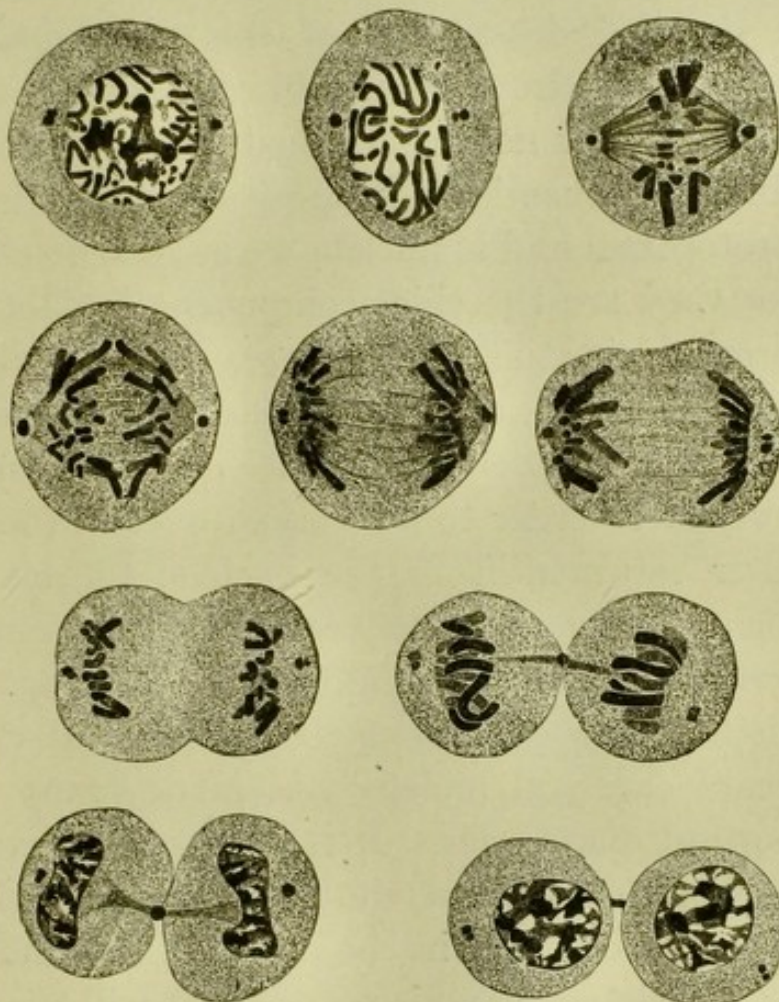


FIG. 11.—Red blood cells of an embryo duck in various stages of division. The pictures show the origin, division and migration of the chromosomes, the spindle, the reconstitution of the daughter nuclei after the division of the cell bodies.—After M. Heidenhain. Magnified 2300.

other piece to the formation of the other nucleus. This process may now be found exactly described in the text-books. Every

* Reference to the so-called direct division of cells, or amitosis, is intentionally omitted. This form of division is rare, and the consideration of it is unessential for our present purposes.

student of medicine, or of biology, has opportunity in his practical laboratory work to see for himself the formations of the dividing nucleus, and I may therefore allow myself to omit a detailed description of this phenomenon. But there is something else I should like to say to you concerning the nuclei. It is now established that the nucleus has an entirely different chemical composition from the protoplasm. In protoplasm and in nucleus we have to do chiefly with proteids, for they are the chief components of both structures. The proteids in the nucleus are, however, in certain respects simpler than those in protoplasm. For this and other reasons, it is believed that the nutritive material must first reach the nucleus in order to be worked over in the nucleus and to be later returned from the nucleus to the protoplasm. The chemical relations between the nucleus and the protoplasm are of the greatest significance. I must ask you to consider that I am not a competent biological chemist. In recent years chemical biology has made many beautiful and important discoveries. It is understood that we must seek the explanation of most vital phenomena in the chemical alterations which occur in the body. If we should ever get so far as completely to understand life it will be only when chemists are in a position to explain vital phenomena chemically. We incline to the belief that the nucleus is absolutely necessary to the functions of life. It is besides instructive to learn that in certain lower organisms, in which we can distinguish no definite nucleus, such as we usually observe, nevertheless nuclear substance occurs scattered in the protoplasm. From such observations we draw the conclusion that for the maintenance of life it is necessary to have not only the complicated protoplasm, but also the presence of the differently complicated nuclear substance. We cannot hope to reach a basis

for the explanation of life until we shall know how the chemical alterations go on in the living substance, which is a highly complicated mixture of many organic combinations of various sorts, all carried by great quantities of water.

A good example of the complication of the phenomena is offered us by the condition of the nucleus in certain unicellular organisms. In the cells of the highest plants and animals the nucleus is always a simple unit, but there are many species of protozoa known in which the nucleus is double, so that there appear to be two nuclei of unequal size, Fig. 12. It has been discovered that the larger nucleus

plays a rôle in the nutrition and growth of the cell while the smaller nucleus has assumed exclusively the functions which lead to the division of the cell. Nature makes here for us an experiment in that she has separated in space the

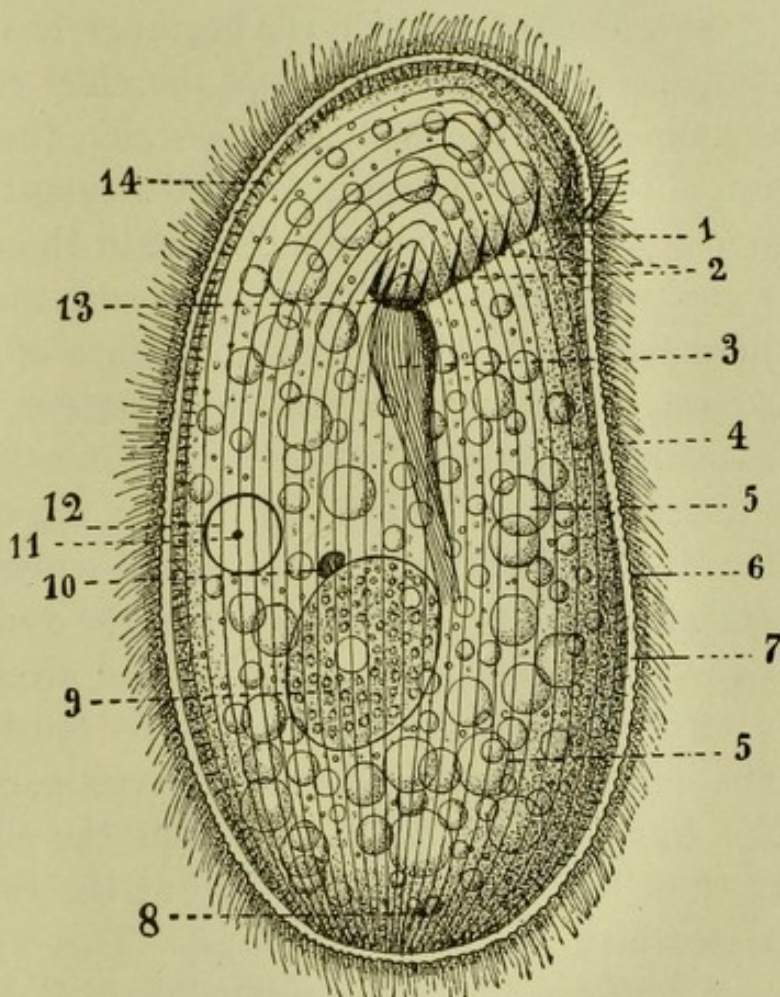


FIG. 12.—A unicellular animal, an infusorium (*Nassala elegans*). Natural length 0.1 mm. 9, Macronucleus; 10, micronucleus.—After Schewiakoff, from Lang's *Vergleichende Anatomie*.

two functions of the nucleus, which are usually carried out by a single unitary nucleus.

Vital phenomena rest on chemical processes by which energy is set free to show itself through the activities of the living being.

The first thing which the beginner learns is that chemical change, or metabolism, plays the chief rôle in all biological phenomena. The biologists describe the intake and excretion of the nutritive material, and attempt to trace the change to which this material is subjected in the cell. Cells possess, of course, no mouth. They can absorb material only through their surfaces. Therefore the surface of every cell is of the utmost importance for the continuation of its life, and the investigation of this surface and its tension has been eagerly pursued of late. Important results have already been produced; as, for example, it has been discovered that the surface tension during the impregnation of the ovum must be changed if the spermatozoon is to enter, and after the spermatozoon is in the interior of the egg the surface tension is again changed. The gifted German-American investigator, Jacques Loeb,⁴ has advanced the hypothesis that the egg has a superficial layer of lipoid substance which at the time of impregnation passes into a soluble condition. This hypothesis has since been confirmed by the experiments of Ralph L. Lillie.⁵

The egg of the sea urchin, after remaining some time in sea water, becomes more resistant so that the spermatozoon cannot penetrate the eggs as easily as when they were fresh. If such resistant eggs are treated with sea water, to which one has added 0.3 per cent. of ether, by which supposedly lipoid substances are dissolved, it is found that the eggs are more easily fertilized. But even if Loeb's hypothesis is not absolutely correct, the phenomenon itself remains extremely

significant because we must assume that almost incredibly small quantities of material occasion alterations in the ovum.

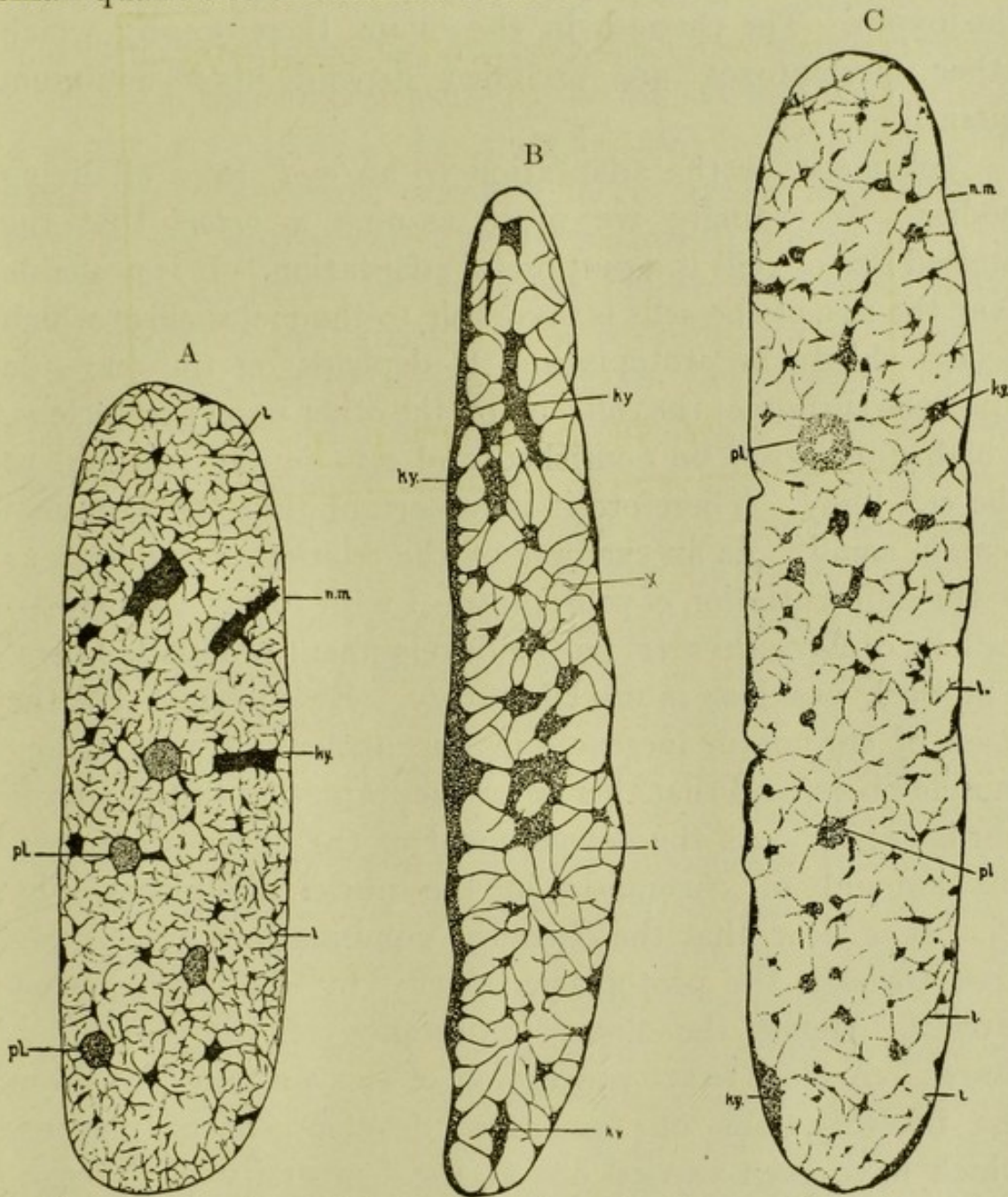


FIG. 13.—Muscle nuclei of the giant salamander (*Necturus*) in various stages. *A*, nucleus of 7 mm. larva before differentiation; *B*, from a 26 mm. larva at the beginning of differentiation; *C*, from the adult animal, 23 mm. long, after completion of the differentiation.—After A. C. Eycleshymer.

So soon as one spermatozoon penetrates the ovum, as is found in the case of most eggs, no spermatozoa can follow. If we

study the phenomena with the microscope we are unable to observe that anything is given off from the spermatozoon to the ovum. The changes in the ovum, therefore, by which other spermatozoa are excluded depend upon minimum quantities.

Teleology, or the adaptation to an end, rules all living bodies. Accordingly we must assume *a priori* that the limited size of cells is a purposeful adaptation. It is probable that the size of the cells is favorable to the metabolism which occurs chiefly in protoplasm. It depends on the one side upon the surface of the cell, and on the other upon the nucleus, which must itself be nourished and also supply material to the cell body. Therefore it is important that the distances remain small. As an example of the relation of the nucleus to the differentiation of protoplasm, I wish to cite the investigations of Eycleshymer⁶ on the development of muscle fibers. The work was done in my laboratory. He observed that the mass of chromatin increases in the nucleus of very young muscle fibers, and that thereafter the formation of the muscle fibrils begins. As the development of the fibrils progresses, the amount of chromatin in the nuclei diminishes, Fig. 13. It is clear that the chemical combinations are distributed through the protoplasm chiefly by diffusion, a slow process. Hence the great importance of the small distances. A more exact conception of this we may gain from the investigations on the early development of pigeons, which have been carried out at the University of Chicago, at the suggestions of Professor Whitman.⁷ The egg of the pigeon, like most other eggs, is fertilized by a single spermatozoon. The influence of this does not at first stretch very far in the ovum, so that the territory which we may designate as saturated is small. All around this territory we have, so to

speak, non-saturated protoplasm, into which a number of spermatozoa make their way and maintain themselves for some time, disappearing, however, in a few hours, and apparently in the same measure as the influence of the fertilization proper expands. In animals, which have relatively small eggs, the whole becomes more rapidly saturated by fertilization, so that only one spermatozoon can go in.

We spoke before of the great influence of small quantities upon the protoplasm. It is certainly the greatest advance of modern physiology that we have become better acquainted with the significance of this phenomenon. We have here to consider especially a new kind of action at a distance which takes place constantly in our own bodies. When, forty years ago, I made my first physiological experiments, the nervous system was the only means known to us to effect action at a distance within the animal body. We studied industriously nerve fibers, sensations in the brain, and the stimuli which passed from the central nervous system to the various organs of the body. Since then we have discovered the phenomenon of so-called internal secretion. The glands form secretions which are further used in the body. The majority of glands have a duct which carries off the secretion; thus, for example, in the case of the liver we have the ductus hepaticus which conducts the secretion of the liver to the intestinal canal. It is known now, however, that there are glands which have no duct, Fig. 14. Nevertheless, these form secretions which are delivered immediately to the blood and then are distributed by means of the circulation through the entire body. It has been learned that each internal secretion, which is formed in very small quantities, exerts a surprisingly great influence on other parts of the body which may be quite remote from the gland. I may mention as in-

ternal secretions the products of the thyroid gland, the hypophysis and the suprarenal bodies. The thyroid gland influences the condition of the muscles; the hypophysis, the growth of bones; and the suprarenal capsule the activity of nerves. In passing it should be remarked that the phenomena are not simple, but complicated. In all cases, however we see that many cells of one kind depend as to their structure

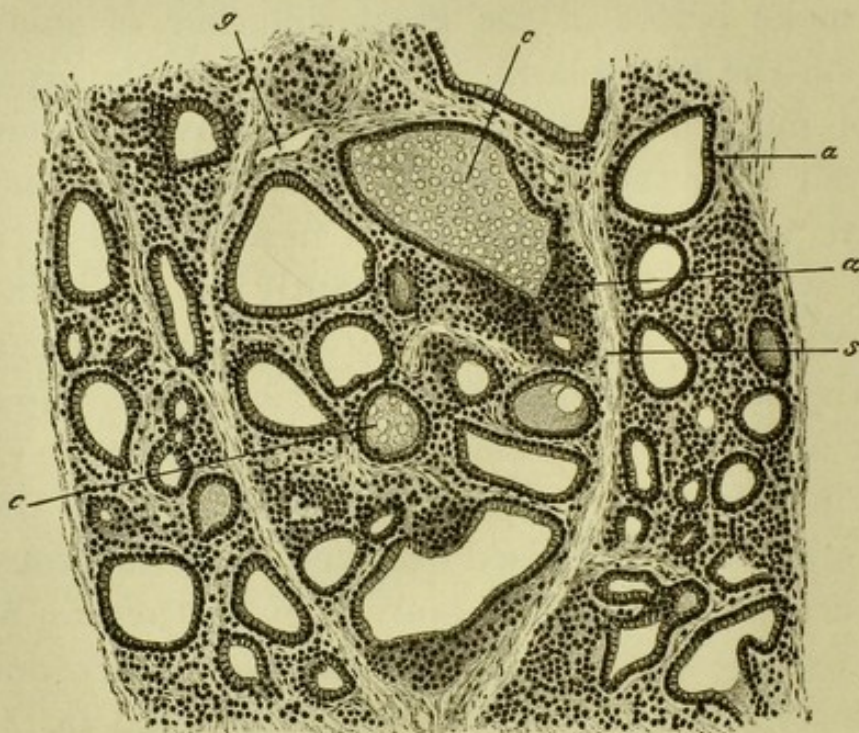


FIG. 14.—Section of a thyroid gland. The organ consists of closed cavities, each of which is bordered by a layer of epithelial cells. Since the gland has no duct, the secretion can be carried off only by the blood.—*After Koelliker.*

and their activity upon the influence of these internal secretions. It is not the case of a single cell, but always of many which have the same constitution.

The brilliant investigations of Ehrlich and others have founded the new doctrine of immunity. In this case we have to do with the phenomenon similar to that of internal secretion. An animal becomes poisoned by pathogenic organisms, and then forms itself a contra-poison, or so-

called antitoxin. That the toxins and antitoxins occur has been demonstrated with certainty, but the quantities are so small that we have not yet succeeded in isolating them. From these and other similar phenomena we learn that the condition, composition and structure of the living substance is of fundamental significance, and is, strictly speaking, more important for the comprehension of vital phenomena than the fact that the physical basis of life shows a strong tendency to form cells.

We may now put into words the deduction which we may draw from to-day's lecture. Our conclusions may be expressed as follows:

The new cell doctrine still recognizes the importance and significance of cells. Cells remain the units of morphology, but from the physiological standpoint they appear as adaptations which, especially by their size and proportions, create favorable conditions for metabolism. The living substance is more important to biologists than its tendency to form cells. Hence we consider the chief problem of biology to be the investigation of the structure and chemical composition not of cells, but of the living substance. The new conception has won its way gradually. It corresponds to so fundamental a change of our views that we are justified in describing the new conception as the new cell doctrine.

II.

CYTOMORPHOSIS.*

Your Magnificence!

Gentlemen!

We endeavored in yesterday's lecture to familiarize ourselves with the new cell doctrine, according to which a much greater importance is attributed to the composition of the living substance than to the fact that this substance has a strong tendency to form cells; all the same, cells remain the most convenient units of biological research, although they can by no means be found always completely separated from one another. But even if the cells are not separated, it is practical and convenient to designate each nucleus, together with its surrounding protoplasm, as a cell. Every fully formed tissue of the animal body has at least one characteristic kind of cells, or in other words the cells of a tissue exhibit among themselves similar relations and similar structure. Hence we can direct our attention to the single cell which we value as the paradigm.

In man, as in the great majority of multicellular animals, development begins with simple cells which arise by the segmentation of the ovum. From the simple cells the tissues of the adult develop gradually. As I told you yesterday, we

* The term cytomorphosis was proposed by me in 1901. The corresponding conception was first definitely propounded in the Middleton Goldsmith Lecture, published in 1901. This lecture has recently appeared in the German translation in my book "Die Methode der Wissenschaft" (Gustav Fischer, Jena). My book "The Problem of Age, Growth and Death" (New York, Putnam's, 1908), treats of cytomorphosis in some detail, although in somewhat popular form.

observe no similar developmental processes in unicellular organisms. The transformation of cells which leads to the formation of tissues is designated as differentiation. In the earliest stages of the embryo the cells are remarkably like one another, Fig. 15, but in the course of their further development they become unlike or different; hence the designation differentiation. How these differentiations arise is an extremely interesting question about which we know very little, because as yet we have become acquainted almost

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FIG. 15.—Section through the posterior part of a rabbit embryo of seven and a half days, to show the three germ layers, each of which consists of undifferentiated cells. Magnification 250.

exclusively only with such alterations as are visible with the microscope. The visible alterations, however, we must assume, are the consequence of chemical processes which we still have to discover. The visible alterations have been studied with the utmost care by many eminent biologists, and we are able to say that they follow strict laws. It is convenient to have for the complete transformation of cells a short, scientific term. As such I propose "*cytomorphosis*." We are now to occupy ourselves with the laws of cytomorphosis so far as these have been determined. The development of simple cells into differentiated we call progressive

development. The first question which we have to answer is: Does a regressive development also occur? The progressive is well known to us and we know much about it. I incline strongly to the opinion that it is the only kind of development, but there are not lacking investigators who have come to the belief that under certain conditions development may be reversed.

My point of view is determined in part by the fact that it has been possible in cases where a regressive development had been assumed to make sure by careful investigation that opinion had been misled by appearances and that in reality the development was progressive in these cases also. I may mention three examples; first, the nerve fibers. If one cuts through a nerve, the fibers in its peripheral part degenerate quite rapidly. After several days, however, under favorable conditions, newly formed nerve fibers appear in the peripheral part. Many investigators have eagerly advanced the view that these nerve fibers rise in their place and that they have been newly formed in the degenerating nerve. More careful research has made it certain that the newly formed fibers have simply grown out upon the ends of the healthy fibers, left in the central part of the nerve. If one cuts off the roots of a tree, the roots which are separated from the trunk decay; but if the tree is left one can find later in their place living roots, which, however, have not arisen from the dying roots, but have grown out from the central healthy parts. The fundamental experiments of Harrison⁸ make it sure that nerve fibers in all cases are formed only in the way mentioned. About the origin of nerve fibers there has been a long controversy. My countryman, Harrison, has occupied himself for several years with this question, and has supported his conclusion by the most varied investigations. Four

years ago he invented a new method to keep isolated cells and pieces of tissue living *in vitro*. Utilizing the new method, he subjected young nerve cells, *neuroblasts*, to observation and was able to see under the microscope nerve fibers grow out from the living cell. Cultures *in vitro* are now made frequently, and we expect from the application of Harrison's ingenious method many valuable discoveries. From time to time we find the paradox justified which says: "New methods are more important for science than new thoughts."

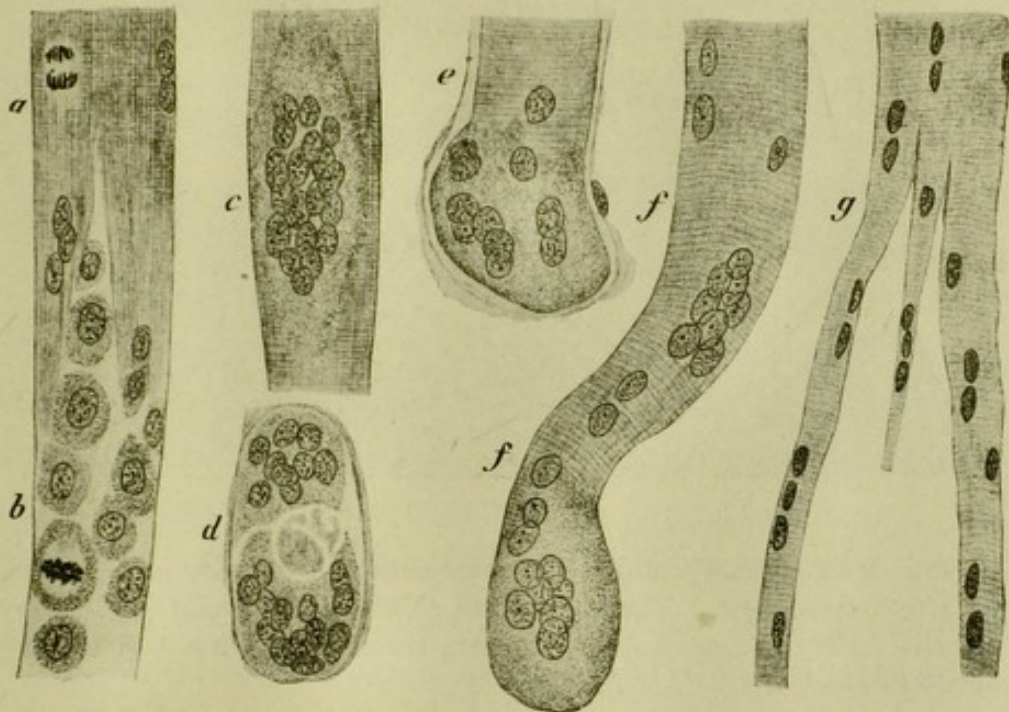


FIG. 16.—Degenerating muscle fibers after experimental injury. *a, b*, after 3 days; *c*, after 8 days; *d*, 26 days; *e*, 10 days; *f*, 21 days; *g*, 43 days.—After Ernst Ziegler.

The second example we get from muscles. If the fibers of a skeletal muscle are mechanically injured they degenerate quickly; later, however, we find new formed muscles. Here the processes are of quite a peculiar sort. Every muscle fiber consists chiefly of muscular substance which we can easily demonstrate by the contractile fibrils. It is the

muscular substance which breaks down after the injury. The muscle fibers, however, contain also the so-called muscle corpuscles, which are nothing more than little accumulations of undifferentiated protoplasm, containing the nucleus, Fig. 16. After the injury these corpuscles do not degenerate, so that undifferentiated protoplasm remains from which the new formation starts. The differentiated part of the muscle disappears and there is in this case no question of a regressive development.

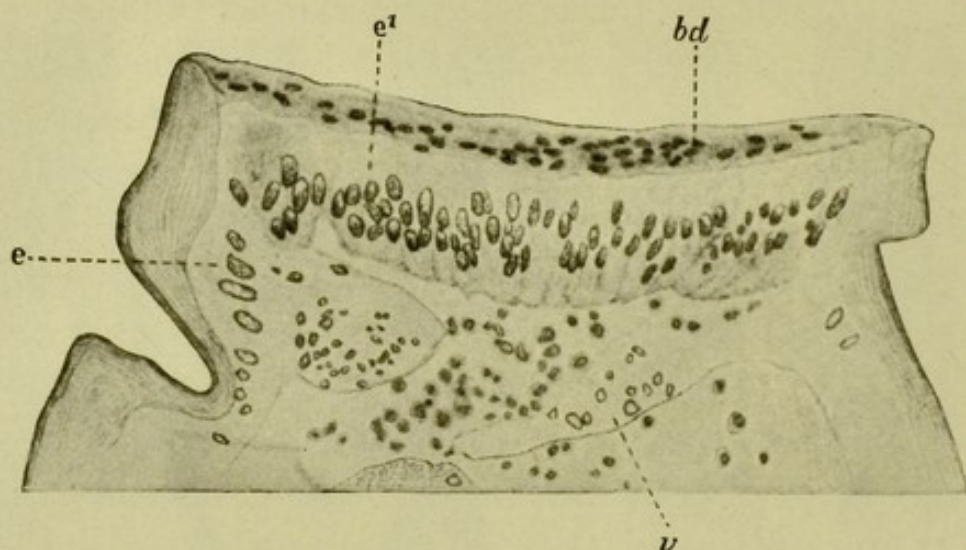


FIG. 17.—Longitudinal section of the regenerating extremity of a young lobster one day after amputation. There is formed at first a blood clot (*bd*) under which the epithelial cells *e*, *e'*, grow across to form the commencement of the new part. Magnification 240.—After V. E. Emmel.

The third example we will take from the lobster. If the extremities of the larvæ of this animal are cut off, the extremities will be newly formed. It was formerly assumed that we had to do in such a case with a new regressive development. The investigation made by Emmel¹⁰ in my laboratory has rendered the real history clear. The cells of the outermost layer of the skin in these larvæ are undifferentiated cells, which after the injury grow and spread over the wounded surface. They then multiply and by their steady growth

create the new extremity. Afterward they differentiate themselves in part in order to form the various tissues which are characteristic for the limbs of Crustacia, Fig. 17. The nerves and probably the blood-vessels penetrate subsequently into the newly formed extremity. To conclude: Until it is shown in at least one case with absolute certainty that regressive development occurs it must remain very improbable in the minds of earnest biologists that such a development occurs at all, or can occur.

Cytomorphosis defines comprehensively all structural relations which cells or successive generations of cells undergo. It includes the entire period from the undifferentiated stage to the death of the cell. The differentiations which occur in the body are very different among themselves, and as is well known these differences are much greater in the higher than in the lower animals. Hence it is by no means easy to recognize at once what is common to these changes, but some important results have already been won. First of all it is to be stated that the differentiation in all cases shows itself by visible new functioning structures in the protoplasm. There exists here between the protoplasm and the nucleus a marked contrast, for, as you have learned, the nucleus acquires, strictly speaking, no new structures, although it also changes with the progressive development.

We know that the visible alterations in protoplasm are initiated by invisible ones. Various experiments afford the proof of this. The first rudiment of the fore-leg of the larva of an amphibian may be cut off and then grafted into another part of the body, where the rudiment will develop further.¹¹ The rudiment, or anlage, at the stage which is specially suited to this experiment, is a little bud on the surface of the larva. Microscopic examination shows that

its cells are simple and more or less similar to one another. Tissues in the stricter sense are not present. In spite of the fact that these cells attain their further development under unnatural conditions they in themselves form muscle fibers, connective tissue and bone. In spite of the fact that the microscope shows us nothing in these cells by which we can recognize their future development, we must assume that the specification already exists. Professor Harrison, as I have already mentioned, devised a method to cultivate tissues *in vitro*. One can cut out from an embryo chick little pieces at will and cultivate them artificially *in vitro* and bring them to further development. In this manner W. H. Lewis has succeeded in studying the specific cell formation. The cells of the mesenchyma grow in the manner of mesenchyma; the cells of epithelium as epithelium. Neither in the nucleus nor in the protoplasm in these cells can we demonstrate peculiarities which we can regard as the causes of the unlikeness of their growth, but surely there exist in these cells peculiarities which are not visible to us and which determine the performances of the cells. It is not going too far to assume that in all cases the invisible alterations of protoplasm precede the visible.

The young cells in an undifferentiated vertebrate embryo have little protoplasm. The first thing that must happen is that the protoplasm grows, a phenomenon which one may easily observe with the microscope. After the protoplasm has grown, differentiation proper may begin. It is always gradual and consists essentially in this, that something new becomes visible in the protoplasm. In part, especially in the so-called epithelium, we have to do with the formation of superficial membranes around each cell. More important probably are the new formations in the protoplasm, Fig. 18.

The developing nerve fibrils I have already mentioned. In nerve cells there appear very fine fibers which develop gradually, making a network in the cell, Fig. 19. There also appear deposits of a substance which reacts to stains differently from the protoplasm and the fibrils, Fig. 18, *k, k'*. The deposits in question have received the somewhat fantastic name of "tig-

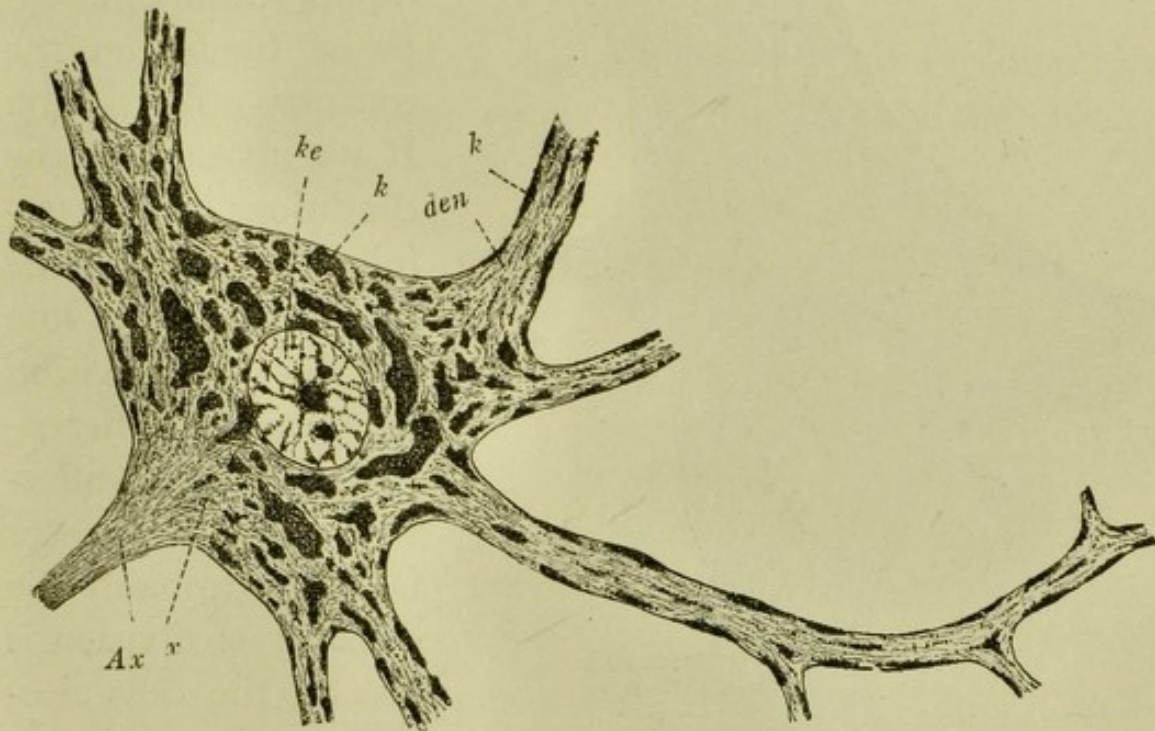


FIG. 18.—Motor nerve cells from the spinal cord of a rabbit. *ke*, nucleus; *den*, dendrite; *Ax*, nerve fiber, and *x*, its origin; *k, k'*, Nissl bodies.—After K. C. Schneider.

roid substance.” We notice also peculiar cavities which form a net-work in the protoplasm of the cell, and are filled with fluid. In the gland cells one sees the material distributed in the protoplasm which is utilized later for the execution of the specific activities of the gland cells, Fig. 20. This material is not the secretion proper, but a primary stage. In quite another wise do the intervening supporting tissues develop, for in them the cells show a strong tendency to separate from one another and to produce special structures in the inter-

cellular spaces. It is not practicable to lay further illustrations before you.

Progressive development is closely connected with another

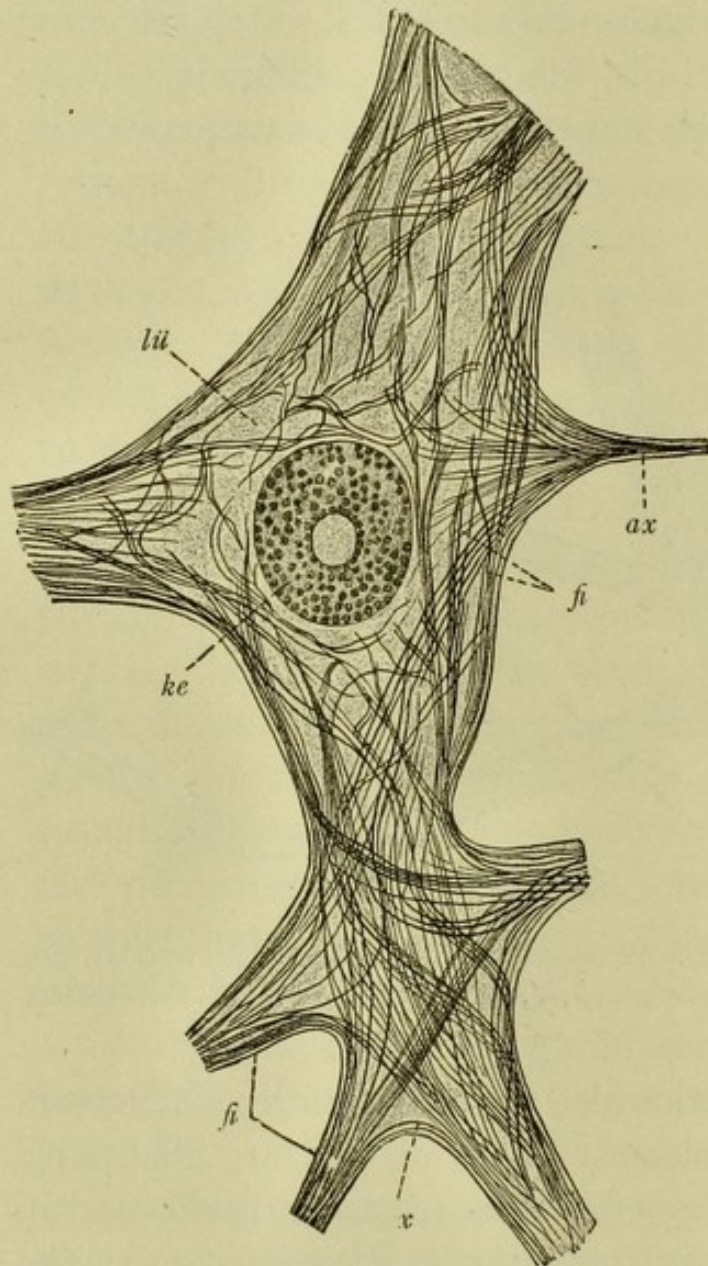


FIG. 19.—Nerve cell from the spinal cord of man. The Nissl bodies have been dissolved out and the cell so-colored that the neurofibrils are brought out. *fi*, fibrils; *x*, fibrils in a dendrite; *ax*, nerve fiber; *li*, space left by the dissolving of the Nissl bodies; *ke*, nucleus.—From K. C. Schneider, after Bethe.

phenomenon. The embryonic tissues grow with immense rapidity, the differentiated tissues on the contrary grow slowly. If we investigate the conditions more carefully we learn that the cells gradually lose the power of division as they are differentiated. If the differentiation progresses far, then probably the capacity of division is lost to the cells altogether. Formerly we had no exact conception of the rapidity of growth in embryos. This is a question about which I have been greatly interested for many years. In the book "The Problem of Age, Growth and Death," which I published in 1908, I

have discussed more fully the alterations of the rapidity of growth with age and its relation to the increase of differentiation. The development of a mammal begins with an extra power of growth. How gradual the increase is it is not yet possible to determine exactly, but certainly the original daily increase is not less than 1000 per cent. This holds true for man also.

Immediately after birth one finds the highest rapidity in the rabbit to be not quite 18 per cent. per day; in the chick not quite 9, and in the guinea pig about $5\frac{1}{2}$ per cent. The relations for man are similar. It is therefore clear that the animals mentioned and man also have lost at the time of their birth 99 per cent. of their original growth capacity. In fact, from the biological standpoint we are really old by the time we are born and the alterations which make us old have for the most part already occurred. The further losses which we suffer from birth to old age are comparatively small, and we live long only because these losses take place slowly. If the progress of alteration after birth should be even only approximately as swift as before birth we should live only a very short time. And in fact the microscope shows us that the multiplication of cells after birth is by no means so great as before, and that it goes on slowly.

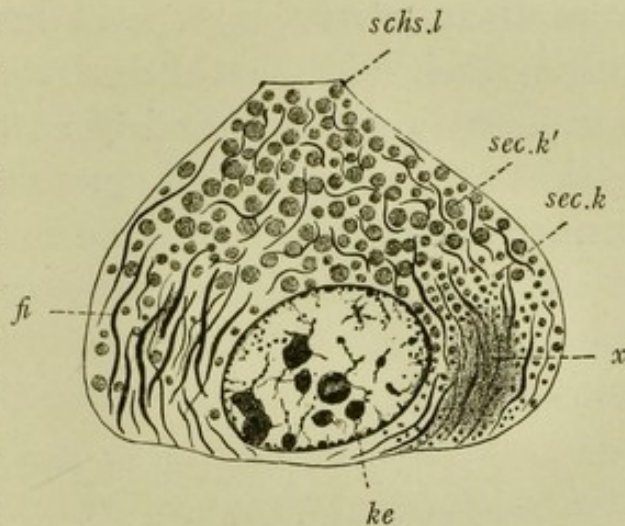


FIG. 20.—Cell from the pancreas of the larva of *Salamandra maculosa*. *sec.k*, *sec.k'*, secretory granules; *x*, formative focus of the same; *fi*, secretory fibrils; *ke*, nucleus; *schs. l*, closing plate.—After K. C. Schneider.

Cytomorphosis includes more than differentiation proper. By continuing it leads to the degeneration of the cell. Degeneration appears in many cases to depend upon the transformation of the entire protoplasm so that no more true protoplasm remains in the cell. Under such conditions the cells do not remain viable. A good example of this process is afforded by the epidermis, the outer skin, the lowest layer of which consists of undifferentiated cells, which can grow and multiply, Fig. 22. Some of these cells liberate themselves from their parent layer and migrate toward the surface. During their migration their protoplasm is gradually changed into horny substance, and when this change is complete the cells have completed their cytomorphosis and are dead. The surface of our body is covered by dead cells. In this case as in all similar cases degeneration leads to the death of the cell. We can accordingly distinguish four chief stages of cytomorphosis.

1. Undifferentiated or embryonic condition.
2. Differentiation.
3. Degeneration.
4. Death.

Only in this succession can alterations of cytomorphosis occur, but it must be added that if regressive development should occur it would form an exception to this rule.

The red blood-corpuscles afford us an excellent example of a complete cytomorphosis. They begin their development as simple cells, with a well formed nucleus but little protoplasm. Next we observe that the protoplasm grows. Not until it has grown sufficiently does it acquire its characteristic color through the formation of hemoglobin, thus becoming a young red blood-corpuscle which may still grow a

little, although the nucleus at the same time begins to grow smaller. After the nucleus has become considerably smaller it is separated from the body of the corpuscle. As to how this separation occurs authorities are still disputing. The part left without the nucleus is the so-called mature blood-corpuscle which, however, is not able to maintain its own but soon breaks down. Every day in each of us numberless millions of blood-corpuscles are disappearing. The cartilaginous cells also pass through a complete cytomorphosis which, when the cartilage is replaced by bone, terminates with the dramatic disappearance of the cells. Cartilage is developed from embryonic mesenchymal cells. The cells enlarge and there appears between them the basal substance which imparts to cartilage its characteristic physical consistency, Fig. 8. The so-called ossification of cartilage begins with the completion of the chondral cytomorphosis, during which the cells pass through rapid degenerative hypertrophy, Fig. 21, which involves the destruction of the basal substance, and which closes with the disintegration, or autolysis, of the cell. Thereupon bone is formed in the place of the cartilage which has disappeared. The nerve cells, at least in vertebrates, pass through their cytomorphosis in a special tempo. Their differentiation advances quite early to the high point at which the cells long remain. The degenerative alterations follow very slowly, so that we usually do not encounter mental weakness in man until advanced age, the weakness being caused by senile atrophy of the brain cells. We are indebted to the peculiar course of the cytomorphosis of the brain for the extraordinarily long-lasting functional capacity of this organ. The leaves of plants offer us an excellent example of cytomorphosis. The leaf bud consists of embryonic cells which grow and differentiate themselves to

form the leaf. Later the cells degenerate and die. The leaf becomes dead and falls. It would be easy to lay before

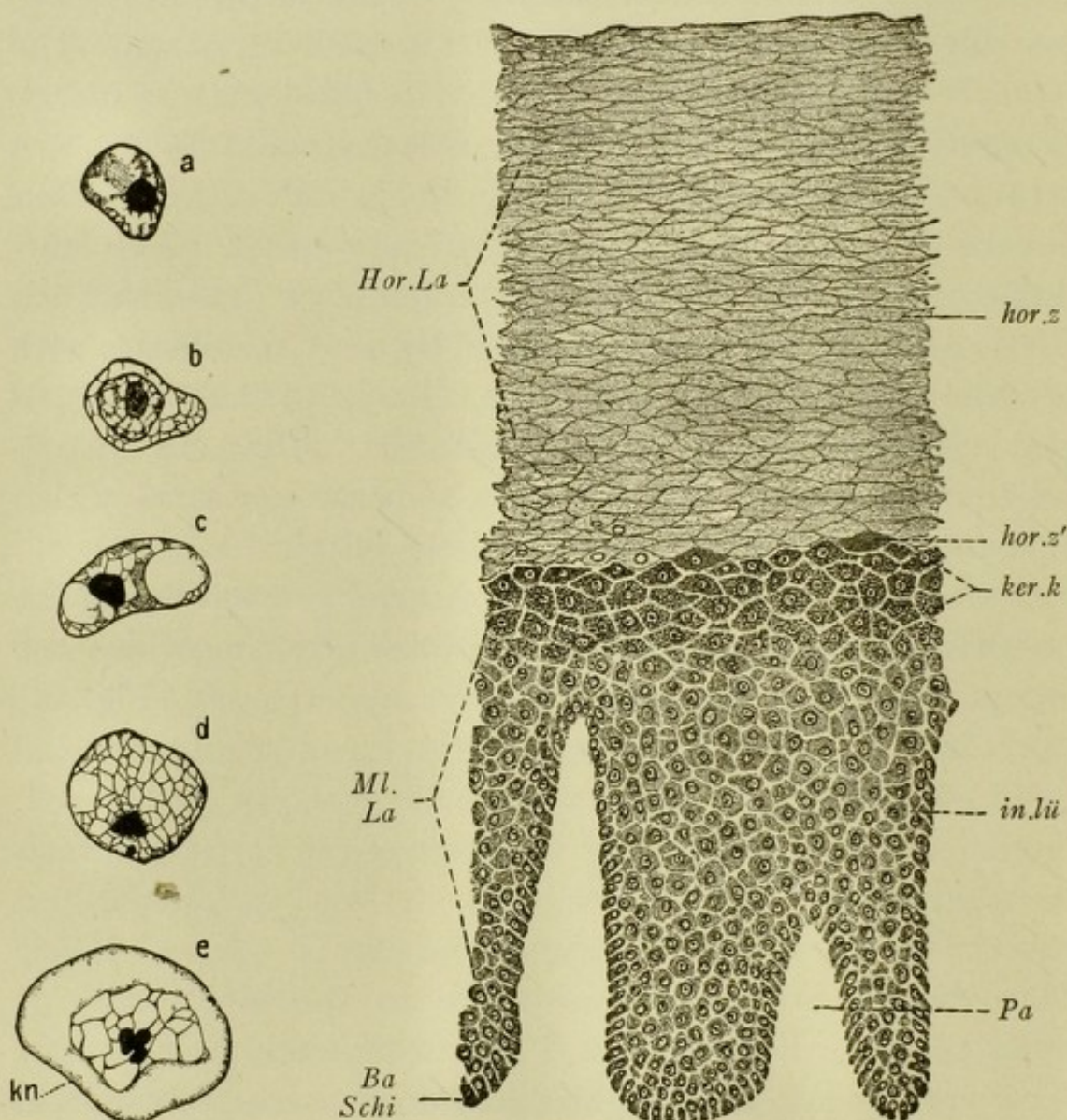


FIG. 21.

FIG. 22.

FIG. 21.—Cytomorphosis of the cartilage cells. From a section of the vertebral arch of a pig embryo. *a-e*, successive stages; in *e*, the letters *kn* refer to the limit of the cavity which is no longer filled by the degenerating cell.

FIG. 22.—Epidermis from the sole of the domestic cat. *Ba. Schi*, basal germ layer; *Hor. La*, *hor. z*, *hor. z'*, horny layer formed by dead cells; *ker. k*, layer of cells which are being cornified; *Ml. La*, middle layer of cells which are migrating upward and at the same time enlarging; *Pa*, site of a hypodermic papilla.—After K. A. Schneider.

you many other examples of completed cytomorphosis of the most various cells. It might, however, be better to pass over to other considerations.

Death and subsequent removal of cells play a great rôle in our lives. Even in early developmental stages we find cells dying and even whole organs which maintain themselves only for a certain period and then disappear almost or completely. Thus there is an embryonic kidney in which only small remains can be found in the adult. It is therefore clear that there must be some arrangement provided to make good the loss of cells. Nature accomplishes this by not bringing all cells to further development and by preserving a stock of less differentiated cells in the body. Of these I have already mentioned an example, the epidermis, the cells of the under layer of which preserve an embryonic character. Only by the presence of these cells which keep the essential embryonic type is the continual renewal of the epidermis made possible. For every hair there remains a special group of embryonic cells upon the hair papilla, which provide for the growth of the hair. Since these cells are not differentiated, they can multiply and thus furnish cells for the formation of the hair. The cells of the hair complete their cytomorphosis, but their sister cells remain on the papillæ undifferentiated. We thus see that while cytomorphosis can go on only in the one direction, it remains true that the cytomorphosis can be arrested and that it may go on in the different tissues with unequal rapidity. Thus it comes that we encounter cells in the adult animal in every possible stage of cytomorphosis. There arise in every one of us every day cells which complete their cytomorphosis, and there are others which have hardly begun it. We cannot understand the relations in the adult animal if we do not consider at once both the daily dying off of old cells and

also the daily multiplication of cells which have remained embryonic.

We recognize that the embryonic cells are of great importance not only during the embryonic period, but also in the adult. How great this importance is is revealed in the investigation of regeneration. Very many animals, if parts of their body are removed, will form the missing parts anew. If, for example, we break off the tip of the tail of a lizard, there will arise a new tip which is formed by the growth of undifferentiated tissues. There are worms which multiply by forming in the middle of their bodies the so-called budding zone. Karl Semper¹³ has studied the process in annelids, and discovered that in them the budding zone consists of cells of the embryonic type. Gradually these cells advance in their cytomorphosis, and so there arises a new tail for the anterior part of the worm and a new head for the posterior part, and thereupon the two parts separate and two complete worms have arisen from the single animal. We are accustomed to designate those animals which have a more complicated structure as the higher. Now it is clear that if an animal is composed of relatively few cells great complexity of structure is impossible. Further we observe that when a highly formed animal is to be produced, nature takes care that a large number of embryonic cells is produced. In the lower animals development is of the so-called larval type. From the little ovum there arises quickly a young animal which lives free and must take care of itself. Such a larva must possess, even if only in simple form, all the principal organs, and since the cells must be so far differentiated that they can take over the various functions, they necessarily lose in part their capacity to multiply, and, what is still more important, the capacity to produce other kinds of cells. We see always that when

a cell has begun to develop in one direction it cannot start out to develop in any other direction. In the higher animals, on the contrary, we find a relatively large egg which has become large through the storing up in it of yolk or nutritive material. The developing ovum can nourish itself for a long time from this yolk. In this type of development we encounter not larvæ but embryos which are characterized thereby that they contain many cells of the embryonic or undifferentiated type. These cells assume definite groupings to form the rudiments or anlagen of the various organs. So that we may say that the anatomical development progresses without there being a corresponding alteration in the structure of the single cells. Thus we observe in the human embryo the stomach, or other organ, which shows the essential characteristics of its total form and of its relations to other parts of the body, and yet consists of cells not differentiated. In my opinion we are justified in regarding the embryonic development as a contrivance to make the postponement of a cytomorphosis possible, in order that the total number of cells available for differentiation shall be larger. Of the great importance of the number of cells we can get some notion by considering the cortex of the brain. The number of pyramidal cells in the cerebral cortex of man is over 4,000,000,000. This number is not astonishing; a cubic millimeter of blood contains between four and five million corpuscles.

The purpose of differentiation is known. Every living cell certainly carries on all the essential functions of life. In the higher organisms we encounter a division of labor. Each organ takes over as its special task one or another function, which the organ performs to the advantage of the whole. These functions are not new; they are always such as are common to the living substance in general, and in

each single organ there comes about, so to speak, an exaggeration of a single function. Protoplasm is sensitive and irritable. In our case, our sense organs take care of the sensations to the advantage of the whole body. Protoplasm has contractility, and this function is assumed by the muscles again to the advantage of the whole body. Similarly, the glands take over the formation of secretions—the excretory organs, the elimination of urea, etc. Now we know that the various structures which we can see in protoplasm, and which are characteristic for the sense organs, muscles, gland cells, etc., determine in each case the special performances of their respective cells. Briefly expressed, the whole meaning of differentiation is physiological. The peculiarities which we can recognize with the microscope in differentiated cells exist in order to render it possible for the cells to accomplish their special activity. It would be superfluous to linger over this conception, to amplify, or even to justify it by a roundabout demonstration. I wish, however, to specially emphasize the fact that the entire doctrine of cytomorphosis renders it clear that structure in living substance is the essential thing. This has become clear to us from the phenomenon of differentiation. We may probably go still further and say that even in those cases in which we as yet cannot recognize any microscopic structure, structure is still present. The conception of the significance of structure—of organization, which we win from the investigation of differentiated cells, applies also to protoplasm. It is well known, as I have already mentioned, that protoplasm is chemically extremely complicated, but the chemical combinations are not simply mixed together as in a simple solution, but are in part separated spatially. When we state that the living substance has organization we base our view not only on the application

of that notion of structure which we derive from the study of differentiated cells, but also on direct observation. Such investigation has not yet brought us very far. It teaches us that protoplasm is not completely uniform, but usually contains fine granules which are unlike among themselves. Micro-chemistry is a nascent science from which we may expect much, although she has presented us yet with but little. It is the science which investigates the chemical substances and processes in cells with the help of the microscope. We have already succeeded in proving that granules, chromidia, fatty substances, lipoids and various proteids exist in protoplasm in a visible form. We have also learned through micro-chemistry something of the distribution of iron and phosphorus in the cell. We have not yet got very far, but far enough to be justified in saying that the organization of living substance is known in part by direct observation.

We are acquainted with another structure in the protoplasm of many cells, the so-called centrosome which we can only allude to here, although its occurrence again demonstrates the importance of organization.

A word more concerning the nucleus. In the nucleus organization can be observed easily and without exception, and since the nucleus also belongs with the living substance, its peculiarities also serve to strengthen us in the belief in the importance of organization. Whoever knows the wonderful history of the chromosomes by his own observation, must be convinced that the nucleus has a very complicated organization.

Now to the conclusion. Cytomorphosis is the fundamental conception of the entire development of all multicellular organisms, and is the foundation at once of morphology and physiology. It explains to us many processes

which we otherwise could not understand. It includes the whole doctrine of the normal and pathological differentiation of cells. The principal conclusion which we may deduce from this doctrine is that all living substance possesses an organization, and that probably without organization life is impossible.

III.

THE DOCTRINE OF IMMORTALITY.

Your Royal Highnesses!

To your Royal Highnesses I wish to express my profound and respectful thanks for the honor of your presence, which has for me a great and unforgettable significance. The participation of your Royal Highnesses in to-day's lecture is a high distinction not only for me but for my university, which we gratefully acknowledge.

Everything living arises only from the living. The phenomenon of propagation of animals and of plants has always excited the interest of mankind. The ancients recognized that only living parents could have a living progeny, and it was said "*Omne vivum ex vivo*." But for a long time the opinion prevailed that life might continually arise anew. We know now, however, with certainty that a new generation of this kind does not occur, and assume that under present conditions a new generation of life is improbable, perhaps impossible. We know too little to venture a positive opinion. Schæfer,¹⁵ the gifted physiologist of Edinburgh, has expressed a supposition that new generation still occurs upon our earth and escapes our observation because we do not know the conditions which render such generation possible. This is an interesting speculation, but with this possible exception we must attribute to the saying, "*omne vivum ex vivo*" absolute validity.

With the progress of our knowledge we have made interesting discoveries concerning the manner in which the uninter-

rupted continuation of the living substance is assured in various organisms. The simplest cases occur in the lower organisms, in bacteria, etc., in unicellular plants and animals. In these the single individual, or the single cell, grows up to a certain size and then divides. In this manner the two daughter cells come to have part of the same substance as the mother cell, and so it goes on. This substance, so far as we can observe, does not change essentially with time. In the higher plants and animals we have in each case to do with many cells and we observe that the functions are unequally distributed among these cells. For the execution of various functions the cells become unlike among themselves. This is the phenomenon of differentiation of which we have already spoken. The majority of the cells are destined for the care of the whole, and perform their special functions. Some of the cells, however, are not utilized in this manner, but serve for propagation. When a flower unfolds in our garden we find in it certain special cells which have to do with the propagation. These do not show such differentiation as we may find in other cells of the plant, but remain at first relatively simple in their structure. The propagating cells mentioned separate themselves from the mother plant and form the seed. As essential in this case it appears that two cells are necessary for the process, one of which we designate as the egg cell and the other as the seminal cell. Two such cells unite and form a new cell, with which the further development begins. The mother plant may then die. We note in this case that the fate of the cells is extremely unlike, in that some of them are given over to death, while others remain permanently alive and serve for the propagation of the species. In the next lecture, in which we shall investigate the development of death, we shall occupy

ourselves with the consideration of the phenomenon of death. At present we shall devote our attention to the propagating of cells.

The kind of propagation which we find in the plant is called sexual and occurs also in animals. It is, however, by no means necessary that the propagation should occur by sexual means. Of the methods which nature applies for the multiplication of living individuals, I should like to mention a few to you briefly.

Many methods of asexual reproduction are known to us. The art of increasing plants in this way is practiced by every gardener, and nature also makes use of the possibilities. Among animals we often find a multiplication of individuals effected by simple division. The zoologist describes to us the column-like growth of certain jelly-fish and the following transverse division of the column, so that a number of discs arise, each of which becomes a jelly-fish. Asexual reproduction occurs among invertebrates in various forms. The peculiar division of certain annelids has been already mentioned. The budding zone is formed, and produces a new head and a new tail. In a parasitic tapeworm we have discovered a vesicular stage in the life cycle. At certain spots upon the wall of the vesicle arise new heads, each of which initiates the formation of a new tapeworm. Specially interesting are the cases of precocious division, which we have learned about recently, and in which we encounter the division of an egg before the embryo proper has developed. Thus Kleinenberg¹⁶ observed in certain earthworms that two individuals develop regularly from one egg, an observation which has been confirmed by the American investigator, E. B. Wilson.¹⁷ Still more remarkable are the occurrences in certain parasitic hymenoptera, in which not merely two but many individuals

are created from a single egg. This phenomenon is termed polyembryony. It was surprising to discover recently that polyembryony occurs in a mammal. In the year 1885 Von Jhering observed that the armadillo regularly produces four embryos in one sac, and he expressed the supposition that they arise from a single ovum. Professor Patterson¹⁸ of the University of Texas has studied the phenomenon carefully in a species which occurs in Texas. The development of ordinary mammals begins with the formation of a small vesicle. At one pole of this vesicle there accumulate a small number of cells in which no differentiation is recognizable. The accumulation is termed the germinal disc and produces the embryo. Patterson obtained eggs of the armadillo in the vesicular stage, and found upon each vesicle four distinct germs discs. Each disc forms an embryo. Thus it becomes certain that in this mammal four embryos, always of the same sex, arise from one ovum.

It is also possible to cause artificial polyembryony with certain eggs. When an egg begins its development, it divides and when the egg is small the division usually produces two cells alike in size. Driesch¹⁹ was the first to make the interesting experiment so to shake an egg in the two-celled stage that the two cells were separated from one another. Under favorable conditions each of the separated cells forms an embryo. The original experiment was made with the eggs of sea urchins. The artificial polyembryos do not attain a normal size, and therefore do not develop quite as do the natural embryos. The experiments of Driesch have been repeated by many Americans and much extended, and indeed with such eagerness that for a certain period we termed our embryologists "egg Shakers." You know probably that the Shakers are a Quaker sect, dedicated to celibacy.

A special form of division is budding, which plays an important rôle, especially among the hydroids. The process is described in all text-books, and need therefore be mentioned merely. A little superficial group of cells begins to grow and forms finally a new polyp.

In the cases considered thus far, a number of cells participate in the propagation. In the case of the so-called parthenogenesis the creation of a new individual starts from a single cell. This cell is an egg, which develops without being fertilized. Great interest was excited by the discovery of artificial parthenogenesis by A. C. Mead.²⁰ In the artificial development we utilize chemical action which replaces fertilization proper, and so excites the ovum that it develops further.

In all these cases the propagation is effected by the separation of living material from the body of a living individual. The separated substance remains continuously alive. The substance may be comprised of many, several, or only one cell. The number of cells is unessential; essential is only that the substance is alive and remains alive.

The separated substance inherits the primitive organization, or, more exactly expressed, has the parental organization, because it is unaltered parental substance. We come up against a question which we unfortunately cannot yet answer: How is the organization regulated? It seems a matter of indifference how the asexual propagation is accomplished. Each time the development proceeds, until the original organization is completed. When the budding zone of annelids forms a new tail in the anterior part of the animal and a new head for the posterior part, we can only say that a regulation of the organization is shown. There is no means for determining more exactly the process. It seems to be clear that this regulation is not to be sought only in the developing cells

themselves but also in part at least in an influence exerted by the rest of the body. In the case of polyembryony, the rudiment, or anlage, possesses the capacity of forming all tissues and organs. During regeneration also, which in many animals may go very far, we see that the complete structure is produced anew and we recognize here again the phenomenon which we call regulation. The physiological explanation of regulation we do not yet possess, although we have learned already a little concerning it.

The sexual propagation plays a greater rôle than the asexual, and is often the exclusive method of propagation, especially in the higher plants and animals. We learned in yesterday's lecture that the cells of the animal body differentiate themselves, that is to say, that their protoplasm acquires new qualities and that their power of division diminishes. Differentiated cells are not suited for propagation. If it should occur that all the cells of an animal or a plant should pass through a complete cytomorphosis, they would all die off, the organism would reach its end, and could produce no progeny. As a matter of fact, however, all the cells do not become differentiated. Of the undifferentiated cells, the necessary number in each species is reserved for the formation of the sexual cells. In phanerogams we find undifferentiated cells in the buds. When the bud forms a flower and sexual cells are developed in connection with it, we learn that some of these undifferentiated cells are made use of. It is entirely unknown to us how the transformation of undifferentiated cells into sexual cells is caused. We can observe with the microscope alterations in the structures of the cells, but the cause of these alterations remains hidden from us. In lower animals we find relations which to a certain extent resemble those prevailing in the phanerogams,

since in them also there occur slightly differentiated cells which are applied for the formation of sexual cells. The other cells, which constitute by far the majority, we name the somatic cells, and therefore say that every animal body consists of many somatic and a few sexual cells. It we pass from the lower to the higher animals, we find that the separa-

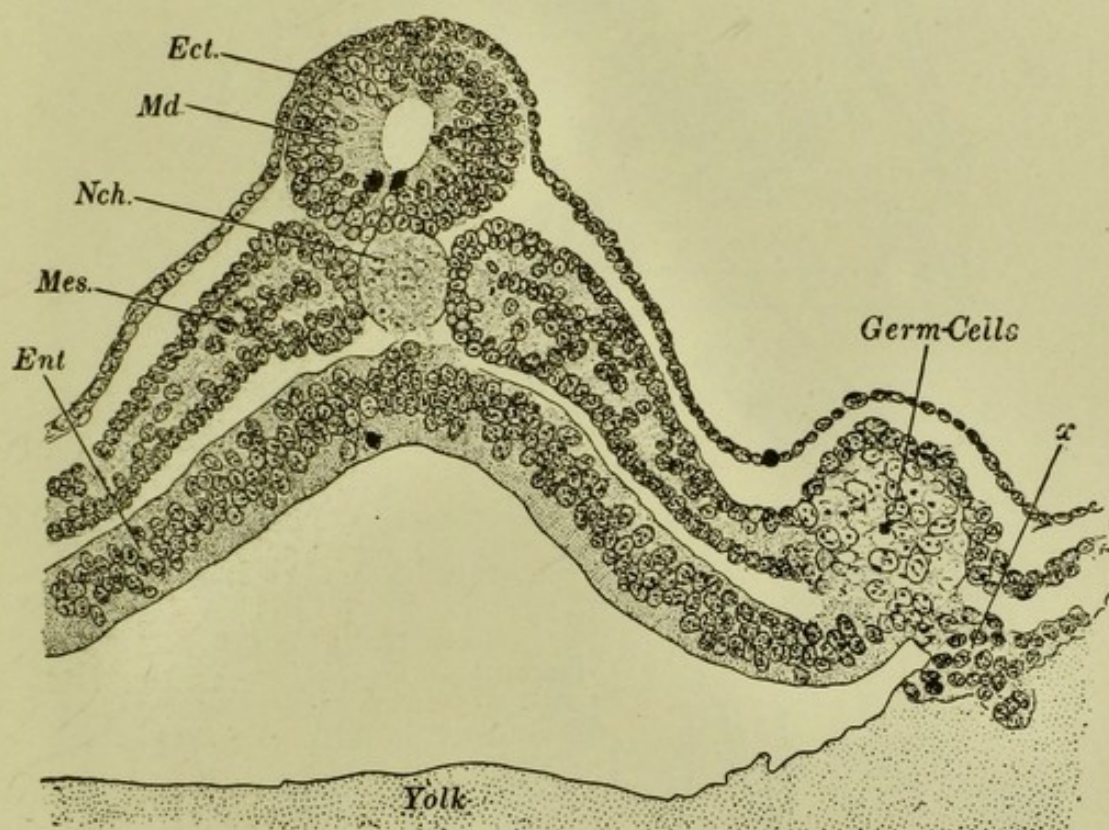


FIG. 23.—Section through the posterior part of an embryo of the dog-fish, *Squalus acanthias*. *Germ cells* designates the group of sexual cells which have united in one group, which still lies far from the position of the future sexual gland. *Ect*, ectoderm; *Md*, spinal cord; *Nch*, axis of the body (notochord); *Mes*, mesoderm; *Ent*, entoderm; *Yolk*, yolk-mass.

tion of the two classes of cells, the names of which we have just heard, becomes sharper. We have succeeded recently in observing the precocious separation, or isolation, of the sex cells in vertebrates. Their number is very small in proportion to the number of somatic cells. In the young embryo

of the dog-fish there lies at either side in the neighborhood of the developing intestinal canal a group of cells, Fig. 23, *germ*

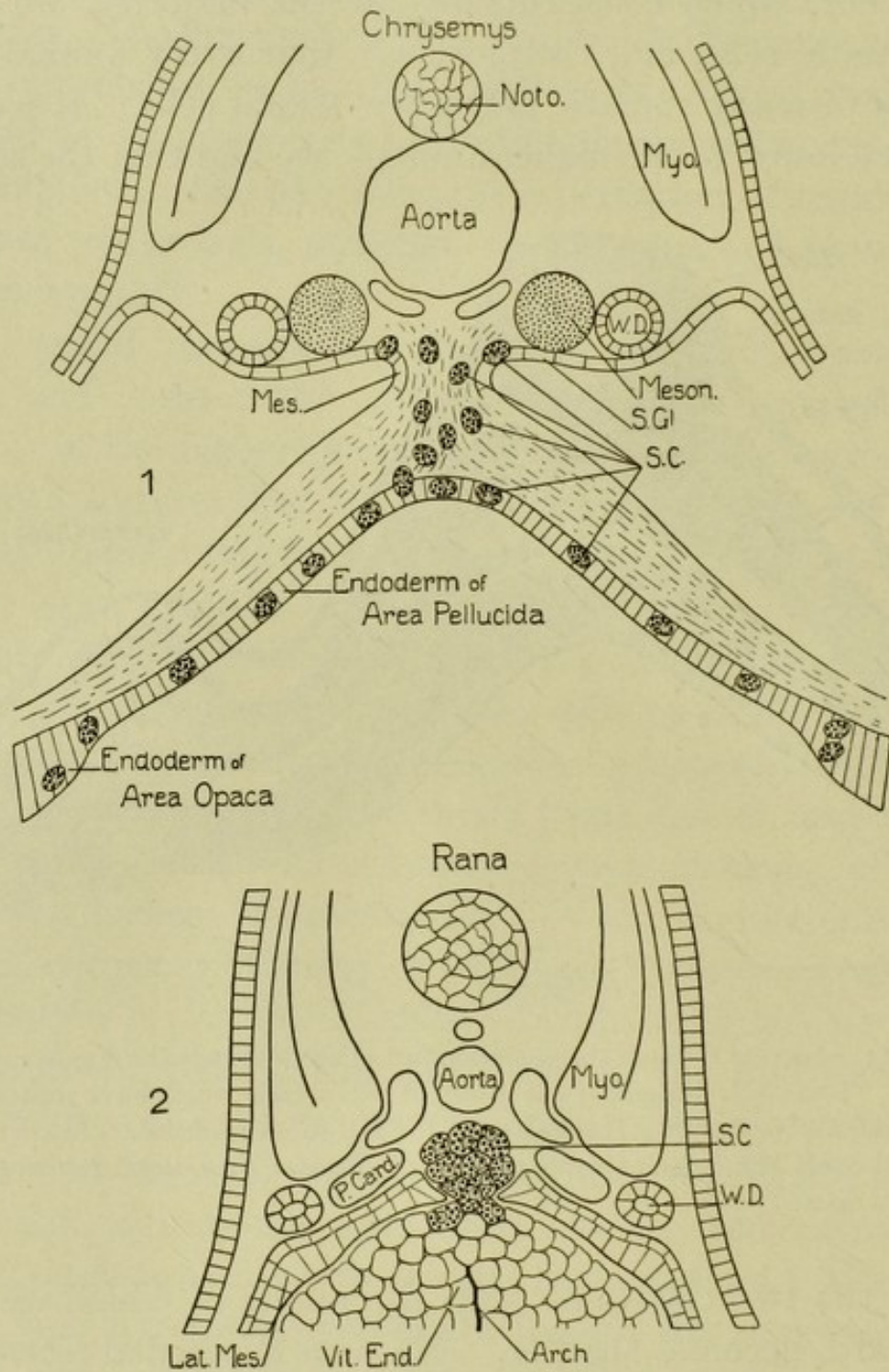


FIG. 24.

cells, which resemble one another closely, and which may be easily distinguished from the other cells of the body. They

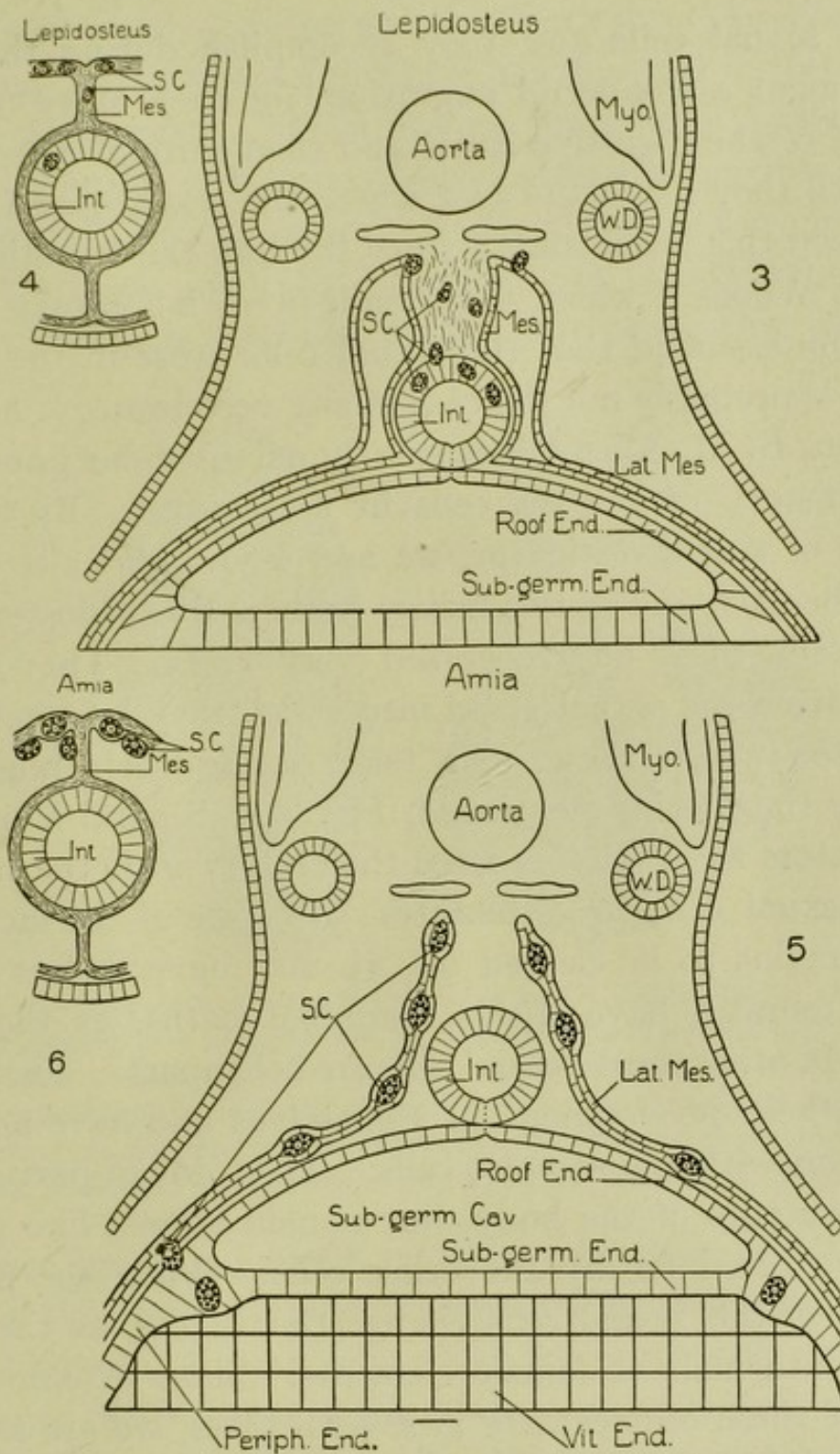


FIG. 24.—Diagrams to show the migration of sexual cells in four different vertebrates. *Arch*, primitive intestine (archenteron); *Int*, intestine; *Lat. Mes*, lateral mesoderm; *Mes*, mesothelium, or wall of the body cavity; *Meson*, embryonic kidney (mesonephros); *Myo*, anlage of the muscle (myotome); *Noto*, primitive axis (notochord); *S.C.*, sexual cells in migration; *W.D.*, renal, or Wolffian duct.—After Bennett M. Allen.

are the sexual cells and they accomplish during the later development a wonderful migration, for they move through the wall of the digestive canal and then through the mesentery until they reach the spot where the sexual gland arises. We know this interesting history through the investigations of F. A. Woods,²¹ which were made in my laboratory. Formerly one assumed that the sexual cells arose in the gland, but this is probably not the case in any vertebrate. Another American, B. M. Allen,²² has greatly enlarged our knowledge of the history of the sex cells in vertebrates. By the researches of this investigator, we now know that also in the turtle, the frog, and in two fishes, *Amia* and *Lepidosteus*, the sexual cells may be recognized very early. They lie at first far from the sexual gland into which they later migrate. The paths which these cells take during their migration differ for the species mentioned, Fig. 24. Several European investigators have also occupied themselves with the history of the sexual cells in vertebrates. In spite of the fact that much remains to be cleared up, we may nevertheless assert that vertebrates have special germinal paths, as they are called. In other words sexual cells are held apart. They pass through their development by themselves and have nothing in common with the somatic cells. They do not participate in the structure of the body, but remain almost like guests which are cared for by the other cells. When the proper time comes the sexual cells change themselves, as the case may be, into male or female elements. Since we know the history of these cells exactly in several cases, we are able to assert that in sexual as in asexual propagation the living substance continues uninterruptedly. This continuation up to the origin of the sexual elements we have actually observed.

In insects also a special germinal path has been discovered. The small egg of these animals is usually oval in form. The French anatomist, Charles Robin, reported in 1862 that a special group of cells appears soon after the conclusion of the segmentation of the ovum. Balbiani showed twenty years later that these pole cells, which are not to be confused with the so-called polar globules or directive corpuscles, afterward

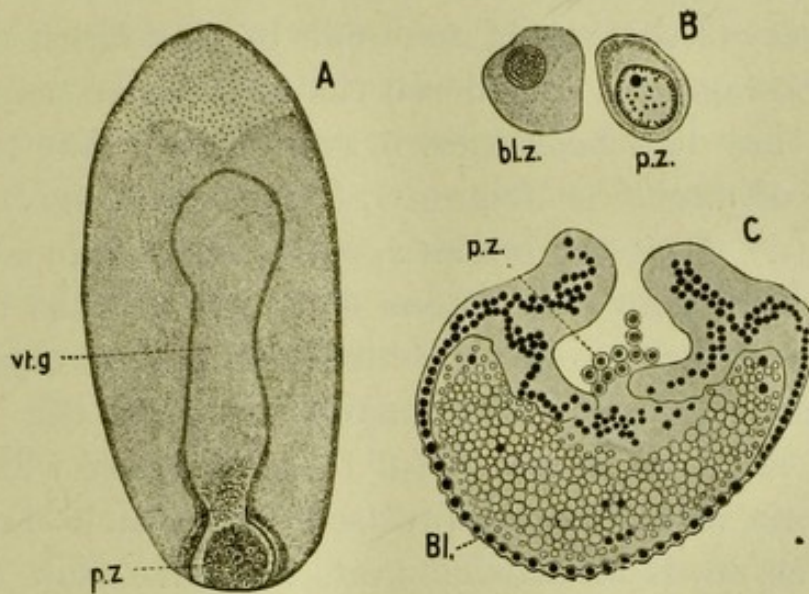


FIG. 25.—Preparations from the egg of a beetle, *Leptinotarsa*. A, the whole egg after completion of segmentation, at the posterior end one sees the accumulation of the superficial sexual cells, *p.z.*, $\times 50$; B, two cells, $\times 850$; *bl.z.*, ordinary somatic or blastodermic cell; *p.z.*, sexual cell (pole cell). C, section through an egg, $\times 105$; *Bl.*, blastodermic layer of somatic cells; *p.z.*, sexual cells which migrate into the interior of the egg, in order to enter the sexual gland proper.—After R. W. Hegner.

pass into the sexual gland. The investigation of R. W. Hegner²³ of Wisconsin University offers us the most exact account of the history of these cells which we possess as yet. From his paper the pictures in Fig. 25 have been taken. The pole cells of Robin are sexual cells which separate precociously from the somatic cells, and after they have completed their migration, change in the sexual gland into sexual elements.

We know for animals as for plants a physiological cause

for the remarkable alterations which produce from a sexual cell, as the case may be, an ovum or a spermatozoon. In the fifth lecture we shall return to the consideration of the visible alterations during this transformation.

Let us now assume that we have eggs and spermatozoa, and occupy ourselves with their further history. Science has acquired correct notions of these elements very gradually. A hundred years have not yet passed since the publication of the discovery of the eggs of mammals by Carl Ernst von Baer. Eighty years ago one considered the spermatozoa as parasites, although they had been known since 1628. The investigations of Koelliker first demonstrated the true significance of spermatozoa. That the semen acted to fertilize ova has been long known, but so long as one did not know the male and female sexual elements of the higher animals one could have no clear conception of reproduction. During the period of ignorance all sorts of wonderful theories arose, which, however, had no value because precisely that which they should explain was, in its essentials, unknown. We must express a warning against theories of this sort, because even to-day we are much inclined to make up for lacking knowledge by theories. It was not until the seventies of the previous century that it became possible to understand the rôle of sexual elements in reproduction through the epoch-making investigations of the gifted Oskar Hertwig. Hertwig was at that time Privatdozent in Jena, and I rejoice that it is permitted me to express here the admiration which all biologists bestowed on his discovery. Hertwig showed that fertilization consists essentially in the union of one spermatozoon with one ovum. Since the ovum is very large in proportion to the male element we are accustomed to describe this union as the penetration of the spermatozoon into the

ovum. Hertwig investigated various species of eggs and observed the same fundamental phenomena in them all. Out of the head of the entering spermatozoon there arises a nucleus-like structure or pronucleus. Before or during impregnation the nucleus of the ovum loses a portion of its contents by a process which we call the phenomenon of maturation. The part of the nucleus of the ovum which remains forms the female pronucleus. The two pronuclei unite and form a new complete nucleus. The fertilization is now accomplished, and further development begins. The fertilized ovum divides, and so does also the so-called segmentation nucleus, which owes its origin to the fusion of the two pronuclei. We see therefore that substances from the maternal side and from the paternal side are employed for the act of propagation. A new individual obtains its life from both parents. In this case also the history is uninterrupted.

W. H. Moenkhaus,²⁵ Professor in the University of Indiana, has furnished us the most brilliant proof of the accuracy of the assertion just made. He reared the hybrids of two fishes, *Menidia* and *Fundulus*. The chromosomes of *Menidia* are noticeably smaller than those of *Fundulus*. In the hybrids Moenkhaus discovered both forms of chromosomes appearing clearly at the time of cell division. This extremely interesting case teaches us by direct observation that living substance from both parents propagates itself in the progeny in visible form.

At the beginning of today's lecture we cited the Latin saying "*omne vivum ex vivo*." It required the prolonged researches of many investigators to reveal to us the ways which living substance adopts in order to continue without a break. The relations may be easily recognized in asexual reproduction, but in the case of sexual reproduction we must

ascertain the history of the sexual cells, the occurrence of sexual elements in all animals, and the internal processes during fertilization, in order to establish the necessary foundation for the modern doctrine of immortality. From the numerous researches made, we draw the safe conclusion that living beings consist of protoplasm and nucleus which have arisen from earlier living protoplasm and earlier living nuclei. The animals and plants of today exist only because protoplasm in itself is immortal. Only when protoplasm changes itself or is destroyed by external influences does it die. To us the verse "*omne vivum ex vivo*" means the immortality of protoplasm.

This fact procures us a better insight into heredity. It is well known to us all that every living species maintains itself with slight alteration. This phenomenon signifies to us that protoplasm possesses the capacity, when supplied with food material, to produce more protoplasm of the same constitution as itself. We can offer no further explanation of this wonderful capacity. For us it is merely a fact which, however, offers us a theory of heredity, namely that the progeny are similar to their parents because they are developed from the same protoplasm. The creation of a new generation appears to us merely as the continuation of the activity and growth of the previous generations.

There has been no lack of theories of heredity. The best of the older theories in my opinion is that of Darwin, which he termed "pangenesis." He assumed that the cells give off little granules or atoms which circulate freely through the whole body and which, when they are supplied with the proper nutrition, multiply themselves by division and then may later develop into cells. Darwin for the sake of clearness has named these granules "cell gemmules," or

simply "gemmules." He assumed that they pass over from the parents to the descendants, and usually develop themselves in the first generation. Darwin's pangenesis explains heredity. It is the hypothesis of a master, and as a succinct and comprehensive explanation of the facts of heredity must always command admiration. Since Darwin's time many modifications of the doctrine of pangenesis have been proposed. These modifications, however, possess for us merely historical interest, for with the progress of science they have become superfluous.

The new doctrine of heredity is due to Professor Moritz Nussbaum, who laid special stress upon the discovery of the germinal paths in animals, for he recognized in these an arrangement to separate special germinal cells from the somatic cells. He concluded that a portion of the germ-plasm is withheld from the developing ovum, kept comparatively unaltered, and employed for the formation of sexual elements, so as to become directly the germ-plasm of a new generation. It is clearly superfluous to still employ the expression germ-plasm which corresponds to speculative needs, and which we may now leave out of consideration. It is simpler to speak merely of living substance. Nussbaum's theory has in the course of time become, strictly speaking, the only theory of heredity which we value.

If the time at our disposal permitted, it would be interesting to analyze carefully some of the theories of heredity which have arisen in association with Nussbaum's doctrine. The majority of these theories search for a special germ-plasm, to use Weissmann's expression. Nägeli speaks of idioplasm. Some authorities have sought to bring heredity into relation with visible parts of the protoplasm or of the nucleus. Oskar Hertwig was the first to interpret the nucleus as the organ of

heredity, a view which many eminent investigators have since defended. We must today admit that the nucleus plays a part in heredity, but not an exclusive rôle. The investigations of two Americans, Conklin²⁶ and Lillie,²⁷ furnish the proof that in certain cases distinct regions can be distinguished in the protoplasm of the undeveloped ovum. When the development proceeds each of these regions plays a special rôle in the formation of the body. It is possible to alter the normal distribution of the substances, which are characteristic for the regions, without killing the ovum. This is accomplished by the centrifuge. Conklin has succeeded in observing in centrifuged eggs that the substances, which have acquired a new position in the ovum, nevertheless form the same structures as before. From these observations he draws the just conclusion that organ-forming substances are present in these ova from the beginning. That which arises in the course of the development of the new individual is, in these cases, certainly determined at least in part by the protoplasm of the ovum. Hence we must admit that the protoplasm also participates in heredity. I do not see how we can accept the theory that the nucleus is *exclusively* the organ of heredity. On the contrary we must say that the essence of reproduction is the continuation of the growth of immortal protoplasm. The history of protoplasm is uninterrupted, and therefore we say: the immortality of the protoplasm and of the nucleus is also the explanation of heredity.

IV.

THE EVOLUTION OF DEATH.

Mortality was formerly regarded as the necessary end-phenomenon of life. It was not until our own times that it appeared probable to us that so-called natural death does not occur with all organisms.

The development of the higher plants and animals begins with the fertilized ovum. By continued division such an egg produces the cells which form the plant or animal, as the case may be. Many years ago Huxley defended the thesis that all cells which arise from a single ovum belong together and constitute a cycle. He further proposed to regard all the cells of a single cycle as constituting the individual proper. The problem of individuality, however, which formerly often occupied thinkers, has lost much in interest and significance, owing to the progress of biology. In the higher animals as in the unicellular, we encounter real individuals, but in the lower multicellular animals we recognize on the contrary no distinct individualities. Thus, for example, in the case of corals and sponges, we cannot speak of individuals. Under these conditions Huxley's conception of the cycle was very seductive to biologists. It could apparently be very well applied to the unicellular organisms because in many of them conjugation had been observed. Conjugation is a phenomenon closely related with sexual reproduction. It was assumed that conjugation served to excite the cell division of unicellular organisms. If conjugation and the fertilization of the ovum are homologous phenomena, then we are justified in regard-

ing in both cases the exciting of cell division as the immediate consequence alike of conjugation and fertilization. In both cases there would arise homologous cycles of cell generations. Thus we should have to deal in both types of organisms with individuals in Huxley's sense. The only difference between the two types, which from our present point of view must be regarded as important, is that the cells in the lower type separate from one another, while in the higher, on the contrary, they unite to form a plant or animal. Death, as we ordinarily observe it, is the breakdown of a multicellular organism, and natural death is a consequence of old age. This consideration leads us directly to the question: Do old age and natural death occur in unicellular organisms? Weissmann, who has written several times concerning death, has not conceived the problem rightly, so that his discussions of death go astray in several essential respects.

The first serious experiments to determine by direct observation whether old age occurs in unicellular animals were carried out by the French investigator, Maupas.²⁸ He reared Protozoa through many generations. Of each generation he took a few individuals, allowed them to propagate themselves and noted the rapidity with which the divisions followed upon one another. He found that the rapidity diminished until a new conjugation occurred, whereupon the animals recovered. Later tests of these results have shown that the experiments of Maupas were open to criticism, in part because at that time the great influence of external conditions upon Infusoria was unknown, so that the possibility remains that the retardation of the division he observed was conditioned not by internal but by external causes. Further, in order to bring about conjugation, he introduced into his cultures newly captured, wild individuals. His cultures, there-

fore, were not kept strictly pure. In America a long series of researches on the rapidity of division in Protozoa has been made, largely upon the instigation of G. N. Calkins,²⁹ who discovered that Infusoria may suffer "*depression*," a result which has been confirmed by further investigations of his own, of his pupils, and of other American investigators. The depression arises gradually, the animals become inert, nourish themselves poorly, and divide slowly or even not at all. If the depression lasts too long the animals may die off. Calkins considered the depression to be senescence, or a growing old. (He has since himself questioned the justness of this interpretation.)

Our conception of senescence is based on the observation of the higher animals and plants, and comprises not merely the increasing weakness, but also alterations in structure which go far and are very striking. The Infusoria during their depression show no corresponding alterations of their organization; hence in my belief we cannot homologize this phenomenon in the Protozoa with the senescence of higher animals. In this belief we are confirmed by the fact that the newer investigations of conjugation make it improbable that it serves to renew and hasten the growth and division of unicellular organisms. Indeed, it is possible that conjugation does not have this function at all. Significant here are the studies of the very talented investigator, H. S. Jennings,³⁰ which demonstrate that conjugation serves to increase variability. Jennings observed that *Paramecium* exhibit considerable variability. During ordinary division the individuals remain more alike, but after conjugation their variation increases. His careful statistics leave no doubt as to his results. It is probable that sexual reproduction also has the purpose of maintaining the variability of the forms. The interperta-

tion that impregnation has the purpose of increasing variability in order to offer room for the play of natural selection originated with Weissmann. (It is said that Treviranus had previously expressed this view, but I have as yet been unable to personally confirm this statement.) Impregnation has also certainly to care both for heredity and for the initiation of further development. We know now that these functions may be separated experimentally. If sexual reproduction be conceived as a modification of conjugation, then we may assume that the function of initiating development was acquired later. Returning to the Infusoria we encounter in them, so far as the available observations go, a so-called depression indeed, but no senescence in the strict sense. (Quite conclusive as to the absence of senescence are the experiments of L. L. Woodruff,* who has maintained a pedigreed race of *Paramecium* for five years without conjugation. If all the possible individuals had survived, they would have made a volume of protoplasm many million times the volume of the earth).

Calkins, as said above, originally interpreted depression as a true senescence and declared the diminution of metabolism to be the essential characteristic of old age. This view has been adopted by C. M. Child³¹ and E. G. Conklin.³² Professor Child has made experiments with a simple worm, *Planaria*. He treated these animals with alcohol by placing them in water to which 1 per cent. of alcohol had been added. The results he obtained are interesting and valuable. He seems to me, however, to go too far when he asserts that if the metabolism diminishes the animals become old. It is true that in the higher animals, when they become old, met-

* L. L. Woodruff: *Biologisches Centralblatt*, XXXIII, p. 34, 1913. Professor Woodruff has informed me that on April 3, 1913, he had the 3650th generation of the mentioned *Paramecium* colony.

abolism becomes slower, but certainly one cannot therefore assert that every lessening of the metabolism implies a becoming old. According to the sum total of our knowledge we must regard organization as the cause of function. This is the only interpretation which a physiologist may admit. When therefore an organization is so altered that the metabolism diminishes, this diminution has to be considered a consequence and not a cause. Metabolism, however, is influenced by many factors, as every practicing physician experiences daily. If we accept Child's opinion we are led logically to the conclusion that each one of us may become alternately young and old according as his metabolism increases or diminishes. We should have to say, for example, that a man who performs strenuous and muscular work was rejuvenated, while on the contrary one carrying on mental work, during which the metabolism is less, might become older. It seems to me clear that we cannot interpret the diminution of the metabolism as a characteristic of age in the sense of Calkins. In other words, we cannot view the depression in protozoa as senescence. Thus we reach the conclusion that natural death, so far as we know at present, does not occur in unicellular organisms, and as a consequence of this we mention the corollary that natural death first appeared in the world as the higher multicellular plants and animals were evolved.

We pass now to the examination of senescence in the higher animals, a theme which has claimed my active interest for many years. If we consider the phenomena as they are known to us all, we recognize at once that a diminution of the rapidity of growth is characteristic of age, and thus we are induced to investigate growth. Obviously we must determine how the rapidity of growth alters with advancing age. For such an investigation it is important to exclude the influence

of temperature, which is known to have a great influence upon growth. Nature makes this exclusion for us in the case of warm-blooded animals. I selected for my own experiments on warm-blooded animals guinea pigs for various practical reason and I maintained a colony of these animals for many years. Every animal of the colony was weighed at definite intervals of age. After many thousands of determinations of the weight

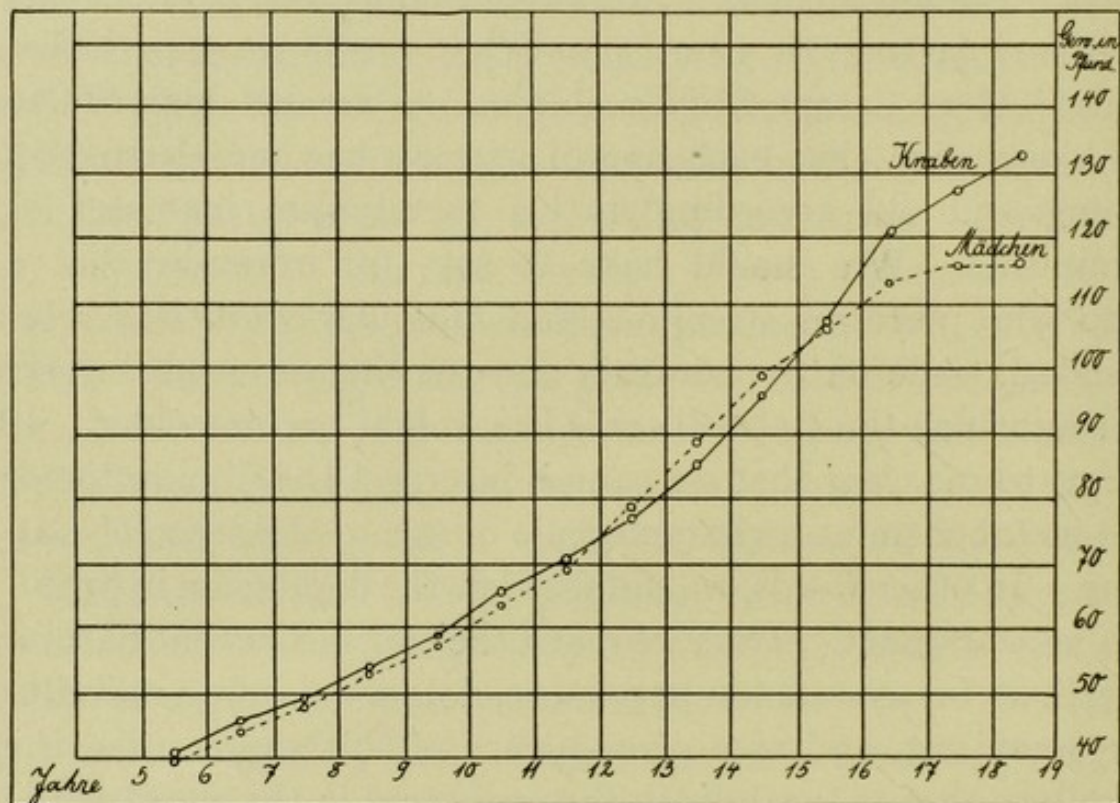


FIG. 26.—Graphic representation of the increase of weight in children of the Boston schools.—After H. P. Bowditch.

(Knaben, boys. Mädchen, girls. Jahre, years.)

had been collected, they were worked over statistically.³³ My first problem was to invent a method which permitted the representation of the rate of growth. Formerly investigators were satisfied to represent growth graphically in a very simple way. Curves were constructed in which the abscissæ corresponded to the age, and the ordinates to the weight, Fig. 26. Such a curve, however, although it represents the

increase of weight, does not show the rate of growth. The real rate can be represented in the following manner with approximate accuracy. From the weight which an animal has on a given day and that which is found at the next weighing, I reckoned the average daily increase during the period between the two weighings, and then changed these increases into the per cent. value of the weight at the beginning of the period. This method may be modified by calculating instead of the daily, the monthly or yearly percentage increases.

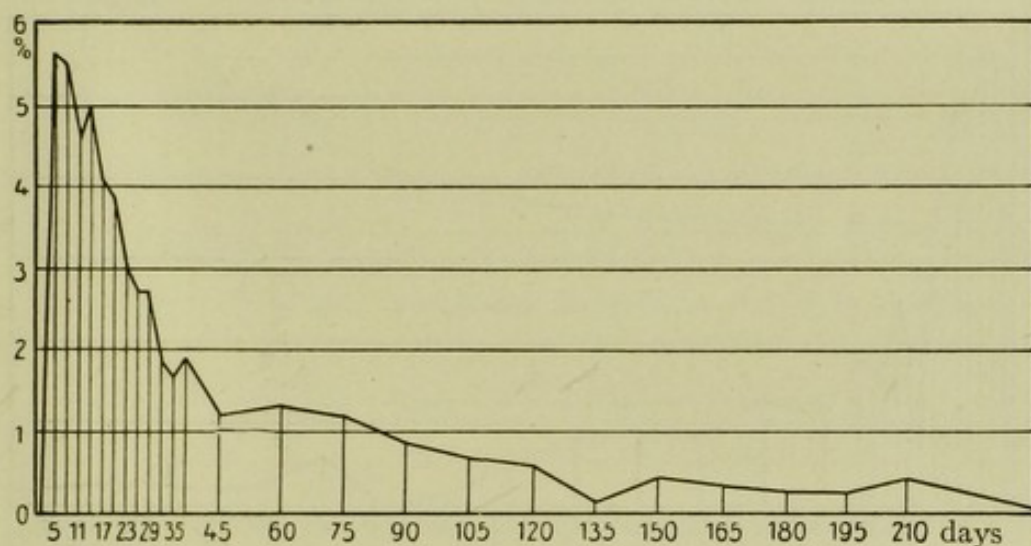


FIG. 27.—Curve of the daily percentage increase in weight of male guinea-pigs.

The method is of course mathematically not exact, since the weight is constantly changing. It suffices, however, for our purposes. It is easy after one has calculated a series of percentage increments in weight to construct a curve. The results obtained in this way I wish to lay before you. When guinea-pigs are born, they suffer in consequence of the great sudden disturbance of their conditions of living a temporary inhibition of their development. They recover within two or three days, and thereupon we observe that they may increase their weight over 5 per cent. in one day, Fig. 27.

By the time they are seventeen days old, they grow only only about 4 per cent. and at forty-five days only a little more than 1 per cent. and from this age on the rate of growth sinks slowly until at the end of the first year it becomes almost zero. The general process is the same in females, Fig. 28, as in males, although certain inequalities occur. It is obvious that if we consider the curves, Figs. 27 and 28, carefully, we can distinguish in them two chief periods, which, however, pass into one another without definite boundaries.

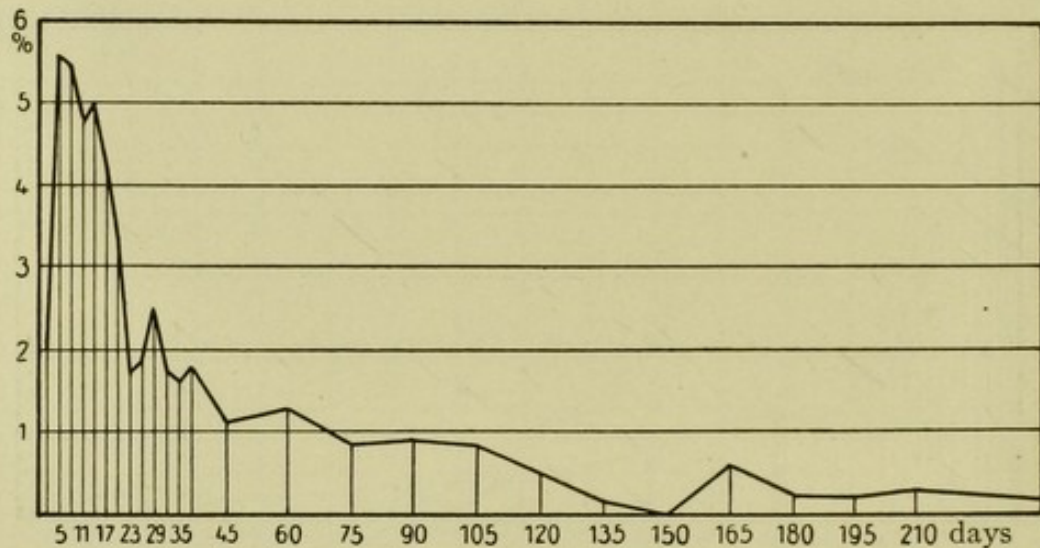


FIG. 28.—Curve of the daily percentage increase in weight in female guinea-pigs.

In the first, shorter period, the rate diminishes rapidly. This period lasts about one and a half months. The second period exhibits a much slower decrease and lasts perhaps ten months. The result was unexpected. If we accept the rate of growth as the measure of senescence, we must say that young animals grow old enormously faster than old animals. Since alterations in the rate of growth of guinea-pigs progress as described, it was to be expected that in still younger stages of development the rate of growth would be found still greater. Now chickens when they enter the world are not so far

developed as guinea-pigs, and much less far developed are newborn rabbits. I have determined the rate of growth in both of these animals, and found that chickens, as soon as

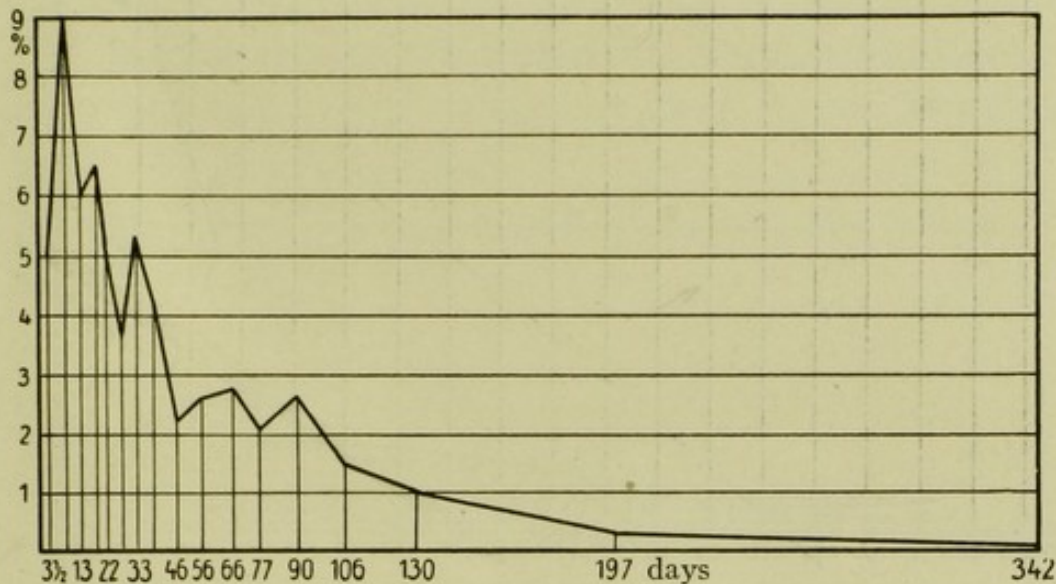


FIG. 29.—Curve of the daily percentage increase in weight in male chickens.

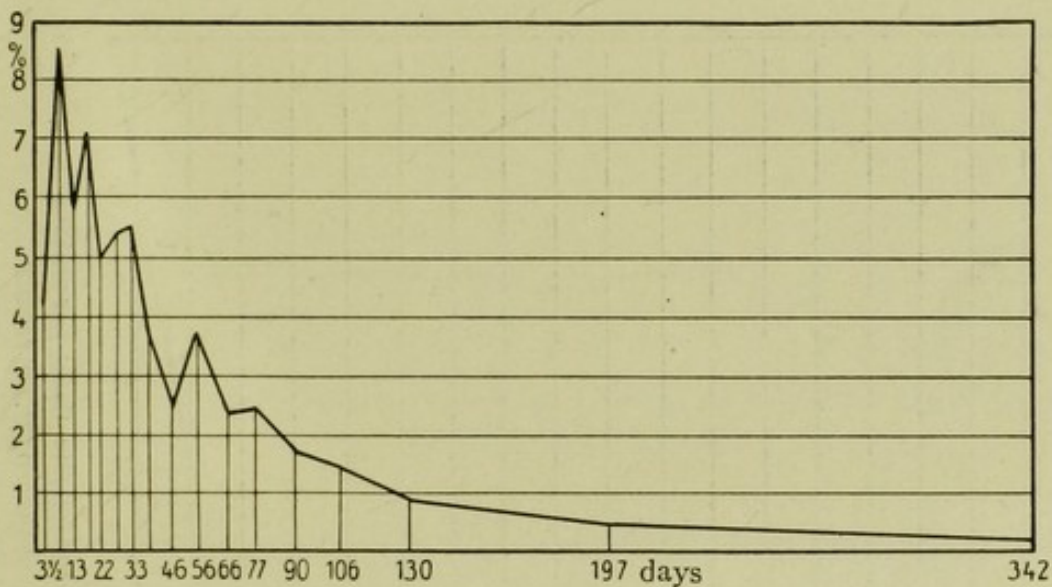


FIG. 30.—Curve of the daily percentage increase in weight of female chickens.

they have recovered from their hatching, may grow as much as 9 per cent. per day, which is much quicker than the guinea-pigs grow. The values for the two sexes are practically equal,

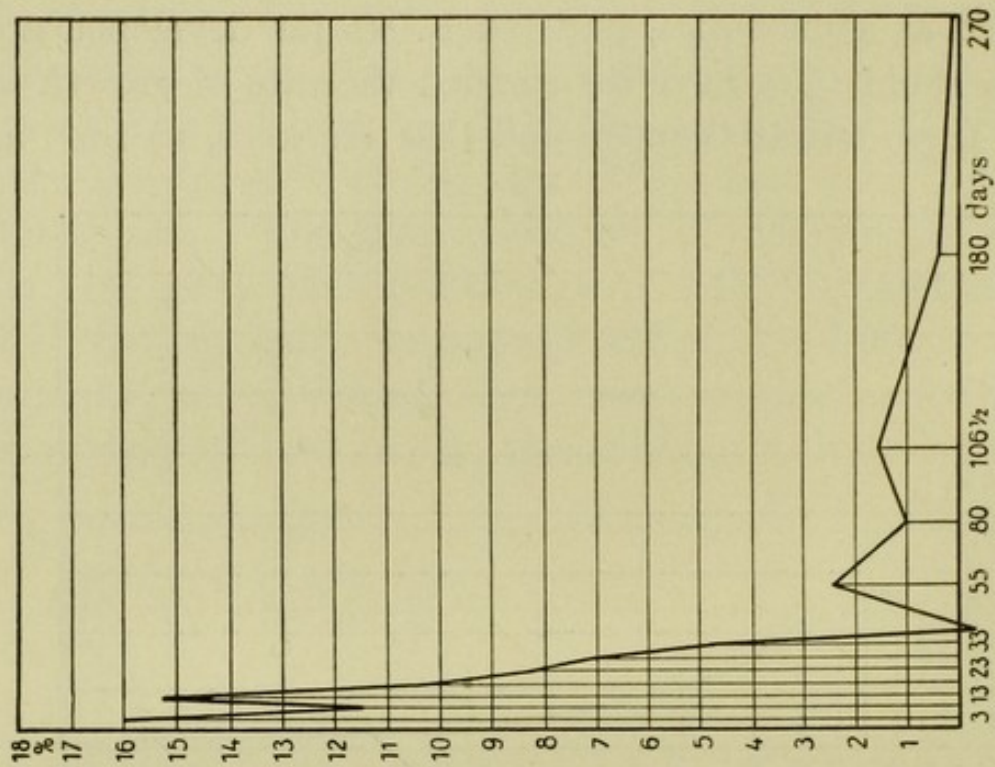


FIG. 31.—Curve of the daily percentage increase in female rabbits.

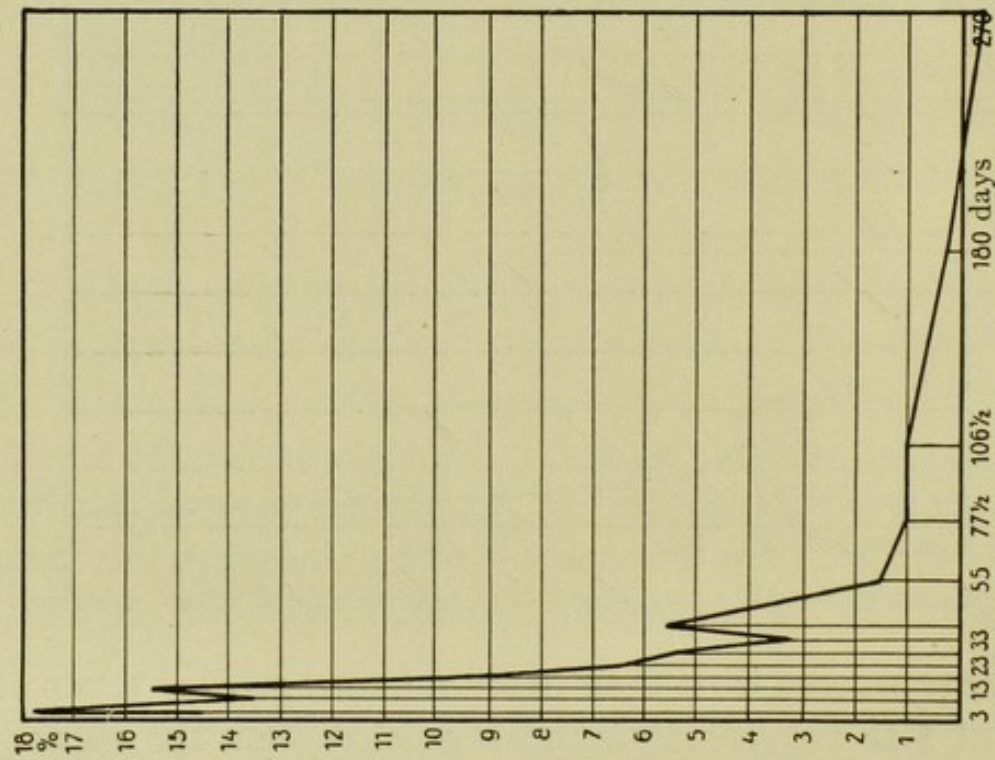


FIG. 30a.—Curve of the daily percentage increase in weight of male rabbits.

Figs. 29 and 30. Even more striking is the rate in rabbits, which immediately after birth may reach for the males almost 18 per cent. per day, and for the females 16 per cent., Fig. 31, *A* and *B*.

We encounter similar phenomena in man, but since man grows much more slowly than the three species of animals,

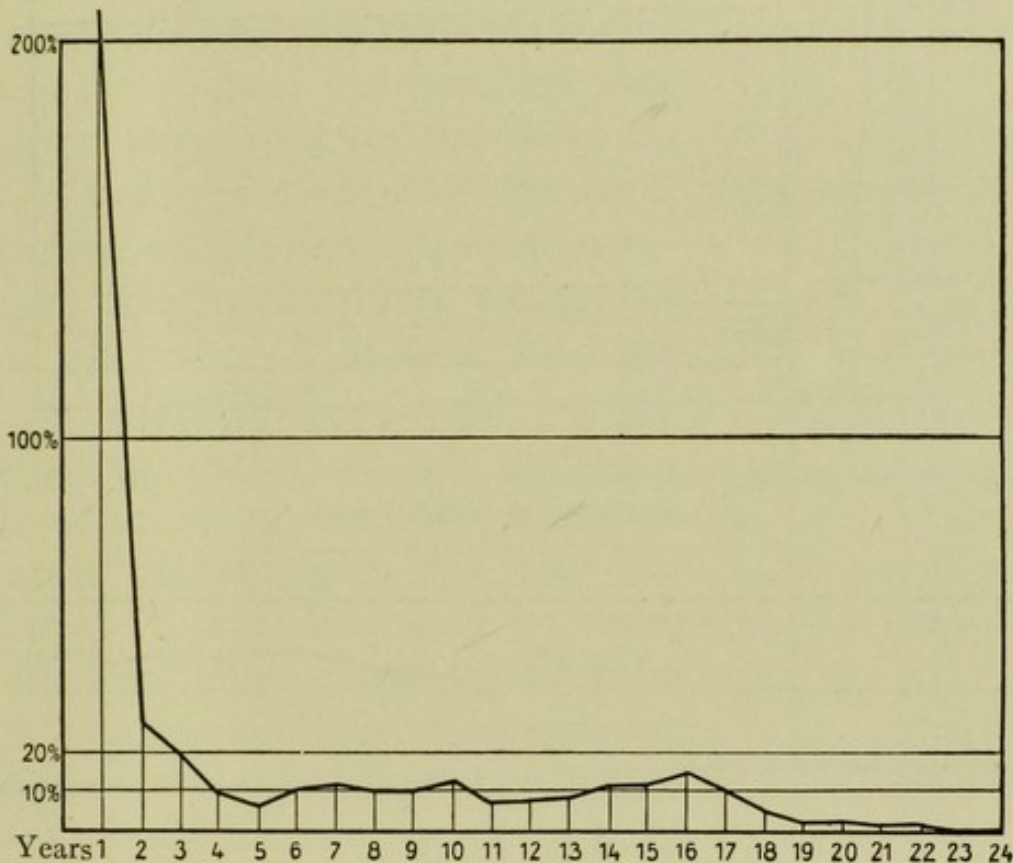


FIG. 32.—Curve of the yearly percentage increase in weight of boys.—*Reckoned from H. H. Donaldson's table.*

the growth of which we have studied, I have reckoned the increases as yearly percentages, Fig. 32 represents the rate of growth for boys, Fig. 33 for girls. The curves fall at first with great rapidity, later much more slowly. Fig. 34 shows the alterations in the rate of growth in another form. The curve corresponds to the observed average weights in the male

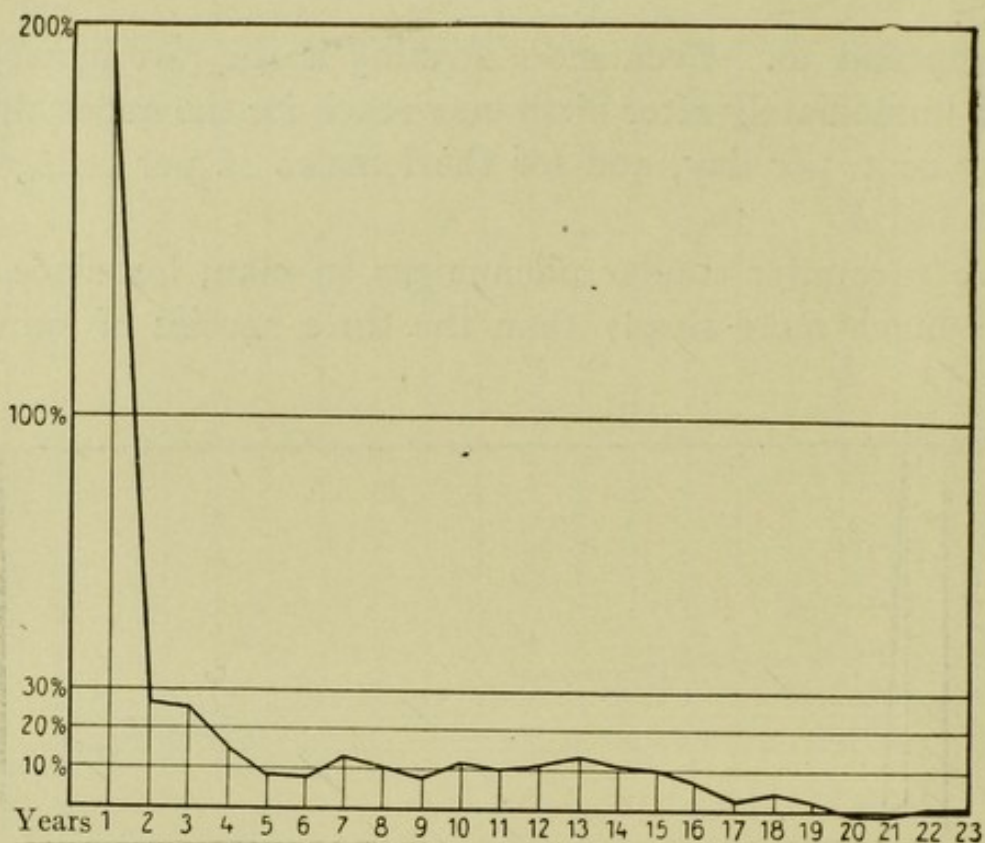


FIG. 33.—Curve of the yearly percentage increase in weight of girls.—*Reckoned from H. H. Donaldson's table.*

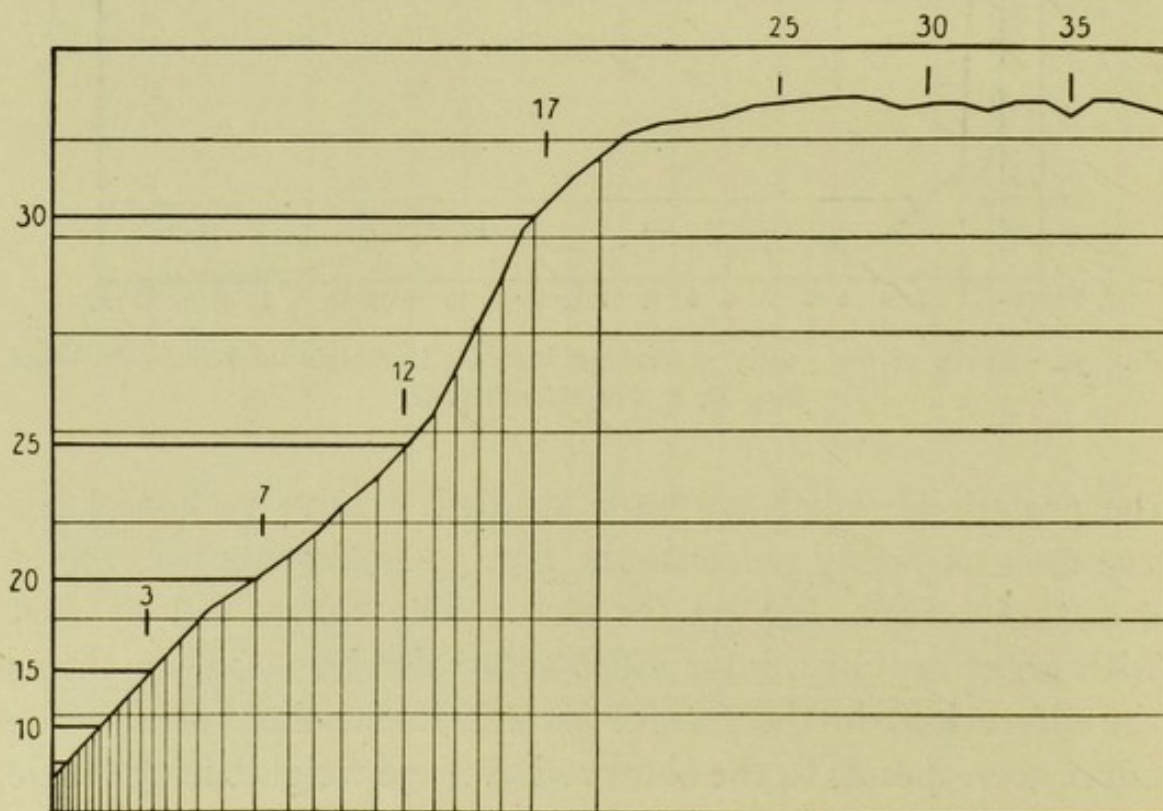


FIG. 34.—Curve of human growth in weight, with vertical lines to mark the duration of 10-per-cent. increases.

sex up to the age of forty years. The vertical lines indicate by their distance from one another what interval is required to permit each time a 10-per-cent. increase of the weight.

We may proceed further and study growth during the embryonic period. Unfortunately this has not yet been done so thoroughly and exactly as for the development after birth. Nevertheless we can assert now that the growth of embryos proceeds faster, Fig. 35, in younger embryos, and that in very young embryos the daily increase is simply enormous. For, as I have demonstrated on a previous occasion, it may reach in very young embryos the value of at least 1000 per cent. Professor Donaldson³⁸ of the Wistar Institute has already published more exact data as to the weight of embryos of the white rat. He has collected further data, and we may expect from him a detailed memoir on embryonic growth. He has completely confirmed my result that there occurs an enormous decrease in the rate of growth during embryonic life. These investigations lead us to the conclusion that the diminution in the rate of growth occurs chiefly during the first developmental periods, and that the diminution after birth is very gradual. Hence if we seek for the cause of this diminution, the facts indicate that we should investigate the conditions during embryonic life because this is the period of loss. We

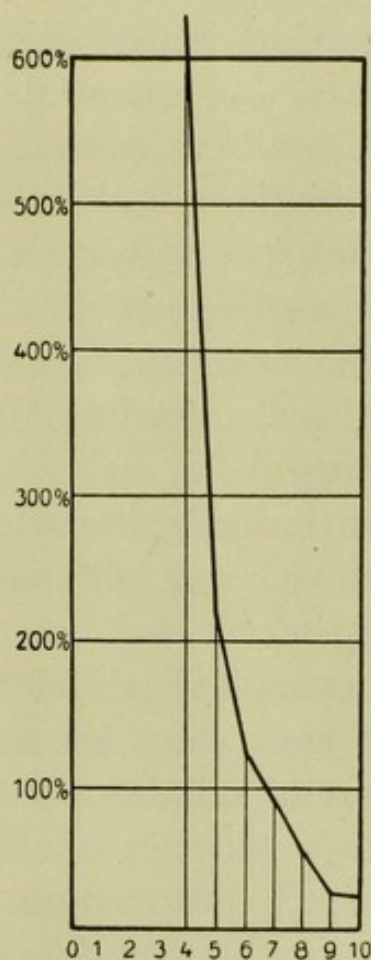


FIG. 35.—Curve of the monthly increase in weight of the human embryo.

may therefore expect that the changes which cause the diminution will be more noticeable in embryos than in older animals.

I have not succeeded in determining with absolute certainty the cause of the inhibition of growth. We find, however, a close correlation between the alterations which occur in the cells of the embryo and the inhibition, which renders it probable that the alterations of the cells are at least one essential cause of the diminution of the growth. The alterations which here come into play are those of differentiation, and in fact differentiation proceeds in young embryos with extraordinary rapidity and in older embryos more slowly. At the time of birth the differentiation is for the most part far advanced, and thereafter continues extraordinarily slowly. Up to the present at least it has been impossible to express our observations of the rapidity of differentiation in statistical form because we do not yet know how to measure differentiation quantitatively. We can merely estimate the degree of differentiation. In spite of the incomplete reliability of this method, I believe that the estimate which has been made answers to the truth. That a causal relation exists between the diminution of differentiation and the rate of growth is confirmed by the fact that direct observation teaches us that undifferentiated cells may divide rapidly and that differentiated cells divide more slowly, and finally that the most completely differentiated cells do not divide at all. The indicated considerations have led me to the conclusion that differentiation is to be considered the essential cause of senescence.

I have already asked you to give heed to the fact that differentiation occurs principally as a transformation of protoplasm. At the same time we learn that in order to render the

differentiation possible the protoplasm must grow in order to furnish the basis for the differentiation. Hence I should like to give the above conclusion the following form: *Senescence is caused by the increase and differentiation of protoplasm.*

The correctness of this conclusion is strengthened by the fact that we find the opposite relations in young cells which have characteristically a nucleus with little undifferentiated protoplasm. During the development of the ovum there arise at first relatively large cells which develop further, and through numerous generations became steadily smaller. Since the ovum usually contains a nutritive yolk, the cells grow by assimilating the yolk. The brilliant investigations of Conklin³² have shown that during the segmentation of the ovum not only is the total amount of nuclear substance increased, but also the total amount of protoplasm in the strict sense. It comes about, however, that the increase of the nucleus is relatively greater than the increase of protoplasm. Conklin determined in *Crepidula* that in the two-celled stage the nuclei form only 0.0117 of the total volume of the ovum, but in the twenty-four-celled stage they form 0.0255 of the volume. Soon there follows a stage with really young cells, as I have above defined them. We distinguish two chief periods of development. The first is much the shorter and is characterized by the preponderating increase of the nuclei. The second is much longer and is marked by the growth and differentiation of the protoplasm. The first is the period of rejuvenation, the second the period of senescence or growing old.

A remark must be here intercalated. The rate of growth and of the division of the cells does not depend solely upon the organization of the cells itself for the time being. The degree

of potential capacity to grow and to divide is presumably fixed by the organization of each cell, but there occur in the body inhibiting influences, perhaps also exciting. Thus it may happen that a cell potentially capable of division cannot divide, or that a cell which has long remained inactive may be excited to division by special newly arisen influences. The phenomena are by no means simple.

The theory of senescence which I have expounded to you was proposed, as you have heard, by myself. All achievements of science originate in this way. They are at first purely personal. Afterward when they have been tested they acquire general validity. And so with regard to my theory, until the discussion is concluded we must wait in order to decide whether this theory or some other which may be brought forward is to be finally adopted.

Some of the theories of senescence we may now discuss briefly. That of Conklin has been previously mentioned. I have already indicated to you the reasons which lead me to designate these theories as insufficient. There are besides a number of theories which have been conceived from a purely medical point of view, and which are little adapted to satisfy a biologist. First of all must be named the theory of Metschnikoff, of which probably all cultivated men have heard. The Russian investigator, who has been working for many years in the Pasteur Institute in Paris, published in the year 1903 a peculiar book with the title, "*La nature de l'homme.*" With the views of life presented therein, we have at present nothing to do. We restrict ourselves to the discussion of the theory of disharmonies presented in this book. According to Metschnikoff, a disharmony arises whenever the structure of an organ is incompletely adapted to the needs of the body. The disharmonies he mentioned do not seem to me very

important, for they refer for the most part to structures whose physiological significance we do not know. It is venturing much to conclude from our ignorance that a disharmony exists. To one physiological disharmony, which he believes he has discovered, our author attributes the very greatest importance. He is of the opinion that our large intestine is too large, and that there occur in it fermentations which produce toxic substances which then act to poison the body. He believes further that these unfavorable conditions become very serious in man with increasing age, and he attributes especially to them the difficulties of the very old. In order to avoid these weaknesses he recommends a treatment which, according to him, is adapted to the suppression of the fermentations in the large intestine. The treatment is simple, for it consists in drinking sour milk. According to his theory the germs pass with the milk into the intestine, where they inhibit the toxic fermentations. It has become in the highest degree improbable that the fermentations in the large intestine have the significance ascribed to them by Metschnikoff, but even if he is right his discovery brings no explanation of senility, as indeed senescence is a very widespread phenomenon and occurs also in animals and plants which have no large intestine.

With how little seriousness Metschnikoff has formulated his theory will be clear to anyone who reads an article by the American physiologist, C. A. Herter.³⁴ Herter, whose early death means a heavy loss for science, showed that we have as yet no proof that sour milk has any influence whatever on the bacterial flora of the large intestine, and also no proof that such an influence would be rather beneficial than injurious to man. The problem of intestinal fermentations is exceedingly complicated.

A similar criticism may be directed against the current medical theory of growing old which seeks to explain the observed weaknesses and difficulties of old men by the condition of their blood-vessels, especially of their arteries. Thus Osler has said a man is as old as his arteries. This view rests upon clinical experiments, for in fact the disturbances in the case of senile weakness, which are occasioned by the altered structure of the walls of the vessels, are especially noticeable and yield valuable symptoms for the diagnostician. We have, however, to do with the consequences, not with the causes, of senility.

Professor Mühlmann has also written repeatedly concerning extreme old age and his memoirs contain many interesting and valuable statements. He offers us also an explanation of senility. The latest memoir of Mühlmann³⁵ of which I know, and which must be here considered, appeared in the year 1910. In it he discusses my theory. The present opportunity does not appear to me suited to discuss Mühlmann's critic fully and to answer it. Permit me to direct your attention to it, because quiet discussion leads to the settlement of scientific problems. I venture to add that I am still convinced that my view can be successfully defended against Mühlmann's attack. Mühlmann writes, strictly speaking, from the medical point of view, or in other words from an anthropomorphic point of view. He is concerned with rendering the phenomena in man more comprehensible without having regard to the corresponding phenomena as they occur in living organisms in general. Investigations which are conducted by such thoughts as we know from experience lead to valuable results. They can, however, only exceptionally bring forth results which are completely satisfying to biologists. Mühlmann attributes

special importance and meaning to the outer surfaces of the body, and to the consequences involved in the greater or less remoteness of the single parts of the body from the outer surfaces. It is very possible that these results have significance for the physiological activities of the body, and it is not improbable that with the increasing age the proportion of the outer surfaces to the rest of the body becomes unfavorable. This interpretation with other related suppositions is presented by Mühlmann. He believes further that the mentioned results act to the disadvantage of the central nervous system by which the gradual destruction of this system is caused, a destruction which progresses until it brings about natural death. Mühlmann's demonstration is not convincing to me, but even if we should grant that he is right, and accept his conclusion that natural death in man is directly caused by degenerative alterations of the nerve cells, we should still not have won a general biological theory of death. As we have already heard, the death of cells plays a great rôle during development as well as in the adult. Any theory of death must reckon with these facts and cannot be sufficiently valid if it does not explain both the natural death of the whole body and also the natural death of the cells which are continually dying off. It is a merit of the theory of cytomorphosis that it maintains its value as an explanation of all forms of death.

We owe to Alexander Götte³⁶ another theory which I wish to mention briefly. According to this theory, natural death is closely connected with the phenomena of sexual reproduction, for it assumes that the maternal organism is exhausted by the effort of reproduction, which thus causes the appearance of old age. We must pay attention to the fact that it was not until after the appearance of Götte's article

in the year 1883 that we have become acquainted with the history of the germ cells. Since these cells, properly speaking, develop independently of the somatic cells, it becomes very doubtful whether they can exert any such influence on the body as Götte's theory requires. Moreover, the fact that a man may live long in health after the reproductive capacity is lost speaks against the theory. The theory of Hansemann³⁷ may be considered to a certain extent as a modification of Götte's. Hansemann seeks the immediate cause of physiological death in the atrophy of the germ plasm, but, as we know, senescence is not a phenomenon which begins at the end of life, but a continuous one which proceeds in young individuals also. It is therefore clear that we cannot explain becoming old by an event which does not occur until the individual is already old.

The various hypotheses which we have just discussed have this in common, that they seek to explain only the death of the whole body, and do not investigate the question of death as a phenomenon of cell life. The theory of cytomorphosis differs from the mentioned theory precisely therein that it regards death as a phenomenon which occurs in single cells. It is, if I am right, the only theory which we possess up to the present time which answers to the demands of biology.

As to the development of death we know little as yet. Naturalists assume that unicellular organisms were developed in the world earlier than the multicellular, or in other words, that they are more primitive and older. We must therefore assert that the first living cells were potentially immortal, as is at present the case for their existing representatives. From this it follows that natural death appeared later. It seems to me probable that death as we now know it in the human race was evolved gradually. In sponges and coelenterates we find

no individualities as in the higher animals. A part of a sponge or of a coral may die and the other part continue living, because the correlation of the parts has not advanced so far, but in these animals preservation of the whole is independent of the preservation of the correlation. In the higher animals the correlation is much more intimate, and therefore individuality more marked, until we reach an animal whose parts work together and must reach definite proportions in order that the working together may be properly carried out. An organism which has attained higher development in this way cannot continue its life if an essential part or an essential organ becomes incapable of functioning. We know that the single organs must have their specific differentiation, and we know further that these differentiations in the majority of cases increase with age, and that it may go so far that the cells of a special organ cannot function any longer. Now if an organ which is essential for the maintenance of the whole body gives out, the entire animal must die. It is *a priori* improbable that in all cases natural death is a consequence of the alterations of the same organ. Thus we know that in certain insects and worms death occurs almost suddenly after the discharge of the sexual products, yet their nervous system may be intact. We may admit that physiological death in man is caused by the breakdown of the nervous system, and yet the practicing physician sticks to his opinion that death in extreme old age occurs more frequently through failure of the blood vessels. We must heed the fact that even in the highest animals, just as in sponges and coelenterates, parts of the body may break down without causing physiological death. Permit me again to direct your attention to the fact that in man not merely single cells but even entire organs may die off. In its essence the phenomenon in these cases is the

same as that which we meet on a larger scale in the cœlenterates.

Has death a purpose? Weissmann has expressed the interesting thought that death is advantageous to organisms. If an organism lived forever it would become, through accidents, more and more injured. By death this is avoided, and at the same time by continuous reproduction the creation of new healthy individuals is provided for. I am, however, not inclined to regard death in itself as advantageous, but rather as a consequence of differentiation. The higher plants and animals have arisen through differentiation—to it we are indebted for our organization which makes us men; to it we owe the possibility of knowing our earth, its inhabitants, and ourselves; to it we owe all advantages of our existence; to it we owe the possibility of carrying on our physiological work much better than the lower organisms; to it we owe the possibility of those human relations which are the most precious of our experiences. These advantages and many others do we owe to differentiation, the price of which is death. The price is not too high. None of us would like to return to the condition of a lower organism which might be capable of continuing its species, and which had to suffer death only through accident. We pay the price willingly. Natural death comes, as we now know, when an essential part of the body yields. It may be the brain; it may be the heart; it may be another organ, in which the cytomorphosis goes so far that the organ can no longer perform the work assigned to it, and when it fails it brings the whole to rest. Thus the conception of death shapes itself in our minds. The mystery remains. The biologist knows the essence of death no better than the essence of life. We say of certain bodies that they live, of others that they are dead. Science at present is incapable of telling

us what the difference between these two conditions is, but we are learning every year more about life and more about death, and we hope that with coming years our biological science will so grow that she will make both life and death comprehensible.

V.

THE DETERMINATION OF SEX.

Your Excellency!

There is probably no phenomenon which has always seemed to mankind at once so interesting and so mysterious as sex. A history of the opinions, speculations, and customs which have arisen in the course of time in connection with the question of sex would be instructive. The progress of science has recently made us acquainted with the material basis of the phenomenon. The most important notion we have acquired is that of the difference between sex and sexuality. We derive our notion of sex from our repeated experiences in connection with man and with domestic animals. We know from our daily life that male individuals possess many peculiarities which the females do not have, and *vice versa*. By the application of the microscope we have discovered sexuality proper, which is not characteristic for the male or female body, but is peculiar exclusively of the sexual products. An animal or plant is a male or female according as the individual in question produces ova or spermatozoa (pollen grains). We note often that secondary peculiarities have been developed in connection with this fundamental difference. The secondary peculiarities are pronounced in man and the higher animals. One of the most interesting books which we owe to Darwin deals brilliantly with the problem of the origin of the so-called secondary sexual characteristics. They are really secondary and without doubt a consequence of the sexual

difference, the essence of which consists in the production of eggs or spermatozoa.

By no means seldom do we find animals or plants which are hermaphroditic organisms and produce both sexual elements. Biologists very commonly hold the opinion that hermaphroditism represents the primitive relation. Analysis of the relations, however, seems to me not to lead to this conclusion, and I propounded in 1892 the hypothesis³⁹ that originally every animal individual is sexually indifferent. Expressed in this form the hypothesis is not exact. It may be more correctly expressed thus: *This sexually indifferent condition is primitive*. We learned in the third lecture the history of the sexual cells. These cells, however, are not sexual elements, but every one of them must pass through a very complicated and remarkable transformation in order to become a sexual element. This fact in my opinion renders it certain that the primitive condition was an indifferent one. After it ensue the alterations which transform a sexless into a sexual individual.

When a cell divides the nucleus usually passes through a so-called mitotic change which leads to the division of the nucleus. During this change chromosomes appear. Each chromosome is a separate granule which is formed by the concentration of a small part of the nucleus, Fig. 11. After the division is completed the chromosomes become indistinct and are at the same time utilized for the restoration of the normal structure of the resting nucleus. Hence the chromosomes are visible only during the process of division. It has been ascertained that the number of chromosomes in each species is constant,* although in different species their number may vary

* This statement is not exact, for in certain cases, ascaris, etc., the number of chromosomes varies with the period of life, and it is probable that in somatic cells

between wide limits. We have also discovered that the number of chromosomes in the sexual elements in every species which has been adequately investigated is about half the number of chromosomes occurring in the somatic cells. When sexual products arise from the sexual cells, each cell divides twice in rapid sequence, so that four sexual elements arise. When male elements arise all four cells normally develop. An interesting and instructive exception will be considered presently. In the case of four female elements, on the contrary, only one cell enlarges and becomes an ovum. The three other cells, which have long been known by the name of polar globules, break down. If we count the chromosomes which appear during this double division, we find in typical cases that their number is reduced one half, so that at the close of the process we have cells, the so-called sexual elements, which contain only half as many chromosomes as the cells of the body, and the original sex cells. More careful investigations have taught us further that the reduction in the number of chromosomes is not always exactly to one-half. We find in certain cases one or several extra chromosomes. The origin and significance of these extra, or accessory, chromosomes has been studied especially in America. American investigations have yielded the very important result that the accessory chromosomes stand in immediate relation to the determination of sex. To collect the facts has cost many years of difficult labor. These facts have made it clear that in all higher plants and animals we encounter two fundamentally different species of cells; first, ordinary cells with the full number of chromosomes; second, special cells which we know as sexual elements, or sexual

the number of chromosomes is subject to minor variations. Compare H. L. Wieman's article in the number for May, 1913, of the *American Journal of Anatomy*.

products, which are characterized by the reduced number of chromosomes. We are now in a position to distinguish sexual elements and body cells by a visible microscopic characteristic, and hence to define the two fundamental forms of cells. A cell is only, then, a sexual element when it has the reduced number of chromosomes. The sexual cells have sexuality. The body in which the sexual elements are brought to development may have sex. The basis of all clear thinking in regard to the questions of sex is the difference between sex and sexuality.

How is sex determined? As yet we cannot explain the relations in hermaphrodites at all. We know only that they have indifferent sexual cells, out of which may be formed male and female elements either at one time, or from time to time, or at different periods of life. We assume that the occurrences are regulated by internal conditions of the hermaphroditic organism. We have also discovered that external conditions may under certain conditions influence the sexual development of hermaphrodites, thus, for example, in melons, which normally produce male and female flowers on the same plant, under the influence of higher temperature only male flowers develop, and under the influence of shade only female. How these results come about is completely unknown.

The investigation of forms of separated sex has proved more valuable. Investigators have long endeavored to discover influences which might determine the sex of an ovum during its development. For some time it was hoped to learn something from the investigation of the proportion of the sexes in various species. The sexual relation is usually calculated by setting the number of females as = 100, and then expressing the number of males in percentage of the number of females. These investigations have as yet yielded no

important generalizations. How great the variations are is shown by the following table:

PER CENT. OF MALES.

Loligo.....	16.6	Man.....	106.9 (105.3?)
Octopus.....	33.3	Domestic dog.....	138.0
Horse.....	98.3	Cottus.....	188.0
Songbirds.....	100.0	Lophius.....	385.0
Herring.....	101.0	Latrodectus.....	819.0
Cat.....	105.0		

There are two series of cases known in which the sex is determined in advance. The first series comprises several species of animals of various classes which produce two sorts of eggs, differing in size. Such eggs occur for example in the worm *Dinophilus*, in many rotifers, as, for instance, *Hydatina*, in daphnids, in *Phylloxera*, and other forms. The large eggs produce only females, the smaller only males.⁴⁰ Oskar Schultze was induced by these facts to maintain that sex is determined in the ovum. More recent discoveries have rendered Schultze's theory superfluous.

The second series of cases is afforded by the eggs especially of various insects which may be developed parthogenetically, as occurs, for example, in *Phylloxera*. The fertilized ova produce females only, the unfertilized on the contrary, according to conditions, either males or females. For a long time it was hoped, though in vain, to secure the explanation of the determination of sex by the exact study of such ova.

Naturalists have long directed their efforts toward discovering external conditions, the action of which determines sex. It appears now to be established that under certain conditions the proportions of the sexes may be altered by external conditions. The experiments of Richard Hertwig, which he published in 1907, excited great interest. They have been extended by his pupil, Kuschkakewitz.⁴¹ Hertwig

demonstrated that delayed fertilization of frogs' eggs produces an excess of males. Unfortunately it is not clear how this result is brought about. An American lady, Miss King, has made extensive investigations⁴² upon the influence of external conditions on the determination of sex in toads' eggs. Nutrition and temperature are apparently without effect, but if the eggs lose water then more females develop. Even if we should pass in review the entire literature upon the determination of sex through external conditions we should not get much further than we could from the examples I have presented to you. We are safe in saying that external conditions are probably not of great importance, and at the most are merely favorable or unfavorable for the development of one sex or the other. The essential conditions must be sought in the cells themselves, and this view has had brilliant confirmation through recent researches.

It is very pleasant for me as exchange professor to have the privilege of reporting a series of American investigations which are of the highest value because they have procured for us entirely new views of the determination of sex. Only recently have similar investigations been entered upon in Europe. The new doctrine arose from the observation of the developmental processes which lead to the formation of the male elements in certain insects. The founder of the doctrine is Professor C. E. McClung,⁴³ who, after serving many years at the University of Kansas, became last autumn Professor of Zoology at the University of Pennsylvania in Philadelphia. His first memoir upon the spermatogenesis of insects appeared in the year 1900, and contains the results of his investigations on the process in the *Acrididæ*. McClung's most important discovery was that one chromosome during the evolution of the sexual elements behaves quite differently

from the rest. It appears when a sexual cell begins its transformation. At this time the chromosomes arise in the reduced number and it is easy then to distinguish the one chromosome which McClung has named the accessory. When the sexual cell has formed the reduced number of chromosomes it is called a spermatocyte. The spermatocyte divides, and at the same time all the chromosomes, including the accessory, also divide. The two daughter cells quickly divide again and so also do the ordinary chromosomes, but this time the *accessory chromosome does not divide, but passes undivided into one of the daughter cells* of the second generation. In this way four cells arise as always in spermatogenesis, and of these four cells two have each an accessory chromosome and two have none such. The four cells pass through further changes in order to become mature spermatozoa. Thus it comes about that we have in these insects two kinds of spermatozoa, for half of them contain a piece of the accessory chromosome and the other half do not. From these facts McClung drew the conclusion that the two kinds of spermatozoa determine the sex, and since he found the accessory chromosomes in the cells of the male body, he further supposed that the accessory chromosomes have to do with the creation of the male sex. The observations of the Kansas zoologists have been repeatedly confirmed by other Americans. They are so easily made and are so significant that we have demanded for several years past that our medical students at Harvard should study the spermatogenesis of grasshoppers. That the accessory chromosome stands in immediate relation to the production of sex must be considered as established, but I must immediately call your attention to the fact that McClung's theory acquired an essential further development through E. B. Wilson,⁴⁴ who, in the investigation of the relations of chromosomes in female insects, was able

to demonstrate that the accessory chromosome does not determine the formation of males but of females. The accessory chromosome was first seen by a German, Henking, and was afterward studied by the American, Montgomery. McClung was the first to recognize its true nature and importance, and to him belongs the honor of having first brought the investigation of the determination of sex upon the proper road.

The formation of the sexual elements is full of meaning and interest, but it cannot be made clear by words alone. On account of the importance of the phenomenon I wish now to show you certain pictures which are suited to clarify your impressions.

The sexual cells, like all cells, are little adapted in their natural state to microscopic observation. Special methods have been invented to overcome this difficulty. In most cases thin sections are made of the organ or tissue which it is desired to investigate. The sections are artificially colored. We should have been able to learn little of the structure of cells without this method. The pictures which I have to present to you have been made from artificially colored preparations. The chromosomes which we wish specially to observe are colored almost black, while most of the rest of the cell appears gray. Our pictures are all, except Fig. 44, drawings for the most part from photographs. In the drawings only the black parts have been put in, and in most of them only the chromosomes are represented. When a sexual cell begins to transform itself into a sexual element the nucleus passes through a series of changes during which the chromosomes assume wonderfully irregular forms, which, however, quickly change again. Our first picture* is a drawing by a

* The picture mentioned was projected on the screen for the lecture, and is not reproduced here. The conditions are similar to those represented in Fig. 52.

student of the sexual cells of a grasshopper such as all our students are given opportunity to see. In every nucleus one finds a single round, dark body, the accessory chromosome. The remaining chromosomes are all drawn out and have irregular outlines, so that the accessory chromosome is conspicuous.

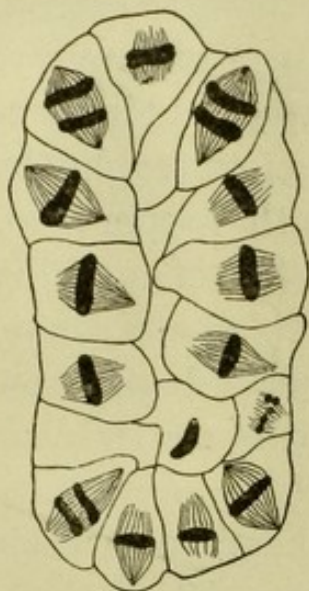


FIG. 36.—*Anasa tristis*. A section of a spermatogoneal cyst. The peculiar arrangement of the spindle is characteristic.

Our next pictures, Figs. 36–40, are taken from *Anasa tristis*, and are after drawings by Miss Pinney. *Anasa tristis* is a species of Hemiptera very common with us. The spermatogenesis of this insect has been investigated by many Americans: by F. C. Paulmier 1899, by E. B. Wilson 1905 and 1907, by Miss Foote and Miss Strobell 1907, by Professor Lefevre and Miss McGill 1908, by C. V. Morril 1901, and by Professor McClung and Miss Pinney 1911. *Anasa* has become, so to speak, a classic animal. As the statements of earlier investigators did not completely agree, Professor McClung and Miss Pinney made a careful reinvestigation. They had at their disposal in part the material used by their predecessors.



FIG. 37.—*Anasa tristis*. Successive stages in the transformation of the nucleus of a sexual cell (spermatogonium). The transformation is the preparation for the development of the sexual element.—After Edith Pinney.

Their memoir is excellent, and I present a selection of their pictures. We will consider first the commencement of the

transformation of the sexual cells. Fig. 36 shows a group of cells, the nuclei of which have assumed the spindle form. We see clearly the fibers of the spindle and the chromatine collected in the middle of each spindle. The chromatine consists of chromosomes which lie crowded together. The remaining pictures which we have to consider represent merely the nuclei. Fig. 37 shows the successive alterations which the

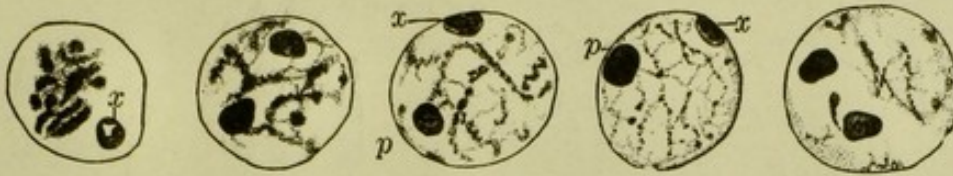


FIG. 38.—*Anasa tristis*. Spermatocyte nucleus in preparation for the first division. *x*, the accessory chromosome; *p*, the plasmasome, a transitory structure which does not belong to the chromosomes, but soon dissolves.

nucleus of a sexual cell passes through when it begins to transform itself into a sexual element. Soon an accessory chromosome becomes distinct, especially in the stages shown in Fig. 38, during which the chromosomes become again dissolved except the accessory, which behaves independently and maintains its integrity. The accessory chromosome has no absolute constant form, but varies greatly. Many of these variations have been pictured by Miss Pinney. Fig. 39 leads us to the first development of the sexual cell (first spermatocyte). We recognize easily the spindle figure. Out of the dissolving skein of chromatine complete chromosomes have arisen. The accessory chromosome lies always at the side of the others. All the chromosomes divide, and we can observe readily in the figures how the two groups of chromosomes diverge and move toward the poles of the spindle. In each group there is one chromosome which has been formed by the division of the accessory. The four drawings in the lower part of Fig. 39 from right to left illustrate the

progressive division of the cell. We notice that in each of the daughter cells there is an accessory element. In ordinary cell division the chromosomes form in the daughter cells a new nucleus which assumes the resting form, in which we can no longer distinguish the single chromosomes. In the case of the developing sexual elements, however, no resting nucleus is produced because the cell at once proceeds to a second division.

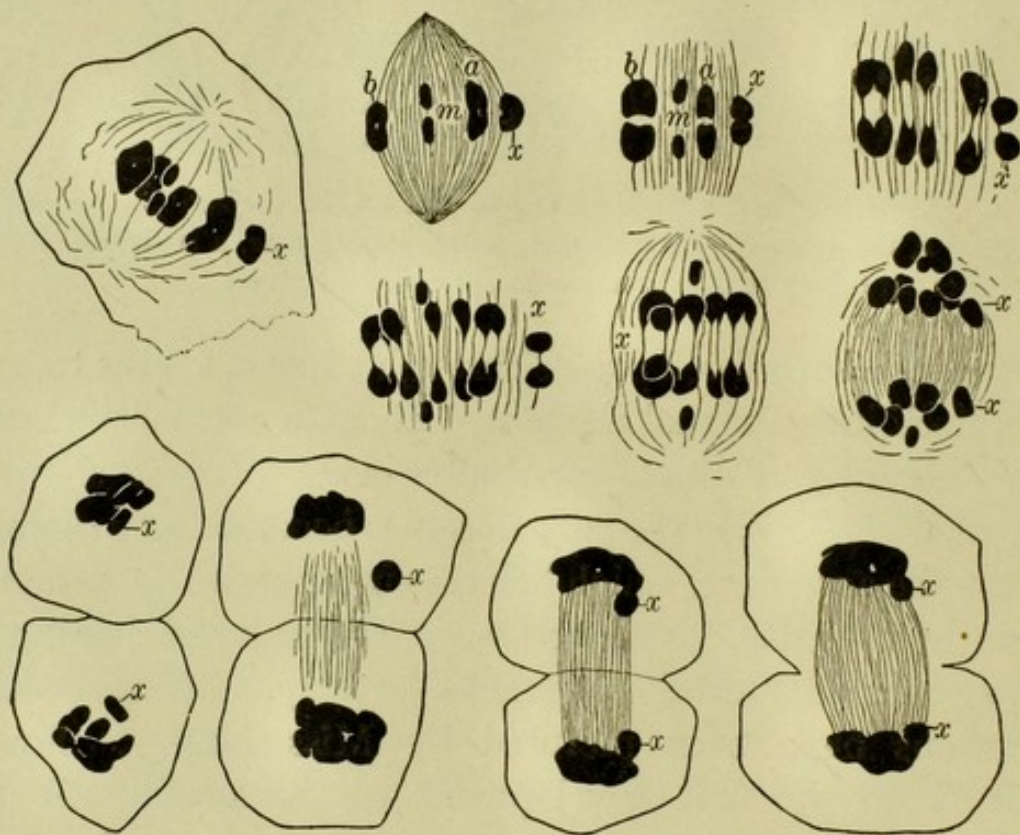


FIG. 39.—*Anasa tristis*. Division of the first spermatocyte. *a*, *b*, *m*, ordinary chromosomes; *x*, accessory chromosomes.

Fig. 40 shows us the successive stages of the second division. During it all the chromosomes divide with the exception of the accessory, which does not divide at all, but migrates into one of the cells. From the original sexual cell there have now arisen four cells, two of which have an accessory chromosome. The four cells change themselves into spermatozoa. In this

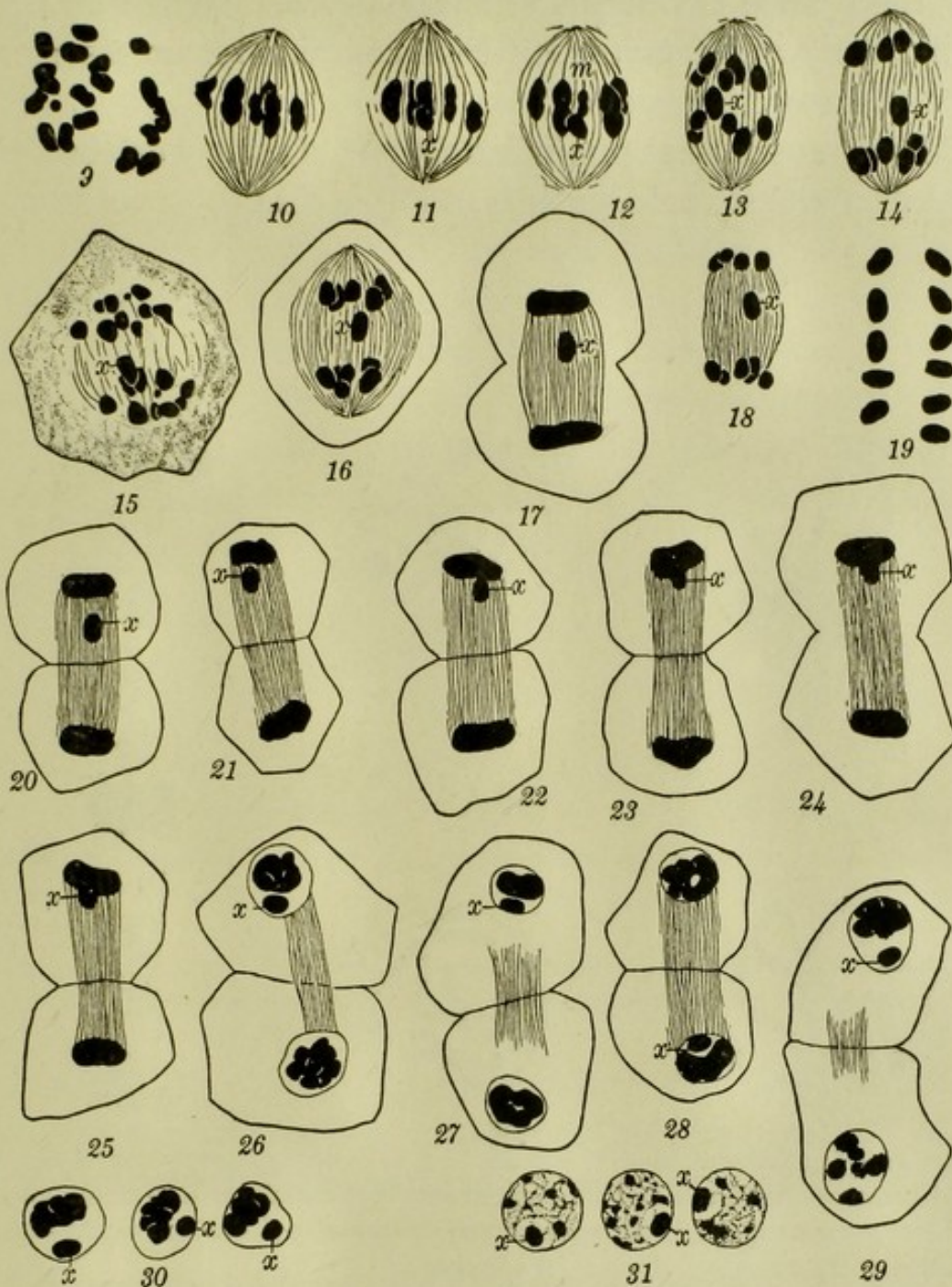


FIG. 40.—*Anasa tristis*. Second spermatocyte division, during which the accessory chromosome remains undivided and partakes itself to one of the daughter cells. *x*, the accessory chromosome; 9, two groups of chromosomes; 19, single accessory chromosomes, each from a cell in the stage of Nr. 18; 30, three daughter nuclei with the accessory chromosome; 31, later stages of the same (each daughter cell forms a spermatozoon).—After Edith Pinney.

way there arise two kinds of spermatozoa. When an egg is fertilized by a spermatozoon that contains an accessory element, a female is produced.

Miss Stevens⁴⁶ has published a series of papers on the development of the sexual elements. Fig. 41 represents the alter-

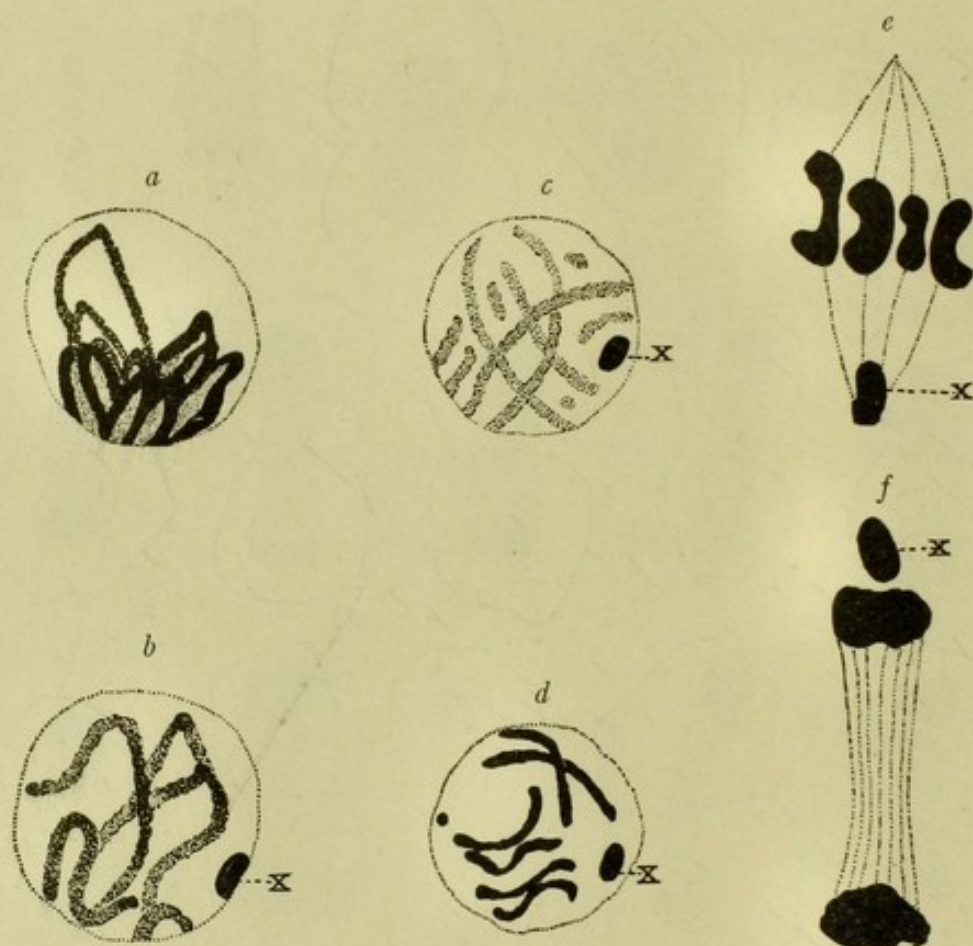


FIG. 41.—*Diabrotica*. *a-d*, *D. vittata*; *e-f*, *D. soror*; *a*, dissolution of the contracted chromosome (first stage after synizesis); *b-d*, transformation of the nucleus of the first spermatocyte; *x*, the accessory chromosome; *e-f*, division of the nucleus of the first spermatocyte.—After N. M. Stevens.

ations as found by her in a beetle, *Diabrotica*. *b*, *c*, *d* show the accessory chromosome clearly. *e* and *f* show us the first division. Half of the daughter cells of the first division have an accessory chromosome, which, however, divides at the second division. The process differs from that in *Anasa*,

but the final result is the same, for there are formed two sexual elements which have and two which have not an accessory chromosome. Miss Stevens has investigated many insects, as also has E. B. Wilson.⁴⁴ Both have made similar discoveries, and they have been able to demonstrate that the accessory chromosome is not always single but may appear in certain eggs as consisting of two, three, four, or even five, parts. They have also observed in some species a second accessory chromosome, which they have designated as the Y-chromosome, and which perhaps also plays a rôle in the determination of sex; but it must not be confused with the



FIG. 42A.



FIG. 42B.

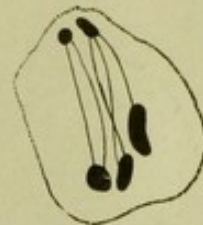


FIG. 43.

FIG. 42.—*Protenor belfragei*. Chromosome groups. *A*, from a cell of a female; *B*, from a cell of a male. The accessory chromosomes are much larger than the ordinary ones.

FIG. 43.—*Protenor belfragei*. Second division of a spermatocyte. The large accessory chromosome is moving undivided toward one pole.

true accessory. Professor Wilson has had the kindness to place at my disposition a number of photographs* of his beautiful preparations, and from these Figs. 42-51 have been sketched. In Fig. 42 the chromosomes are very distinct. In Fig. 42 *A*, we can count very easily twelve ordinary chromosomes and two accessory. Fig. 42 *B* is similar. It also shows twelve ordinary chromosomes, but only one accessory. The

* During the lecture the original photographs were projected by the lantern. I use this opportunity to express my very sincere thanks to Professor Wilson, both for the loan of the photographs and for his generous permission to make drawings from them.

first of the two pictures is from the cell of a female, the second from the cell of a male. In these cases we recognize at once that the female cells are distinguished from the male by having two accessory chromosomes. Wilson was able to demonstrate that the eggs of these insects always contain one accessory chromosome. When such an egg is fertilized by a spermatozoon that contains an accessory chromosome, then the egg

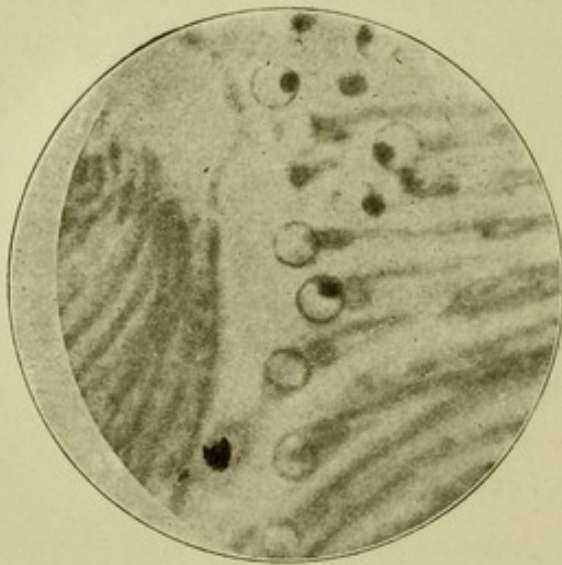


FIG. 44.

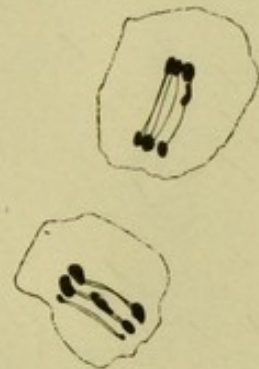


FIG. 45.

FIG. 44.—*Protenor belfragei*. Photogram of a group of young spermatozoa with and without the accessory chromosome. (See text.)

FIG. 45.—*Alydus pilosulus*. Second division of the spermatocyte. The accessory chromosome lies separated from the others, does not divide, and is going toward one of the poles.

develops with two accessory chromosomes in its nucleus, and there arises a female, but if such an egg is fertilized by a spermatozoon that contains no accessory chromosome then a male is produced. Fig. 43 is a somewhat incomplete picture, but shows clearly that during the second division the accessory chromosome has migrated undivided toward one pole. An extremely interesting photograph, Fig. 44, shows a group of spermatozoa. The so-called heads are circular. Half of

them contain a still distinct accessory chromosome, which in the other half of the heads cannot be seen. This picture affords unquestionable proof that there really are two kinds of spermatozoa. The next picture, Fig. 45, is from *Alydus*, and demonstrates to us again the second division and the wandering of the accessory chromosome. Next follows a drawing of *Pyrrhochoris*, Fig. 46, which represents the second

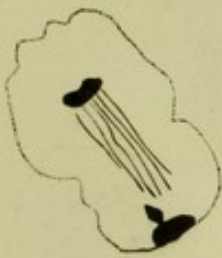


FIG. 46.



FIG. 47.

FIG. 46.—*Pyrrhochoris apterus*. Division of the second spermatocyte.

FIG. 47.—*Anasa tristis*. ♂ Two views of dividing female nuclei (oogonia).

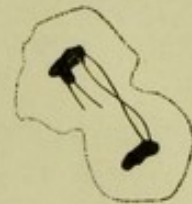
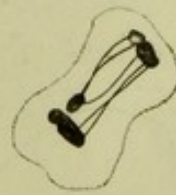


FIG. 48.

FIG. 48.—*Anasa tristis*. ♂ The second spermatocyte division. The accessory chromosome is lodged at one pole and is lacking at the other.

division almost completed. Both cells are clearly recognizable, but only one of them contains an accessory chromosome. Next follows a drawing from *Anasa*, Fig. 47, which is shown because it presents to us two views of the cell division. In the upper cell we have a side view of the spindle, and we notice at once the so-called equatorial plate which is formed by the collocation of all the chromosomes in the equatorial plane. The lower cell is a view of an equatorial plate seen from the spindle pole. Next comes a picture from *Anasa*, Fig. 48, which shows us the second division nearly completed. The wandering of the accessory chromosome is very clear. We pass now to the consideration of *Galgulus*, Fig. 49. The

picture shows us a polar view of an equatorial plate of the second division. The ordinary chromosomes form a circle; in the center we see the accessory chromosome, which in this genus is not simple but quadripartite. Fig. 50 is a drawing from *Syromastes*, offering a polar view of the first division. Wilson discovered in this genus a double accessory chromosome which does not lie in the center of the equatorial plate but outside the circle of the remaining chromosomes. Quite similar is the last photograph of our series, Fig. 51, which is

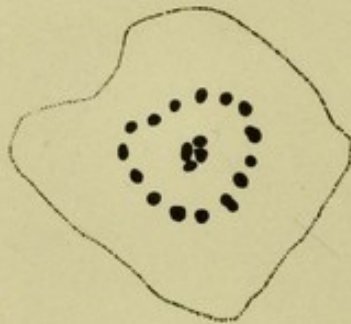


FIG. 49.

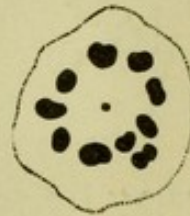


FIG. 50.

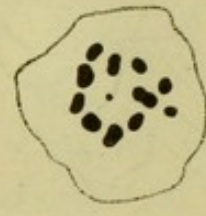


FIG. 51.

FIG. 49.—*Galgulus oculus*. Polar view of the equatorial plate of the second spermatocyte division. The accessory chromosome is quadripartite, and lies in the center.

FIG. 50.—*Syromastes marginatus*. First spermatocyte division. The accessory chromosome is bipartite and lies peripherally.

FIG. 51.—*Metapodius terminalis*. First spermatocyte division. The accessory chromosome lies peripherally, and alongside it is a Y-chromosome.

taken from *Metapodius*. In this case the accessory chromosome is simple and lies outside, while near it occurs a Y-chromosome which is very similar in appearance to the accessory, but differs from it in its further development. In the center of the equatorial plate lies a minute chromosome, the meaning and history of which is not yet completely cleared up. The photographs from which these drawings were made are very beautiful and render the relations perfectly clear.

Miss Stevens was a gifted and eager investigator, whose early death brings a heavy loss. In the year 1911, she pub-

lished the discovery of an accessory chromosome in the guinea-pig.⁴⁷ Her pictures are reproduced in Fig. 52, and show the unquestionable accessory chromosome indicated by the letter *x*. Guyer,⁴⁸ also an American, has described the accessory

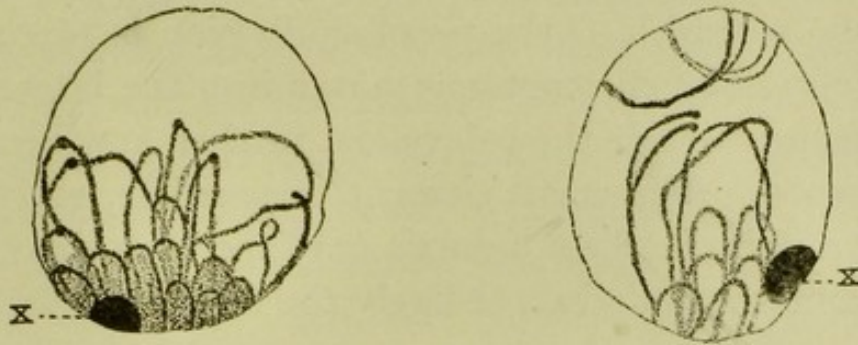


FIG. 52.—Guinea-pig. Spermatocyte nucleus in the preparatory stage (immediately after the synizesis), in which the accessory chromosome becomes distinct.—After Miss Stevens.

chromosome in birds and in man, and it has been found in other animals also.

That the spermatozoa really determine sex has been confirmed by a capital investigation of T. H. Morgan.⁴⁹ *Phylloxera* and *Aphis* lay eggs which develop parthenogenetically.

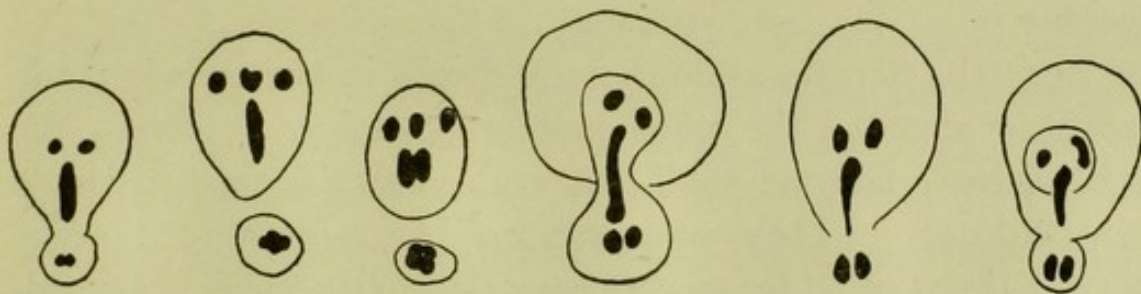


FIG. 53.—The unequal spermatocyte division. *a-c*, in *Phylloxera*; *d-f*, in *Aphis solicola*.—After T. H. Morgan.

After several generations, and under conditions which are in part known to us, the females deposit eggs, which are fertilized. All fertilized eggs develop into females. This phenomenon does not contradict the new doctrine of sex determina-

tion, but on the contrary agrees with it fully. Morgan discovered that when the sexual cells in the male develop in order to produce spermatozoa, they form at their second division two elements of unequal size. Fig. 53 reproduces two series or Morgan's original pictures. In the first series, *a-c*, and also in the second, *d-f*, the peculiar division is represented. The big accessory chromosome moves into the larger of the two elements, which then develops further and becomes a spermatozoon. The small element, meanwhile, shrivels up. Thus there arise in these animals only spermatozoa with the extra chromosome, and accordingly the fertilized ova become females.

American investigations, both those mentioned and others related to them, lead us to the conclusion that sex is determined by peculiarities of the cells, and not by external conditions. If an external factor influences the proportion of the sexes, this must happen, according to our new interpretation, by interfering with the development of one or the other sex. In the case of hermaphrodites, interference may act by favoring the transformation of indifferent germ cells in one direction or another.

That the determination of sex dwells in the cells is made probable also by the phenomenon of polyembryony. We have already learned that four embryos arise from a single Armadillo egg. They are always of the same sex. So also in the case of small insects, the parasitic Chalcidæ. According to the investigations of Bugnion, Marshall and Silvester, many embryos arise from each single egg, and they are all of the same sex. We can explain this wonderful phenomenon only by the assumption that the sex of the egg is determined from the start.

It must be mentioned that, according to the investigations

of Bältzer, the sex of Echini is determined not by the spermatozoa but by the egg. According to him, the Echini have two kinds of eggs which differ in their chromosome relations.

The investigation of the determination of sex must be pursued much further. It is above all important to ascertain whether the conditions which have been discovered in insects recur in all animals and plants. We ask at the same time, what are the relations in hermaphrodites? We cannot at present even guess the answer to this question.

It must also be distinctly emphasized that the causal relations are not clear. We have learned through the memoirs which have been cited that the nuclei of a female in a considerable number of animal species contain more chromatine than the nuclei of a male. We are unable, however, to bring this peculiarity into causal relation with the difference of sex. It is quite possible that the excess of chromatine is only the expression of more essential peculiarities, although the greater probability remains that the accessory chromosome is the material cause and basis of sex.

Mortiz Nussbaum considered the two sexual elements as homologous. He wrote in 1880: "Es treten somit bei der Befruchtung nicht zwei heterogene Elemente zusammen, die einander ergänzen und . . . es treffen sich vielmehr zwei homologe Zellen, von denen die eine zum Zweck der Konjugation sich in eine beweglichere Form umgegossen hat." The homology of the mature ovum with a spermatozoon has been generally accepted. The new investigations make this doubtful.

We know at present four different species or types of cells. Two types are diploid, that is to say, they have the full number of chromosomes; and two types are haploid, that is to say, they possess the reduced number of chromosomes.

- A. Diploid cells.
 - 1. Cells of the female body.
 - 2. Cells of the male body.
- B. Haploid cells.
 - 3. The female elements (mature ova and polar globules)
 - 4. The male elements (spermatozoa).

We suspect besides that there is a fifth kind of cell, the indifferent, which we shall perhaps later learn to recognize in hermaphrodites and lower organisms.

Thus we reach the conclusion of to-day's lecture. We advance the hypothesis that sex rests upon a physical basis, which we recognize by differences in the proportion of chromatin in the cells of the male and female body. The epoch-making discoveries of my American colleagues awake joyful excitement among biologists. We are pupils of German science, and in carrying out the investigations, the results of which I have presented to you today, our investigators have striven to equal the German ideal. May our activity express to you our gratitude!

VI.

THE SCIENTIFIC CONCEPTION OF LIFE.

Your Excellencies!

Biology is the supreme science from which we still await the solution of very many problems. Unfortunately, biology has not yet become a united science, but consists of sundry disciplines more or less separated from one another. The number of species of living beings is enormous, so that it is impossible for a single investigator to become familiar with all the phenomena. According to a recent estimate of Pratt,⁵⁰ published in 1911, the number of known animal species is 522,400. The number of species yet to be described is certainly also very great, and we have further to reckon with the considerable, though smaller, number of species of plants.

We all know that there are two chief types of naturalists: first, of those who incline to observation; and second, of those who incline to experiments. It occurs very exceptionally only that a naturalist is gifted equally in both directions, and hence we see that biologists for the most part are either morphologists or physiologists. We divide up biology into single sciences merely to adapt it to the capacity of the individual. An able savant may perhaps be a zoologist, an embryologist, a biological chemist, a physiologist, or a paleontologist, but he cannot be a real biologist. We can expect only from the future such a fusion of the results of our many and many-sided biological investigations as will create a true and real biology. To attain this result the work of many men will be

necessary through many years. The contribution of any one man will always be very modest in comparison with the whole task, but we shall certainly succeed by our united efforts in collecting so many generalizations that we shall ultimately possess a unified biological science which will have a much higher and farther-reaching significance for us than our present biology, which consists of single sciences imperfectly fused. This more complete biology of the future will I believe be recognized by all as the supreme science. We foresee that it will answer many questions which philosophers have striven for thousands of years to solve. Philosophy, strictly speaking, is occupied chiefly with biological phenomena. Consciousness, the relation of the soul to the body, the origin of reason, the relations of the external world to psychical perception, and most subjects of philosophical thought are fundamentally biological phenomena which the naturalist investigates and analyzes. If these fundamental problems of human thought are ever to be solved, the solution will be presented to us, according to my conviction, not by philosophers, but by naturalists. I can express my thought better perhaps by saying that the future fusion of philosophy and biology, or the inclusion of philosophy in biology, is to be expected. Historically, there is a deep cleft between philosophers and naturalists. The philosopher takes existing knowledge, meditates upon it, and endeavors by deep thought to draw from his knowledge for his own satisfaction the longed for general conceptions. The naturalist, on the contrary, strives to widen his knowledge, and to make new observations. He wishes to increase the number of known facts, being controlled by the conviction that the generalizations will follow upon the increased acquaintance with facts. For both the philosopher and the biologist the final goal is the same, for

both desire to win their generalizations. The philosopher suffers from the disadvantage that he would like to have a complete system, a coordinate and harmonious explanation of all existence. The naturalist desires this also, but he has more patience and does not expect to reach his goal so quickly, but rejoices every time that he advances a small distance and is able so to order the facts known to him that he can deduce a natural law. The naturalist utilizes hypotheses as much as the philosopher. The naturalist's hypothesis is not intended to complete a system of thought, but merely to indicate a way by following which he may discover facts as yet unknown. During our present debate it is very important not to forget the differences between philosophical thinking and scientific investigation. As you might anticipate, I hold the scientific method to be the better and more certain, and therefore cherish, as stated, the opinion that the solution of the great problems of human existence, if it is ever achieved by us, will be accomplished through biology.

The conception of life is very uncertain, but we are able to place certain foundation stones for the erection of this conception. In other words, biology has already achieved some important generalizations, several of which have been mentioned in the previous lectures.

At the start, emphasis must be laid on the fact that life is known to us only bound to matter. Only through matter can life express itself, only through matter act upon the world, and only through matter be influenced by the world. As we heard in the first lecture, the minimal amount of living substance, which makes life possible, is relatively great, and probably so great that we can see it with the microscope. I at least regard it as improbable that there are invisible living beings.

The opinion is widespread in unscientific circles that life may occur without a material basis. We encounter this opinion in almost all religions, for they teach the survival of the soul, at least of man. In recent years repeated attempts have been made to prove these religious doctrines scientifically. Thus, the spiritualists assert that they can demonstrate the existence of living men without material bodies. It may be asserted without overventuring that the majority of biologists do not consider this spiritualistic demonstration as sound. Exceptions are rare. The most famous of such exceptions is Alfred Wallace, co-founder with Darwin of the theory of natural selection. He remains even in his extreme old age an eager follower of spiritualism. I have conversed with him a few times on the subject, and got the impression that he keeps the whole field of spiritualism separated from science, and that he completely sets aside in the discussion of spiritualism those criteria which he would inevitably put up in the case of scientific investigation. No impression was made upon him by the numerous instances in which it had been proven that alleged spiritualistic phenomena were due to cheating. He demanded that cheating should be proved in every case before he could yield his faith. Is not the whole doctrine of the spiritualists, properly speaking, a psychical phenomenon, which we are not to attempt to explain as a real phenomenon of the outer world?

There has been founded in England a society for psychical research. This society includes among its members men of good standing, who have carried on very serious investigations. The formation of the society was a consequence of observations made in Cambridge, from which the conclusion was drawn that men may communicate with one another directly without using the means previously known to us.

This mode of communication was named telepathy. When the British Association for the Advancement of Science held its meeting in Montreal (1886), I made the acquaintance of several of the leaders of this Society. At that time it seemed possible that telepathy was a real phenomenon, and therefore in response to the suggestions of these gentlemen we founded a society for psychical research in America. After a number of years, the scientific men who had founded the American society withdrew, in part because it was found out that the alleged phenomena of telepathy, which were first described, were produced by cheating. The English society is still active, and now defends the doctrine that vital phenomena may occur without the usual material body, and that it is possible to enter into communication with the spirits of the dead, although only under conditions which occur rarely. If this doctrine could be scientifically assured, it would constitute the greatest discovery of our time. The demonstration is, however, little convincing. In Germany, so far as I know, psychical research has received little attention. In England and America one hears and reads much about it. Of course, we cannot assert *a priori* that survival, in the sense indicated above, is impossible, yet the biologist is likely to stick to his assertion that the presence of the material basis is the exclusive substratum for life.

Where does the living substance come from? So far as we know at present it arises only from itself, it propagates itself, and can be created only by itself. If it should once be entirely destroyed, life on our earth would cease. Formerly this view did not prevail, for it was believed that spontaneous generation occurred in the world. In mediæval times learned men adhered contentedly to the idea that the insects which appear in decaying meat arise by spontaneous

generation from the meat. Francesco Redi's famous experiments brought the first proof that the insects arise only when insect eggs are laid in the meat. For a still longer time it was considered possible that the simplest organisms, bacteria, etc., could be formed by spontaneous generation. The experiments of Pasteur, made not many years ago, brought the final proof that this also is impossible. On Pasteur's discovery is based the antiseptic treatment of the surgeon, which has for its object simply to prevent the entrance of the microscopic germs which cause sepsis. We must regard it as an assured conclusion of biology that spontaneous generation has never been observed, and many naturalists incline to assert that it never will be observed by us.

Thus we come back to the question, where does the living substance come from? Helmholtz⁵¹ and, following him, Arrhenius have defended a hypothesis according to which life reached this earth from outside. This hypothesis assumes the occurrence of very small living germs, about of the size of the smallest individual germs known to us as occurring on the earth, which are driven hither and thither in space, and may accidentally hit the earth, or which perhaps are brought on meteorites, or, according to the hypothesis advanced by Arrhenius, by the beats of waves of light. The hypothesis is bold and interesting. If it is correct, the possibility exists of our receiving organisms which differ from all species hitherto occurring on the earth, and which therefore might initiate a new evolution of living beings. But even if we assume the correctness of this hypothesis, it still offers no answer to our question, because it assumes the previous existence of living substance. Alongside this theory occurs a new hypothesis of spontaneous generation. This second hypothesis is, so to speak, a side product of the doctrine of evolution. After the

astronomers had asserted the evolution of our planetary system, after the geologists had asserted the evolution of the world, followed Darwin, who convinced us of the necessity of assuming the evolution of plants and animals. Evolution leads us back to a time when the conditions on our earth were such that life, as we now know it, must have been impossible. Life appeared later. It is therefore clear that somehow living substance must have arisen on the earth. Thus it became an intellectual necessity for us to assume in this sense the spontaneous generation of life. Those who make this assumption have, strictly speaking, only *one* explanation to offer, namely the supposition that proteid molecules could be formed, under the then prevailing conditions, and by chance so come together and unite in combination with other substances that they would produce the first living substance. If we may venture to pass judgment on this hypothesis we must bear in mind that it is merely the expression of our desire to meet the assumed needs of the doctrine of evolution. The hypothesis has no further real scientific foundation. Pflüger⁵² has endeavored in a clever and interesting memoir to determine speculatively the possibility of the origin of proteid substances, but he did not get beyond speculation. To be exact, we must consider that we have reached the new doctrine of spontaneous generation through our inability to conceive the origin of life otherwise. I imagine a very interesting and instructive book, which is to be on the theme how often the scientific man has been led to false conclusions through the assumption "it must be so because we cannot conceive it otherwise." We may never say in science, it is impossible. The time of scientific surprises is not over. A few years ago, physicists thought that they had already discovered the basic phenomena of their science, and yet they are all today occu-

pied with so transforming their fundamental conceptions that they will correspond to the discoveries of recent years. Some surprises will surely come in biology, and therefore I prefer to take an agnostic position in regard to the doctrine of spontaneous generation, and to cling to the possibility that the final explanation will be found in some unexpected direction, or will be given by some phenomenon as yet wholly unknown to us. It is much achieved that we can now maintain the statement that protoplasm, under which term we include the nucleus, is the physical basis of life.

Let us now pass to the consideration of the general activity of protoplasm. First of all, we must regard metabolism which we must look upon as the basic phenomenon of life. Very many chemical substances are taken up by protoplasm which in part are worked over into new chemical combinations, by which the growth of the living substance is made possible, and at the same time the necessary material is produced for the performance of work. In consequence of the performance of work simple chemical compounds arise which cannot be further used by the protoplasm, and are therefore discarded, and are designated by us as excretes. In order to maintain life, the stream of matter through the protoplasm must continue. We have no occasion to assume that metabolism is more than a series of chemical processes.

By nourishing itself, protoplasm grows, and as a consequence thereof follows the multiplication or proliferation of cells. We know also that when protoplasm grows, the new formed protoplasm is similar to that already present. The self-maintenance of its own peculiarities is highly characteristic of protoplasm and we recognize in this peculiarity the basis of heredity. The question of variations is a very different one. The doctrine of evolution forces us to the assump-

tion that protoplasm, in spite of the fact that so far as we can observe it propagates itself and in this propagation remains like itself, nevertheless alters in the course of time. The continuous, slowly progressive change of protoplasm which has led to the origin of species, we designate as the phylogenetic variation. Many experiments on variation have been made in recent years. In one direction our knowledge has been greatly extended. The so-called Mendelian variation is certainly known to you. It is remarkable that the variations which have been found in the investigation of the Mendelian law are not new variations, but on the contrary in such cases as have hitherto been analyzed with certainty, we have to do with the dropping out of a character. This is illustrated by the beautiful experiments of Professor Morgan⁵³ of Columbia University on *Drosophila*. The eyes of this small fly vary in their color. Morgan has succeeded in proving by his experiments that four factors determine the color of the eye, and that all variations in the color are caused by the dropping out of one or more of these factors. The variations arise by the exclusion of a character which is present in normal individuals. We still have to discover the origin of new variations, although we have already some indications of the answer to this problem. I should like to discuss the matter if time permitted, but I must restrict myself to a single example. Professor Stockard⁵⁴ has made experiments at the Biological Station at Woods Hole, which led him to the fine discovery that the addition of minute quantities of magnesium chloride to ordinary sea water creates some wonderful modifications in the development of bony fishes. He employed for his experiments *Fundulus heteroclitus*, a species of minnow very common at Woods Hole. Eggs which are kept in the magnesium water produce embryos which appear normal in

most respects. They show, however, a tendency toward fusion, in the median line, of the two eyes which normally are lateral. The fusion may go so far that a fish is produced which has only one eye in the median line of the head. Such an embryo is called a Cyclops. It is thus shown that an alteration in the chemical conditions produces an extraordinary alteration of the development. In this connection we may mention also the interesting discovery of artificial parthenogenesis by A. D. Mead,²⁰ which has been confirmed by Loeb,⁵⁶ Matthews⁵⁵ and others. These investigators have demonstrated that eggs may be excited to further development through various chemical means without being fertilized in the normal manner. An egg which has remained unfertilized and does not receive the chemical excitation will break down. The fate of the egg may be completely altered by a relatively small chemical treatment. In all these cases we must ascribe the striking alterations of the vital processes to chemical action.

The immediate microscopic observation of cells during their physiological activity teaches us that the phenomena of life depend upon their material substratum. We know, for example, in muscles, which have been recently carefully investigated by Meigs,⁵⁷ very instructive relations. There are two kinds of muscle fibers, the so-called smooth and the striated. The smooth muscles occur chiefly in the internal organs. When they contract they give off water which may be found between the single fibers. When they expand they take up the water again. The striated muscles are for the most part connected with the skeleton. Their fibers are much larger than the smooth muscle fibers, and have in their interior very fine contractile fibrils, Fig. 9, which I have already had occasion to mention. When the striated muscles contract,

water is taken up by the fibrils, to be given up by them again when the muscles elongate. The movement of water in the two types occurs in opposite senses during contraction. In smooth muscles it moves out from the fibers, in striated, into the fibrils. Meigs' investigation was carried out in part in my laboratory, and I have been able to confirm his results by the inspection of his preparations. The contraction of muscles thus appears to depend on the movements of fluid within the muscle, and muscular contraction is a chemical-physical phenomenon. Nerve cells contain in their normal condition small masses, commonly designated as Nissl's bodies. When a nerve cell functions these masses are used up during its activity. The observations of C. F. Hodge⁵⁸ of Clarke University are very convincing. He investigated the central nervous system of swallows. He collected some birds in the morning when they were fresh, and again others at the end of the day when they were exhausted by many hours of flight. He found it easy to demonstrate that the content of the nerve cells was used up during the day, and that the exhausted cells showed clearly the loss which they had suffered. He also found that certain nerve cells in a very old man have a permanently exhausted appearance and were therefore no longer capable of functioning. (Mention should be added of the very extensive investigation of the exhaustion of nerve cells by Dr. Crile, an account of which he presented to the American Philosophical Society in April, 1913.) When we consider that our highest performances are functions of our nerve cells, we must admit that our psychical activity also depends upon the activity and the using up of living substance. If we pass to the organs of the so-called vegetative life we find similar conditions. The secretion of glands, as we first learned through the investigations of R. Heidenhain, is formed

usually from substances which we can easily see under suitable conditions in the gland cells. When the gland functions, these substances, which often may be seen as granules in the protoplasm, are metamorphosed chemically, in order to form the secretion which is given off by the gland. Very exact recent investigations of these processes have been made by the American, Bensley.⁵⁹ As we heard in the fifth lecture, we can distinguish in the nuclei of sexual cells in many animals a so-called chromosome which differs from the remaining chromosomes. It claims our special interest because it occurs in the cells of the female body, but on the contrary is not found in the cells of the male body; hence, as we heard, the hypothesis that these chromosomes determine the sex. As we have already considered these relations, it will suffice merely to mention the chromosomes. In conclusion let me again direct your attention to the fact that always as we grow old we can observe visible modifications of the cells.

The phenomenon of metabolism and the phenomenon of the visible alterations which can be observed in cells, lead to the conclusion that the life processes are explicable by the chemical properties and the structure of protoplasm and nucleus.

This explanation is called the mechanistic theory of life, and has found acceptance with the majority of biologists. It cannot be doubted that the mechanistic explanation is stringently sufficient for most vital processes. Whether it is sufficient to explain all the phenomena of life is a question in regard to which opinions diverge. On one side there are the Monists and their friends, and on the other the Vitalists and Dualists. There are biologists who make a dogma of the mechanistic theory and defend their doctrine with a vehemence which recalls the theological discussions of the Middle

Ages. They express their opinions with limitless certainty and listen unwillingly if one does not agree with them. We, however, must consider the question more quietly and remain remote from over-eagerness, and this chiefly because there are important vital phenomena known to us which up to the present at least cannot be made comprehensible by the mechanistic theory.

Of such phenomena I take the privilege of enumerating three:

1. Organization.
2. The teleological mechanism.
3. Consciousness.

Organization is characteristic of life, but exactly what the organization of living substance is, is by no means clear to us. We have already discussed this. We only know that organization is created by uniting various chemical substances, some of which form small masses which remain separate from one another. We know also that the living substance always contains in solution certain salts. Water is of course indispensable. We possess no knowledge how this mixture arises, or how it is capable of maintaining and increasing itself. We may indeed say that we must assume that this organization is to be explained mechanistically, but then we really merely say that we have hit on no better explanation hitherto and that properly speaking we cannot give a real explanation at all. So long as the essence of organization is completely unknown, we must refuse with decision to admit the complete sufficiency of the mechanistic theory.

One of the most wonderful properties of life is the teleology, with which the vital functions are carried out. The changes in a living animal or in a living plant progress as if the

organism was working conscious of its aim. How did this vital teleology arise; how has it maintained itself? That teleology is to be explained by the mechanistic theory is again an assumption, the justification of which we still await.

Consciousness is the most obscure problem of biology. Hitherto, the philosophers, and more recently, the psychologists, but not the biologists, have occupied themselves with the study of consciousness, and they have, it seems, only got so far that they can make it clear to us that consciousness is an ultimate conception, that is to say, a conception which cannot be further analyzed. In an address,⁶⁰ which I delivered in the year 1902, as President of the American Association for the Advancement of Science, I endeavored to make clear the importance of consciousness in the evolution of animals. I adhere today to the opinion then expressed that the phylogenetic development, especially of vertebrates, was dominated by the evolution of consciousness. If this is the case, it offers an important proof of the great importance of consciousness in animal life, and in fact we are forced to ascribe to consciousness the leading rôle in evolution. It can have importance only if it influences the life of animals. Consciousness is active. In the address mentioned above I stated that according to my conviction it is impossible to avoid the conclusion that consciousness stands in immediate causal relation to physiological processes. What is consciousness? There are so far as I know only three possible explanations from which we must choose. According to one view, consciousness is not a real phenomenon, but a so-called epiphenomenon, something that accompanies the physiological processes without exerting any influence upon them. As a celebrated psychologist expressed it to me, consciousness is merely the other

side of the alterations in the protoplasm of the brain cells. According to a second view, consciousness is a special form of energy. This view, strictly taken, I believe to be purely metaphysical. No observations or experiments are known to me which even suggest that energy can be transformed into consciousness. As you have doubtless already perceived, I am not inclined to regard consciousness as a condition of the protoplasm or as a form of energy. If we admit, as according to my interpretation we must admit, that consciousness plays an important rôle in life, then it must be able to act in some way upon the body. Such an action can reveal itself only by the transformation of energy somewhere in the body. Thus we are led directly to the hypothesis that consciousness may cause the transformation of energy, and that it is itself not energy.

I acknowledge the great significance and importance of the mechanistic theory of life. A pupil of Carl Ludwig may not turn away from this theory, for it has proven of the highest value in science, and has guided many investigations to fortunate termination. But must we carry our enthusiasm for this view, for which we are indebted chiefly to the great Leipzig physiologist, so far that we become immediately converts to the dogma that this theory suffices for all the phenomena of life? I do not belong to those who wish to establish monism as the definite and final philosophy. On the contrary the possibility still remains that we must accept a dualistic philosophy as the desired solution. According to this philosophy we recognize in the universe energy and consciousness. We biologists, however, are not philosophers. We make no assumption to offer you final explanations. The conception of consciousness which I have laid before you is not a philosophical speculation, but a scientific hypothesis

which is brought forward because it makes the totality of vital phenomena more comprehensible. It would be supremely interesting to know and we hope that in the future it will be known what consciousness is. But the first question for the biologist is: Is consciousness a true cause?

And now for our final conclusion. Life is bound to matter. Vital phenomena are alterations of the living substance which we describe by saying that they are transformations of energy. But there always remains the possibility that consciousness cannot be explained mechanistically, that it is neither a condition of protoplasm, nor a special form of energy, but something of its own kind, not comparable with anything else that we know, and that it reveals itself by causing transformations of energy.

There still remains for me to thank you for the attention with which you have honored me, and for the extreme hospitality which I have enjoyed here. May the University of Jena grow and prosper! Of her I shall carry with me to my distant home memories to which I shall always return with joy so long as I live. To her I say farewell, and to you, thanks!

NOTES.

1. Carl Heitzmann, Microscopical morphology of the animal body in health and disease. 8vo. pp., xix, 849. New York, 1885. F. H. Vail and Co.
2. C. O. Whitman, The inadequacy of the cell theory.
3. E. B. Wilson, The cell in development and inheritance. Second edition. New York, 1900.
4. J. Loeb, *Arch. gesamt. Physiol.*, 1907, Bd. cxviii, s. 7.
5. Ralph L. Lillie, Certain means by which star-fish eggs naturally resistant to fertilization may be rendered normal and the physiological conditions of this action. *Biol. Bulletin*, XXII, 328-346, 1911.
6. A. C. Eycleshymer, The cytoplasmic and nuclear changes in the striated muscle-cell of *Necturus*. *Amer. Journ. of Anat.*, III, 285-310.
7. Professor Whitman made extensive experiments concerning heredity in pigeons, and for this purpose he kept a large flock of these birds. At his invitation several students availed themselves of the opportunity to make a careful study of the early development of pigeons. The resulting studies offer us by far the most exact descriptions of the early development of birds which we possess. Compare:
 E. H. Harper, The fertilization and early development of the pigeon's egg. *Amer. Journ. Anat.*, III, 349-386, 1904.
 Mary Blount, The early development of the pigeon's egg with especial reference to polyspermy. *Journ. of Morphol.*, XX, 1-64, 1909.
 J. Thomas Patterson, Gastrulation in the pigeon's egg. A morphological and experimental study. *Journ. of Morphol.*, XX, 65-123, 1909.
8. R. G. Harrison has published many experiments on the origin of nerve fibers:
 1901. *Arch. f. mikrosk. Anatomie*, Bd. LVII, 354-444.
 1903. *Arch. f. mikrosk. Anatomie*, Bd. LXIII, 35-149.
 1904. *American Journ. of Anatomy*, III, 197-220.
 1906. *American Journ. of Anatomy*, V, 121-131.
 1907. *Journal of Experimental Zoology*, IV, 239-281.
 1907. *Anatomical Record*, No. 5.
 1908. *Anatomical Record*, No. 8.
 1908. *Anatomical Record*, II, 385-410.
 1910. *Arch. f. Entwicklungsmechanik*, XXX, Tl. II, 15-33.
 1910. The outgrowth of the nerve fiber as a mode of protoplasmic movement. *Journ. Exp. Zoology*, IX, 787-846.

In the last-mentioned article he describes the observations made upon *in vitro* cultures, and pictures in detail the outgrowth of the axis-cylinders (nerve-fibers) of young nerve cells. Harrison has definitely solved the problem which has long been disputed.

9. C. S. Minot, Age, Growth, and Death, p. 201, where the literature is also given.
10. V. E. Emmel, A study of the regeneration of tissues in the regenerating crustacean limb. *Amer. Journ. Anat.*, X, 109-158.
11. As far as I know, H. Braus was the first to graft rudimentary extremities. Compare *Verh. Anat. Ges.*, XVIII and *Anat. Anz.*, XXVI. His experiments have been repeated and extended by W. H. Lewis and R. G. Harrison.
12. W. H. Lewis and Mrs. Lewis conjointly have made experiments upon the *in vitro* cultures of embryonic tissue. Compare *The Anatomical Record*, VI, 195 and 207.
13. Carl Semper, Die Verwandtschaften der gegliederten Tiere, iii. *Sempers Arbeiten. Zool. Zootom. Institut Würzburg*, Bd. III, 115.
14. The text deals with the law of genetic restriction, which can be found more definitely stated in my "Laboratory Text-book of Embryology," 2nd ed., p. 14.
15. E. A. Schäfer, Life: its nature, origin and maintenance. (Presidential Address before the British Association for the Advancement of Science, Dundee, September, 1912). Longmans, Green & Co., London, 1912.
16. W. Kleinenberg, The development of the earth-worm, *Lumbricus trapezoides*. *Quart. Journal of Microsc. Science*, XIX, 206-244, 1879. (Compare also, *Zeitschr. wiss. Zool.*, XLIV, 1886.)
17. E. B. Wilson, The germ bands of *Lumbricus*. *Journ. of Morphology*, I, p. 183.
18. J. T. Patterson, A preliminary report on the demonstration of poly-embryonic development in the Armadillo. *Anat. Anzeiger*, XLI, 369-381. (Cites also the earlier works of Newman and Patterson, et al.)
19. Hans Driesch, Entwicklungsmechanische Studien I. *Zeitschr. f. wiss. Zoologie*, LIII, 160.
20. A. D. Mead, Biological Lectures at Woods Hole, Boston, 1898.
21. F. A. Woods, Origin and Migration of the germ-cells in *Acanthias*. *American Journ. of Anat.*, I, 307. (The so-called "precocious segregation" of the sexual cells of fishes was first more exactly described by C. H. Eigenmann.)
22. B. M. Allen has determined the history of the sexual cells in four vertebrate types.
 1911. *Amia*, *Journal of Morphology*, XXII, p. 11.
 1911. *Lepidosteus* *Journal of Morphology*, XXII, p. 2.
 1907. *Rana*, *Anat. Anzeiger*, XXX, 339.
 1906. *Chrysemys*, *Anat. Anzeiger*, XXIX, 217.
23. R. W. Hegner, The origin and early history of the germ-cells in some Chrysomelid beetles. *Journal of Morphology*, XX, 231-296, 4 Taf., 1909.

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25. W. G. Moenkhaus, The development of hybrids between *Fundulus heteroclitus* and *Menidia notata*. *Amer. Journ. of Anat.*, III, 39-65, 1904.
26. E. G. Conklin, Karyokinesis and cytokinesis, etc., of *Crepidula* and other Gastropoda. *Journ. Acad. Nat. Sciences*, Philadelphia, XII, 1902.
The organization and cell lineage of the Ascidian egg. *Journ. Acad. Nat. Sciences*, XIII, 1-119, 1905. (See p. 93 ff.)
27. F. R. Lillie, Embryology of the Uniomidae. *Journ. of Morphology*, X, 1895.
Differentiation without cleavage in the egg of the annelid *Chaetopterus pergamentaceus*. *Arch. für Entwicklungsmechanik*, XIV, 1902.
(The works of E. B. Wilson, *Arch. f. Entwicklungsmechanik*, XVI, and *Journal of Exp. Zoology*, I, may also be compared. Further, the treatise of Yatsu's *Biol. Bulletin*, VI.)
28. E. Maupas, Recherches expérimentales sur la multiplication des Infusoires ciliés. *Arch. Zool. Experim.*, 1888.
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 1. 1905. *Journal of Experimental Zoology*, II, Heft 3.
 2. 1905. *Journal of Experimental Zoology*, Bd. II, Heft 4.
 3. 1906. *Journal of Experimental Zoology*, Bd. III.
 4. 1909. *Journal of Experimental Zoology*, Bd. VI, Heft 2.
 5. 1909. *Journal of Experimental Zoology*, Bd. VI, Heft 2.
 6. 1910. *Journal of Experimental Zoology*, Bd. IX.
 7. 1911. *Journal of Morphology*, XXII, 71.
45. The following researches on the spermatogenesis of Anasa are known to the author.
 - Fr. C. Paulmier, 1899, *Journal of Morphology*, XV, Suppl.
 - E. B. Wilson, 1905, *Journal Exp. Zoology*, II
 - E. B. Wilson, 1907, *Science*, XXV, 631.

Foote and Strobell, 1907, *Biological Bulletin*, XII.

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Lefevre and McGill, 1908, *American Journ. Anat.*, VII, 469-485.

C. V. Morril, 1909, *Biological Bulletin*, XIX.

C. E. McClung and Edith Pinney, An examination of the chromosomes of *Anasa tristis*. *The Kansas University Science Bulletin*, V, No. 20, 349-380.

To those who would like to acquaint themselves further with this subject, this excellent article is especially recommended. It is distinguished by its concise, clear and exhaustive presentation.

46. Miss N. M. Stevens studied chromosomes in many insects with great skill and success.

1908. Diptera. *Journal Exp. Zoology*, V, 359.

1908. Diabrotica. *Journ. Exp. Zoology*, V, 453.

1909. Coleoptera. *Journ. Exp. Zoology*, VI, 101.

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Compare also *Biol. Bull.*, XVIII, 73-75, 1910.

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Heterochromosomes in the guinea-pig. *Biol. Bulletin*, XXI, 155-167.

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Accessory chromosomes in man. *Biol. Bulletin*, XIX, 219-234.

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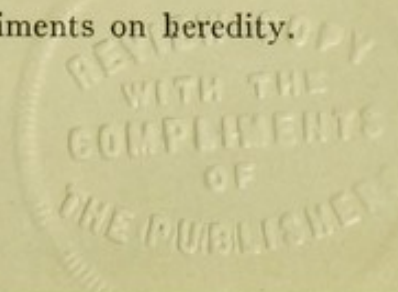
50. H. S. Pratt, *Science*, 1912. The author states the following estimations of the number of known species of animals:

Linné.....	1758	4,236
Agassiz and Bronn.....	1859	129,530
Ludwig (Leunis).....	1886	272,220
Pratt.....	1911	522,400

51. Helmholtz is not the author of the hypothesis that meteorites brought life to our earth. As early as 1871 it was introduced by Sir William Thompson in his Presidential Address before the British Association. So also the hypothesis of Arrhenius, which, according to Schäfer, was originated by Cohn (1872) and Richter (1875).

52. E. Pflüger, Ueber die physiologische Verbrennung in den lebendigen Organismen. *Pflügers Arch. gesamt. Physiol.*, X, 251-367, 1875. (See p. 339 ff.)

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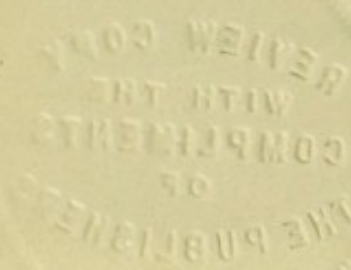
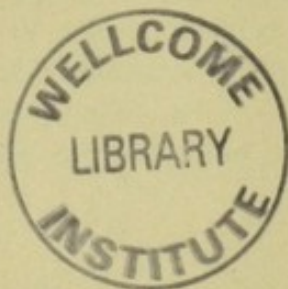
The larvæ live on fruits and complete their metamorphosis in about three weeks. Thus one can cultivate many generations of these small flies very easily and quickly. The principal investigation on the eyes will appear soon in the Journal of the Academy of Sciences, Philadelphia. The experiments, however, are still being carried on. Morgan has published other researches on *Drosophila*. See *Science*, XXXII, p. 120; XXXII, p. 496; XXXIII, p. 534; XXXIV, p. 384. Also, *Journal Exp. Zool.*, XI, 365-411, 1911. (Heredity in eye color, with figures.)

54. C. R. Stockard, The development of artificially produced Cyclopean fish—"The magnesium embryo." *Journ. Exp. Zool.*, VI, 285-337, 1908.
55. A. P. Matthews, Some ways of causing mitosis in unfertilized *Arbacia* eggs. *Amer. Journ. Physiol.*, 1900, VI, 343-347.
56. J. Loeb, On the nature of the process of fertilization and the artificial production of normal larvæ (*Plutei*) from the unfertilized egg of the sea-urchin. *Amer. Journ. Physiol.*, 1900, III, 135-138.

On the artificial production of larvæ from the unfertilized eggs of the sea-urchin (*Arbacia*). *Amer. Journ. Physiol.*, 1900, III, 434-471. (Preliminary communication, *Ibid.*, 135-138.)

Experiments on artificial parthenogenesis in annelids and the nature of the process of fertilization. *Amer. Journ. Physiol.*, 1901, IV, 423-459. (Compare also *Ibid.*, 178-184).

57. E. B. Meigs, *Zeitschr. f. allgem. Physiologie*, 1908, VIII, 81. *Amer. Journ. Physiol.*, 1908, XXII, 477. *Amer. Journ. Physiol.*, 1912, XXIX, 317.
58. C. F. Hodge, Changes in ganglion cells from birth to senile death. *Journ. of Physiol.*, XVII, 129-134.
59. R. R. Bensley, Studies on the pancreas of the guinea-pig. *Amer. Journ. of Anat.*, XII, 297-388, 1911.
60. Charles S. Minot, The problem of consciousness in its biological aspects. Presidential address before the American Association for the Advancement of Science. *Science*, XVI, 1-12, 1902. German translation in the volume, "Die Methode der Wissenschaft," published by Gustav Fischer, 1913.



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