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THE PROGRESSIVE
SCIENCE SERIES

# THE PROBLEM OF
# AGE, GROWTH & DEATH

CHARLES. S. MINOT

The Science Series

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# The Problem of Age, Growth, and Death

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# of
# Age, Growth, and Death

## A Study of Cytomorphosis

Based on Lectures at the Lowell Institute
March, 1907

By
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To

ANGELO MOSSO

SENATOR OF THE KINGDOM OF ITALY

PROFESSOR OF PHYSIOLOGY AT THE UNIVERSITY OF TURIN

THIS VOLUME IS DEDICATED

BY THE AUTHOR

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# INTRODUCTORY LETTER TO SENATOR MOSSO

MY DEAR MOSSO:

It is now over a third of a century since we were together in Leipzig as fellow-workers in the laboratory of Professor Carl Ludwig, on whom we look back as the greatest teacher of the art of scientific research whom we have ever known. He was a master of both the two great methods of biological study—observation and experiment. From him we learned to regard the living organism as an apparatus, of which it was necessary to learn both the construction and the working, and always to seek the explanation of the working on the basis of the construction. Although we have followed different lines of inquiry, the fundamental conceptions taught us by Ludwig have remained dominant. I look with admiration upon the number and importance of your scientific achievements. The pupil has proved himself worthy of the master, and has taken a master's place.

You will find in this volume, I trust, evidence of Ludwig's continued influence upon my work, and of my effort to follow upon a lesser scale your example. The years which have passed since those delightful student days have brought many changes, and have transformed us into members of the older generation. Therefore, I hope that you will regard the dedication of this volume on age to yourself as not inappropriate. As I write I recall our parting in the forest of Fontainebleau, our meeting on the glacier above Zermatt, our paddling together in a canoe on an American lake along the edge of the primeval forest, and many other experiences which we have shared. These were in our younger days, and now our interest in what is essential among the effects of age has a personal as well as a scientific foundation.

This book deals with a series of important biological problems, yet it is essentially a study of a single phenomenon,—the increase in the amount of protoplasm. The increase to be considered is not that which takes place at large in the body of the growing animal, but that which takes place within the limits of single cells, and occurs in such a manner that the proportion between the cell-body and the nucleus in volume, or bulk, is changed—the cell-body becoming relatively either larger as more frequently happens, or smaller, as happens in special cases.

By the study of the proportionate volumes of the nucleus and the cell-body we can demonstrate, I believe, certain laws governing that proportion, and prove that the variations of the proportion establish conditions which are fundamental to the correct conception of the problems of growth, differentiation, death, and sex. It is my endeavour, by following the precepts of Ludwig, to prove the existence of another set of correlations between the structure of cells and their function, which hitherto has been unrecognised. The primary correlation of the variations in proportions, which can be demonstrated, is with the age of the organism. Accordingly, the investigation of age and growth occupies a large share of the volume.

The subjects discussed in this book have received in part, hitherto, relatively little attention from biologists, hence the scientific literature dealing explicitly with them is rather scanty, although there are almost innumerable observations recorded in various writings, which have a bearing on the problems to be solved. Under these circumstances I have been forced, necessarily, to rely almost exclusively upon my own investigation; accordingly, the conclusions have a personal character in the sense that they have not yet been subjected to the critical judgment of biologists. Nevertheless, I hope that they will commend themselves to you.

My own active interest in growth as a biological problem goes back twenty-nine years, when I published an article on "Growth as a Function of Cells,"[1] followed by another, "On Certain Laws of Histological Differentiation."[2] These two papers, however, were of a somewhat theoretical character. Feeling strongly the necessity, which I should feel still more

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[1] *Proceedings Boston Soc. Nat. Hist.*, xx., 190 (1879).

[2] *Ibidem*, p. 201.

strongly now, of getting to direct facts, I started a series of observations on the growth of animals, which have been continued for a long period, during which the research has expanded far beyond its original scope. While carrying forward my experiments on growth, various conclusions suggested themselves; some tentative, others more or less definite. These have been partially and briefly published at various times.[1] To review these publications now would serve little purpose beyond possibly establishing the claim of priority, and I will therefore merely enumerate them. Moreover, in the course of the following pages the more important results contained in these earlier papers are brought together. My experiments on growth led to a memoir[2] published in 1891, in the English *Journal of Physiology*. It dealt with the growth of guinea-pigs and is to be regarded as the starting point or foundation of the present work. Since then the experimental work has been continued, and data concerning the growth of other animals collected. They are given in the course of the following pages.

[1] "Death and Individuality," *Journ. Sci.*, vii., 72–77 (1885), reprinted, *Science*, iv., 72–77.

"Researches on Growth and Death," *Proc. Soc. Arts* (Mass. Institute Technol.), Meeting 310, p. 50–56.

"The Formative Force of Organisms," *Science*, vi., 4–6 (1885).

"Researches on Growth and Death and Biological Problems," *Proc. Amer. Assoc. Adv. Sci.* for 1884, 517–521.

"The Physical Basis of Heredity," *Science*, viii., 125–130 (1886).

[2] "Senescence and Rejuvenation," first paper, "On the Weight of Guinea-Pigs," *Journ. of Physiol.*, xii., 97–153, pls. I.–III. (1891).

In 1890, in an address[1] delivered before the Section of Biology of the American Association for the Advancement of Science, at the Indianapolis meeting, I first presented the view that there is a distinct correlation between the amount of protoplasm and the rate of growth, as determined by the experiments just referred to. In an article[2] entitled "Ueber die Vererbung und die Verjüngung," which has been translated and republished in the *American Naturalist*, certain other general aspects of the quantitative study of protoplasm are dealt with. Finally, part of the conclusions developed were embodied in the "Middleton Goldsmith Lecture,"[3] before the New York Pathological Society, in March, 1901.

May I explain my point of view a little more fully? The proper object, the final purpose, of biology is the discovery of the nature of life. The existence, or non-existence, of a vital force is a problem concerning which a great many dogmatic assertions have been put forth. It is evident, however, that all opinions as to the essential nature of vitality, however much they have differed otherwise, are pretty much alike in lacking both scientific foundation and intellectual value. The agnostic position is the only possible

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[1] "On Certain Phenomena of Growing Old," *Proc. Amer. Assoc. Adv. Science*, xxix.

[2] "Ueber die Vererbung und Verjüngung," *Biol. Centralbl.*, xv., 571–587. Transl." "On Heredity and Rejuvenation," *American Naturalist*, xxx, 1–9; 89–101.

[3] "The Embryological Basis of Pathology," *Science*, N. S., xiii., 481–498; also *Boston Med. Sur. Journal*, cxliv., 295–305.

and defensible one for a scientific man to occupy, who is loyal to the spirit of research. We may then assume with little risk of mistake that no hypothesis of life yet offered requires serious scientific consideration. A confession of agnosticism is here a positive contribution to the truth. On the other hand, there is no reason for giving up the endeavour to get nearer to the final goal of biology because attempts to reach it by the short cut of speculation have always failed. Indeed, at the present time much work is being done towards answering general questions, the answers to which appear necessary preliminaries to attacking the problem of life itself.

Before the American Association for the Advancement of Science, in 1879, I read a paper "On Conditions to be Filled by a Theory of Life," which was published in abstract only.[1] It contained an enumeration, as complete and exact as I could make it, of phenomena which any tenable hypothesis of vitality must explain; the effort being made to generalise the statements to the farthest legitimate scientific limit, thus reducing as far as possible the number of phenomena. The result was a very vivid impression on my mind of the inadequacy of all hypotheses of vitality, and that impression is to-day undisturbed. Had circumstances permitted I should have devoted myself entirely to the study of general problems, but necessity early led me into teaching embryology, and in the acquisition of even my partial mastery of that

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[1] This abstract is reprinted as Appendix V to this volume.

intricate science so much time was absorbed, that I was forced to give up the hope with which I started out, and have only the present book to offer as a fragment towards the fulfilment of the original plan of researches upon general biological phenomena.

If one starts with the purpose of getting nearer a solution of the final problem of life, it is not difficult to devise numerous researches which would be likely to gain for us insight into the fundamental phenomena of biology. It was from the indicated standpoint that it seemed to me that one of the most promising opportunities for attack was offered by the changes which age effects in organisms. These changes had been then, and indeed have been since, very little studied in a systematic way or from any general standpoint. It is assuredly one of the most general phenomena in the life history of organisms that they become old. From the age of zero at the moment of sexual impregnation, animals and plants, broadly speaking, both pass through a series of changes until, barring accidents, they reach their limit of life; by which we mean the maximum longevity achieved by each individual under the optimum of conditions. Organisms are created young and grow old, and the old produce young successors. Senescence is a problem of living matter, and, so far as known, has no parallel in non-living matter. It is an essential feature of life. It finds its most familiar expression in the gradual loss of the functional powers of the organism, its end is death. My book is the outcome of an attempt to learn something as to the essential character and the cause of that loss.

Age causes many progressive changes in the organism, but none which are more obvious and more accessible to exact study than those of growth. Thus I was led to make my first experiments on growth. It soon appeared that the scope of the inquiry was expanding, and it has not been until now that the matters included have become sufficiently co-ordinated to justify their collective publication,—and yet the research remains fragmentary, narrow, and incomplete. I can make no pretence of having solved the manifold problems of senescence, but I hope that you will at least find some of them more clearly formulated than hitherto, and also some real additions to our positive knowledge.

For the purpose of studying growth as a function of age it was desirable to eliminate the influence of external conditions of a variable character as far as possible; the readiest way to accomplish this was to choose a self-regulative organism; accordingly one of the higher vertebrates was considered preferable, because of all organisms they are the most independent of outside circumstances. It remained only to pick out a convenient species; various considerations led to the choice of the guinea-pigs, *Cavia cobaya.* This animal offers the following advantages: it bears confinement well, is robust and but little liable to disease, breeds readily, is easily managed and fed, and gentle when handled; its maintenance is much less costly than that of a larger animal, an important consideration, as upwards of one hundred were kept at a time for several years.[1] Another important advantage depends on the fact that nearly every individual is marked with spots and blotches of brown and black differently from all others, so that they all can be readily told apart without any artificial marks, and hence it is easier to follow the growth of individuals. Occasionally there is one all white, but such white ones can be marked with spots of nitrate of silver on the hair. Guinea-pigs are so unintelligent that I have been unable to feel any interest except scientific in them, which perhaps also has been advantageous.

Later, as recorded in Chapter III., a limited number of determinations of the weight of growing rabbits and chickens was also made.

All these animals were kept in summer in suitable spacious pens in the country; in winter, in large boxes in well lighted and ventilated rooms, warmed by artificial heat. They were carefully tended most of the time by myself; the endeavour was to secure continuously the best hygienic conditions by unremitting attention; it was my habit to make two visits daily. They were fed with the best food obtainable.

To measure the growth the weights were taken of the growing and adult individuals, the weight being the only available measure for the whole animal,—and the only one permitting comparisons between

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[1] During one winter upwards of eighteen barrels of carrots, three tons of hay, twenty-six bushels of oats, and some other food were eaten by my guinea-pigs.

different species of organisms. The weighings were made in the morning before the animals were fed. But they were kept always supplied with dry oats; this practice is desirable because it helps essentially in preserving the animals in good condition. It does not entail a sufficient error in the weights to be objectionable, because it is more or less constant and is not very large, as the animals will not eat a great deal of grain when they have plenty of other food. No fresh food was left in the pens or boxes over night.

In all the weighings there is necessarily an error. A positive error, because the digestive tract, particularly the wide cœcum, contains always considerable quantities of undigested matter; moreover, the bladder may hold a greater or less quantity of urine. A negative error, because every illness, even a very slight indisposition, and every injury, such as a bite, for instance, causes a greater or less loss of weight. The quantitative values of these errors are presumably not very great; they probably counterbalance one another to a certain extent in the averages, which may be accepted as approximately accurate.

The advantage of these experiments over statistics taken from man lies especially in the fact that the same individuals are followed through the whole period of growth. Otherwise we may reach erroneous conclusions; thus in girls there is a very great acceleration of growth during the two or three years preceding puberty, that is, the epoch of the first menstruation; the acceleration shows itself also in a curve constructed from averages taken from a large number of observations upon many girls, but the variation appears less than it is for the individual and gives therefore an erroneous impression of the actual degree of prepubertal acceleration. This falsification necessarily ensues from the individual variations in the age of the first menstruation,—for the accelerations in one girl may occur at an older age than in another and a younger age than in a third, hence when a long series of observations is averaged the result shows an acceleration much longer in duration, but smaller in amount, than is characteristic for the individual. Thus Dr. B. A. Gould found that the stature of American soldiers increased steadily up to thirty-five years to 1.7391 metres, which was the maximum average height for any age. This observation does not prove that the growth period for Americans extends to thirty-five years, for the result noted may be due to more vigorous men growing more and surviving (but not growing) more years than the smaller and weaker men. The average at thirty-five is greater than at thirty because—if the suggested explanation is correct—the shorter men have died off. This might be decided by statistical study of the relation of the ages at death from disease to stature. It would certainly be worth while to investigate the problem, with a view of ascertaining whether there is any correspondence between the length of life and the size of individuals. A positive answer to the inquiry is to be expected. To return: —we have seen that if we do not compare the same individuals with one another we cannot be sure of correctly measuring the phases of growth. As guinea-pigs nearly complete their growth in one year, it was possible to make the requisite number of observations within a reasonable period, which is not the case with man.

In regard to my studies on the structure of cells in relation to growth, nothing special as to methods is to be said, as I have employed only the well-known standard procedures of histologists and embryologists.

If the conclusions formulated in this book concerning cytomorphosis, senescence, and rejuvenation are correct, they will have direct bearing on many lines of investigation concerning growth, reproduction, regeneration, degeneration, and pathological changes. If the conclusions are correct they will open, I hope, the way to many new interpretations. But I must stop.

Let me, however, close this lengthy letter with the request that you accept the dedication of this volume as a memento of our long friendship, and as an expression of my admiration and attachment.

Yours faithfully,
CHARLES SEDGWICK MINOT.

HARVARD MEDICAL SCHOOL,
BOSTON, MASSACHUSETTS, Jan. 13, 1908.

# The Problem of Age, Growth, and Death

# PROBLEM OF AGE, GROWTH AND DEATH

## I

### THE CONDITION OF OLD AGE

THE subject of age has ever been one which has attracted human thought. It leads us so near to the great mysteries that all thinkers have contemplated it, and many are the writers who from the literary point of view have presented us, sometimes with profound thought, often with beautiful images connected with the change from youth to old age. We need but to think of two books familiar more or less to us all—that ancient classic, Cicero's *De Senectute*, the great book on age, one might almost say, from the literary standpoint, and that of our own fellow-citizen, my former teacher and professor at the Medical School, Dr. Holmes, who in his delightful *Autocrat* offers to us some of his charming speculations upon age. From the time of Cicero to the time of Holmes numerous authors have written on old age, yet among them all we shall scarcely find any one who had title to be considered as a scientific writer upon the subject. Longevity is indeed a strange and difficult problem. Many of you doubtless have had your attention directed recently to the republished translation of Cornaro's famous work[1] and know how sensible that is, and as you read it you must have perceived how little in the practical aspect of the matter we have passed beyond the advice which old Cornaro gave to us, and yet silently in the medical laboratories, and in the physiological and anatomical institutes of various universities, we have been gathering more accurate information as to what is the condition of persons who are very old.[2]

We know, first of all, from our common observation, that the very old grow shorter in stature. We see that they are not so tall as in the prime of life. The figures which have been compiled upon this subject are instructive, for they show that at the age of some thirty years the average height of men—these figures refer to Germans—is 174 centimetres. It remains at that, however, only for a short period; then it decreases

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[1] Luigi Cornaro's work was originally published at Padua in 1558 under the title of *Trattato de la vita sobria*. English editions have been issued by George Herbert, by an anonymous editor (London, 1768), and G. H. Evans (1836), all which included other "discourses." The translation alluded to in the text was issued at Milwaukee in 1903 by Wm. F. Butler, and in the same volume the reader will find more apposite matter. Cornaro was born in 1464 and died in 1566. "He resigned his last breath without any agony, sitting in an elbow chair, being above an hundred years old."

[2] Addison, in the *Spectator* (Oct. 13, 1711), wrote of Cornaro and thus commends him: "The 'Treatise' I mention has been taken notice of by several eminent authors, and is written with such a spirit of cheerfulness, religion, and good sense, as are the natural concomitants of temperance and sobriety."

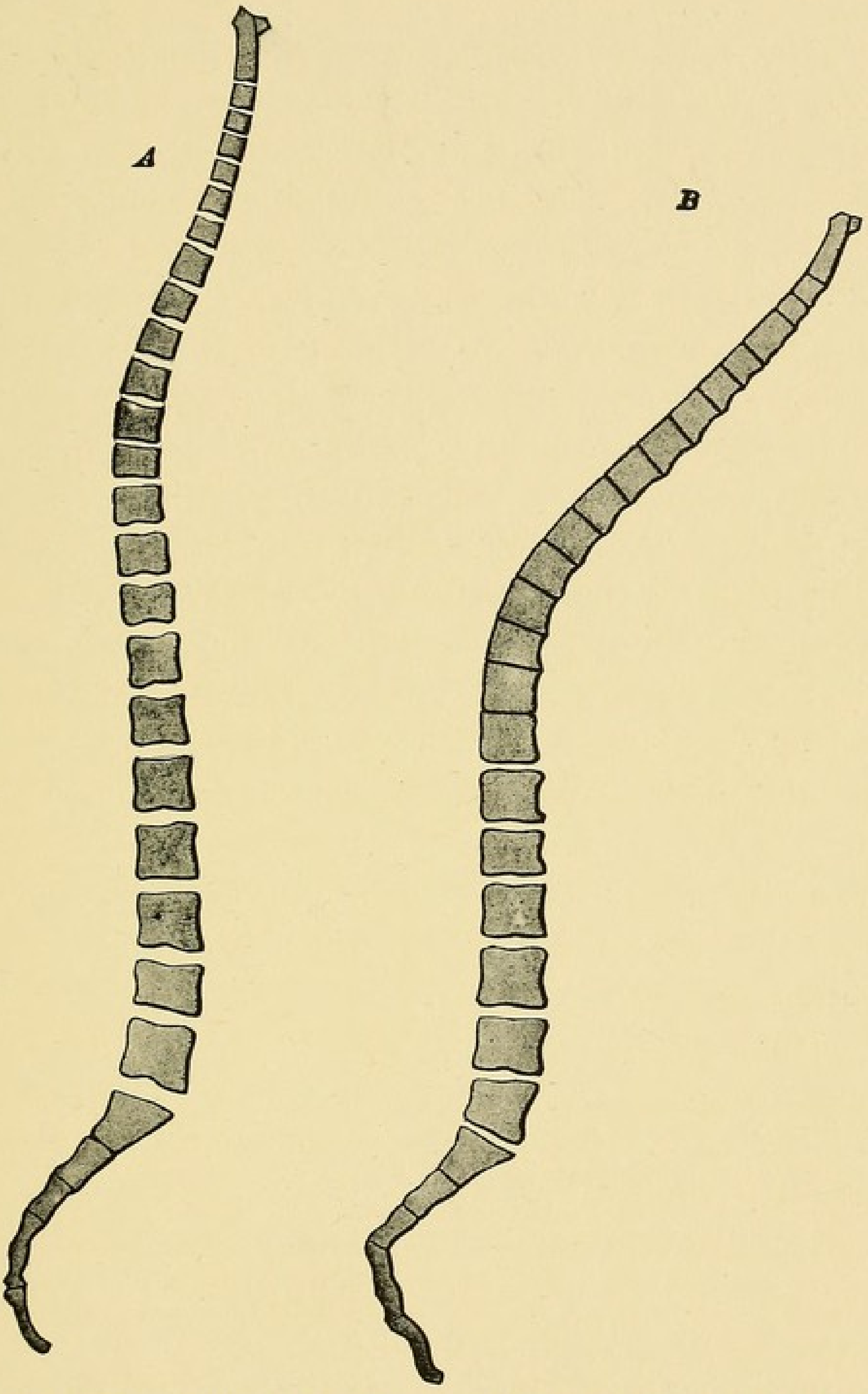


FIG. 1. TWO HUMAN VERTEBRAL COLUMNS IN SECTION. *A*, female of about 35 years. *B*, male of 83 years (an extreme case of senile fusion and flexure of the vertebræ).

and at forty it is already less; at fifty decidedly less; and at sixty the change has become more marked; until at seventy years we find that the height has shrunk from 174 to 161. There it remains, or thereabouts, through the remainder of life, though there may be a small further diminution. This decrease in stature is due largely to the changes in the vertebral column. First of all there is a stoop. The vertebral column is, to be sure, never straight, but in old age it becomes more curved, and the result is a falling of the total stature. But this is not the chief cause, for in addition to this the softer cartilages and elements of the spinal column become harder, change into bone, and as that change occurs they acquire a less extent and become smaller, and the result is that the vertebral column as a whole collapses somewhat and thus increases the diminution of height.

We find, as we look at the old, a great change to have come over the face. The roundness of youth has departed; the cheeks are sunken; the eyes have fallen far back; the lips are drawn in. All of these changes indicate to us, when we think upon them, the fact that there has been a certain shrinkage and shrivelling of that which is within and beneath the skin. Expressed in technical terms, we should call this an atrophy, and to anatomists the mere sight of the face of a very old person, Fig. 2, reveals at once this fundamental fact of an atrophy of the parts, an actual loss of some of their bulk, which is one of the most characteristic and fundamental marks of old age. The gait becomes shuffling, the foot is no longer lifted free from the ground, as the old man walks along. He does not rise upon his toes, but the sole of the foot is kept nearly flat and as he drags it cumbrously forward it is apt to strike upon the sidewalk. This indicates to the physiologist a lessened power in the muscles, a lessened control over the action of these muscles, an inferior co-ordination of the movements, so that there has been in the old man, judged by his gait alone, a physiological deterioration as well as an anatomical atrophy. We notice too his slow speech, often difficult hearing, and imperfect sight.

All of these qualities show a loss, and we commonly think of the old as those who have lost most, who have passed beyond the maximum of development and are now upon the path of decline, going down ever more rapidly. One of the chief objects at which I shall aim in this course of lectures will be to explain to you that that notion is erroneous, and that the period of old age, so far from being the chief period of decline, is in reality essentially the period in which the actual decline going on in each of us will be least. Old age is the period of slowest decline—a strange, paradoxical statement, but one which I hope to justify fully by the facts I shall present to you in this course.

In the old person you note that there is in the mind some failure and also loss of memory—less mental activity, greater difficulty in grasping new

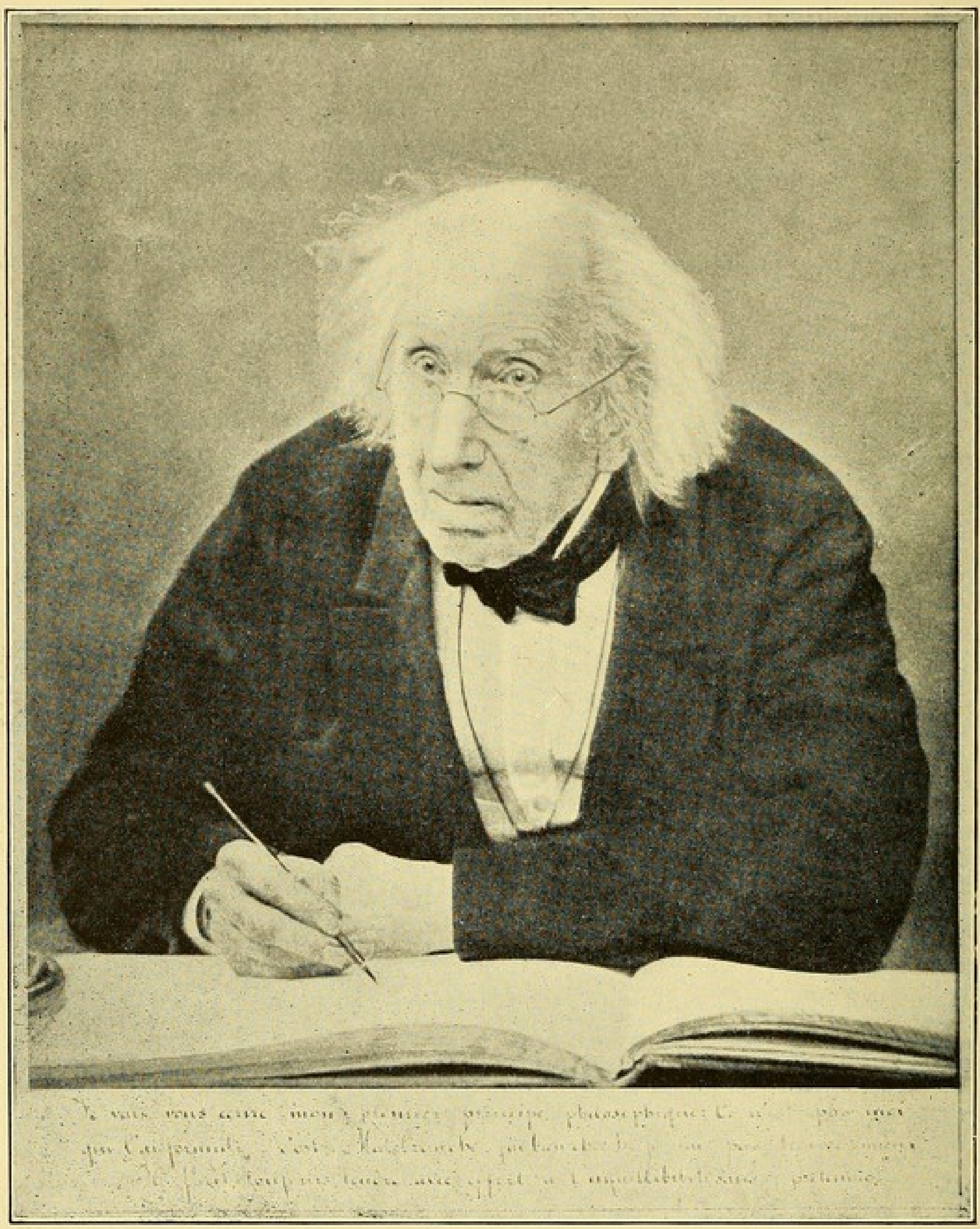
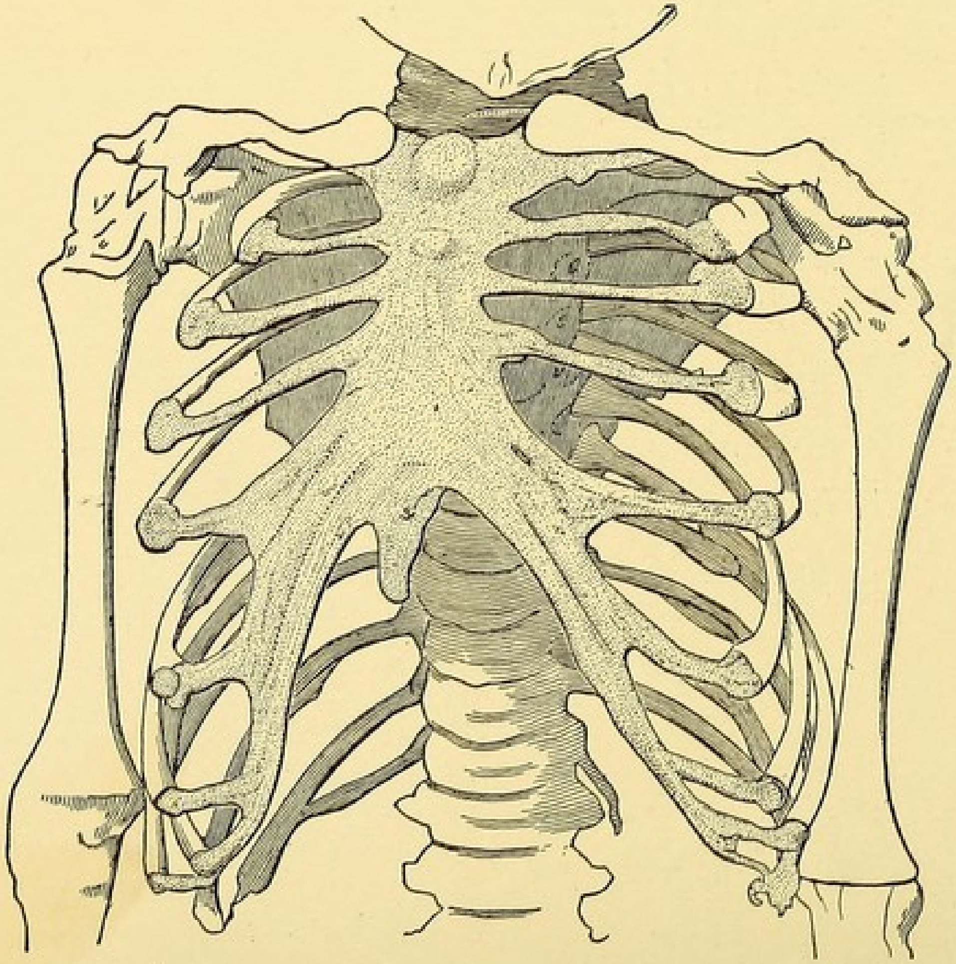
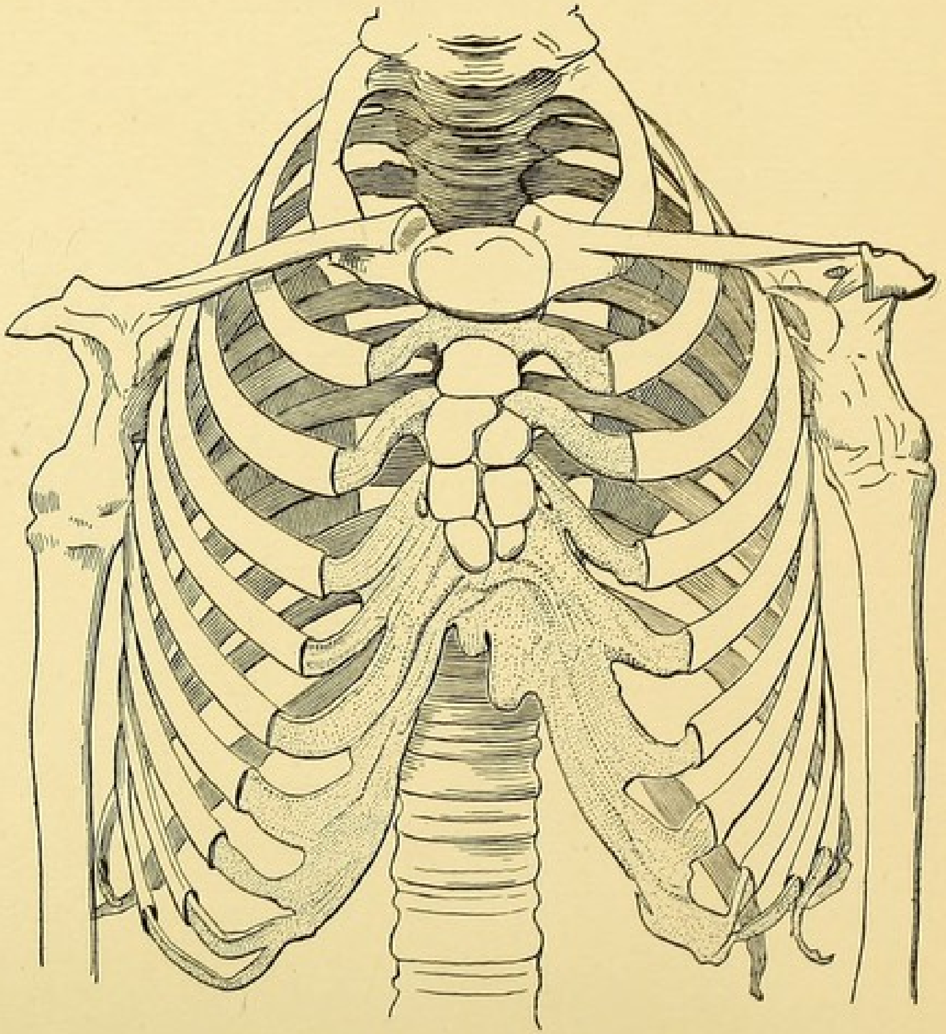


FIG. 2. PHOTOGRAPH OF CHEVREUL, taken on his one hundredth birthday. He was asked to write in an album and replied: "Que voulez vous: que j'écrive sur votre album? Je vais écrire mon premier principe philosophique, ce n'est par moi, qui l'ai formulé, c'est Malebranche—'On doit tendre avec effort à l'infallibilité, sans y prétendre.'" Chevreul was born Aug. 31, 1786, and died Aug. 9, 1889. For the privilege of using this portrait I am indebted to Dr. Henry P. Bowditch, to whom the interesting original belongs.

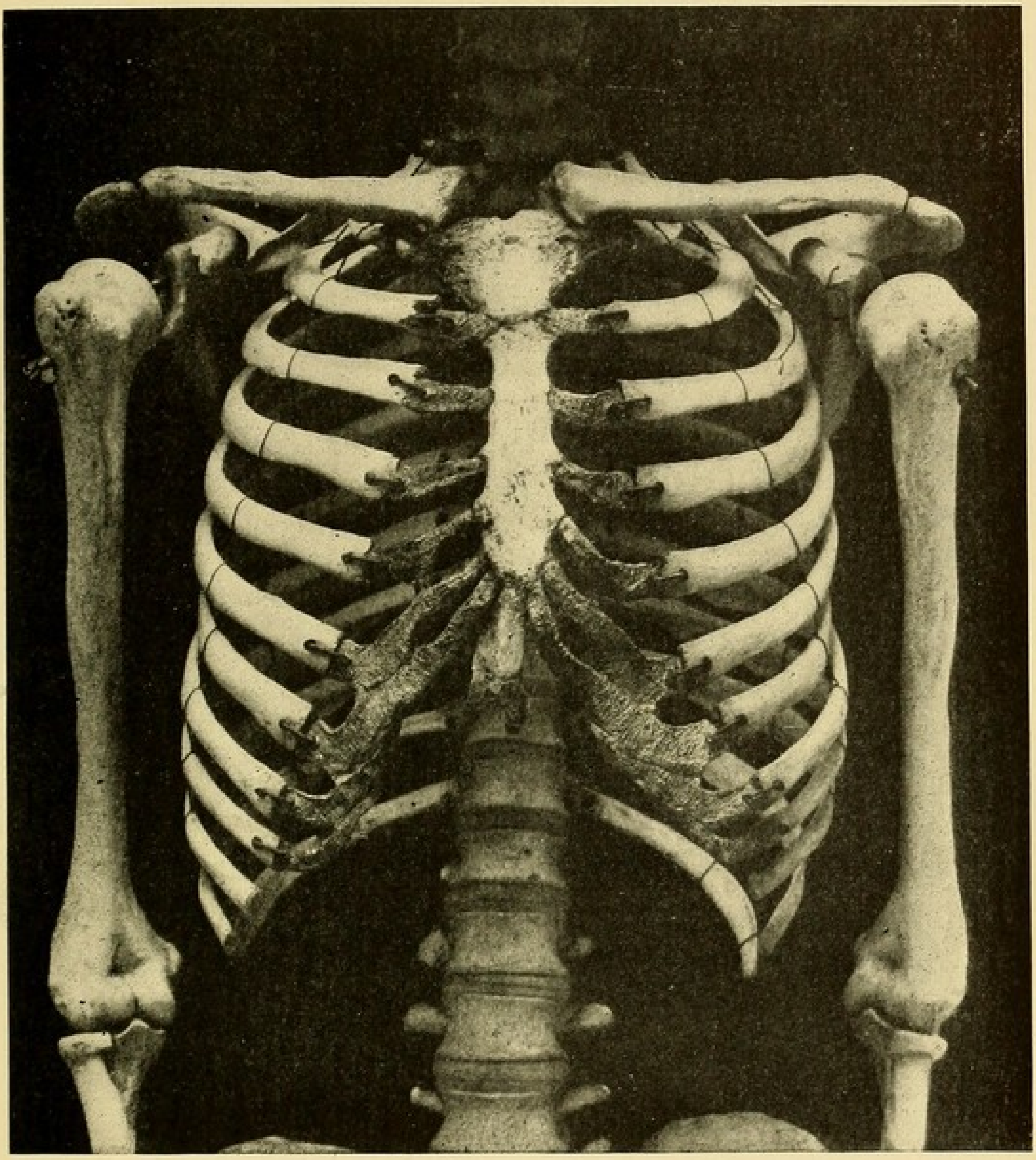
FIG. 3. PHOTOGRAPH FROM A CHILD AT BIRTH. The photograph is owned by Dr. H. P. Bowditch, by whose courtesy the present reproduction is published.



(A) Child at birth, reduced from life-size



(B) Child at seven years, much reduced.



(C) Adult, thirty years, very much reduced from life.

FIG. 4. RIBS AND STERNUM, to show the progressive ossification of the cartilage, which is indicated by stippling.—From specimens in the Warren Museum of the Harvard Medical School.

thoughts, assimilating new ideas, and in adapting himself to unaccustomed situations. All this betokens again the characteristic loss of the old. And as we turn now from these outward investigations to those which the anatomist opens up to us, we learn that in the interior of the body, and in every organ thereof, the species of change which I have referred to as characteristic of the very old is going on and has become in each part well marked.[1] Let us first examine the skeleton. In youth many parts of the skeleton are soft and flexible, like the gristles and cartilages which join the ribs to the breastbone, but in the old man these are largely replaced by bone. Bone represents an advance in organisation, in structure, as we say, over the cartilage. The old man has in that respect progressed beyond the youthful stage; but that progress represents not a favourable change; the alteration in structure from elastic cartilage to rigid bone is physiologically disadvantageous, so that though the man has progressed in the organisation or anatomy of his body, he has really thereby rather lost than gained ground. Indeed in the skeleton this principle of loss is already revealing itself.[2] In the interior of the bones of the arms, of the legs, we find

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[1] Especially valuable are the data concerning men and women of over eighty years collated by Sir George M. Humphry, in his book, *Old Age*, published at Cambridge (England) by Macmillan & Bowles in 1889.

[2] The senile alterations in the jaw of man have been studied by Josef Kieffer, ("Beiträge zur Kenntniss der Veränderungen am Unterkiefer und Kiefergelenk des Menschen durch Alter und Zahnverlust," *Zeitschr, für Morphol. u. Anthropol.*, xi, 1–82, Taf. i–iv, 1907). An important paper, offering good illustrations of the general principles described in the course of the present lecture.

a spongy structure, bits of bone bound together in many different directions, as are the spicules or fibres in a sponge, and by being bound so together they unite lightness with strength. As you know, a column of metal, if hollow, is stronger than the same amount of metal in the form of a rod. So with the bones. If they have this spongy structure, if their interiors are full of little cavities with intervening spicules acting as braces in every direction, then they acquire great strength with little material (Fig. 5). Now in the old much of the internal spongy structure is dissolved away and there is left (Fig. 6) barely more than an external shell. Partly on this condition depends the greater liability of the bones in the old person to break. If we examine the muscles we see that they have become less in volume, and when we apply the microscope to them we see that the single fibres on which the strength of the muscles depends have become smaller in size and fewer in number.[1] Professor B. Morpurgo[2] by an ingenious experiment has demonstrated that exercise increases the size of the muscles by increasing the size of the single fibres. Exercise produces a true physiological hypertrophy but no increase in the number of the fibres. This important discovery suggests the idea that senile muscular diminution is due chiefly if not exclusively

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[1] This statement is the one currently accepted—but I have found, as yet, no exact investigation upon the relative size and number of the muscle fibres in old persons.

[2] B. Morpurgo, "Ueber Activitäts-hypertrophie der wilkürlichen Muskeln," *Virchow's Arch. Pathol.*, Bd. cl., 522–554 (1897).

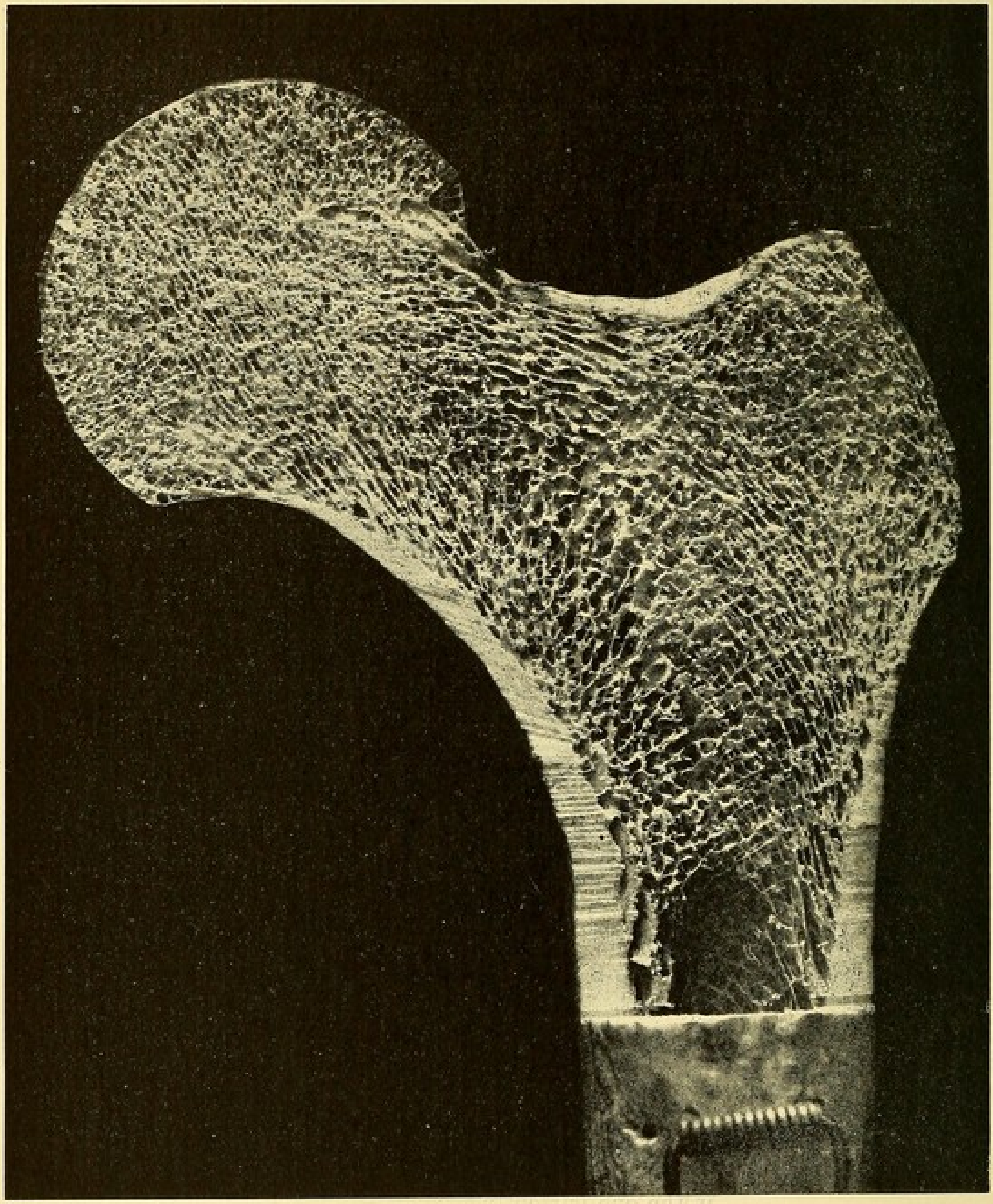

Fig. 5. Section of the Head of the Thigh Bone of a Man of Thirty-seven Years.—Compare Fig. 6.

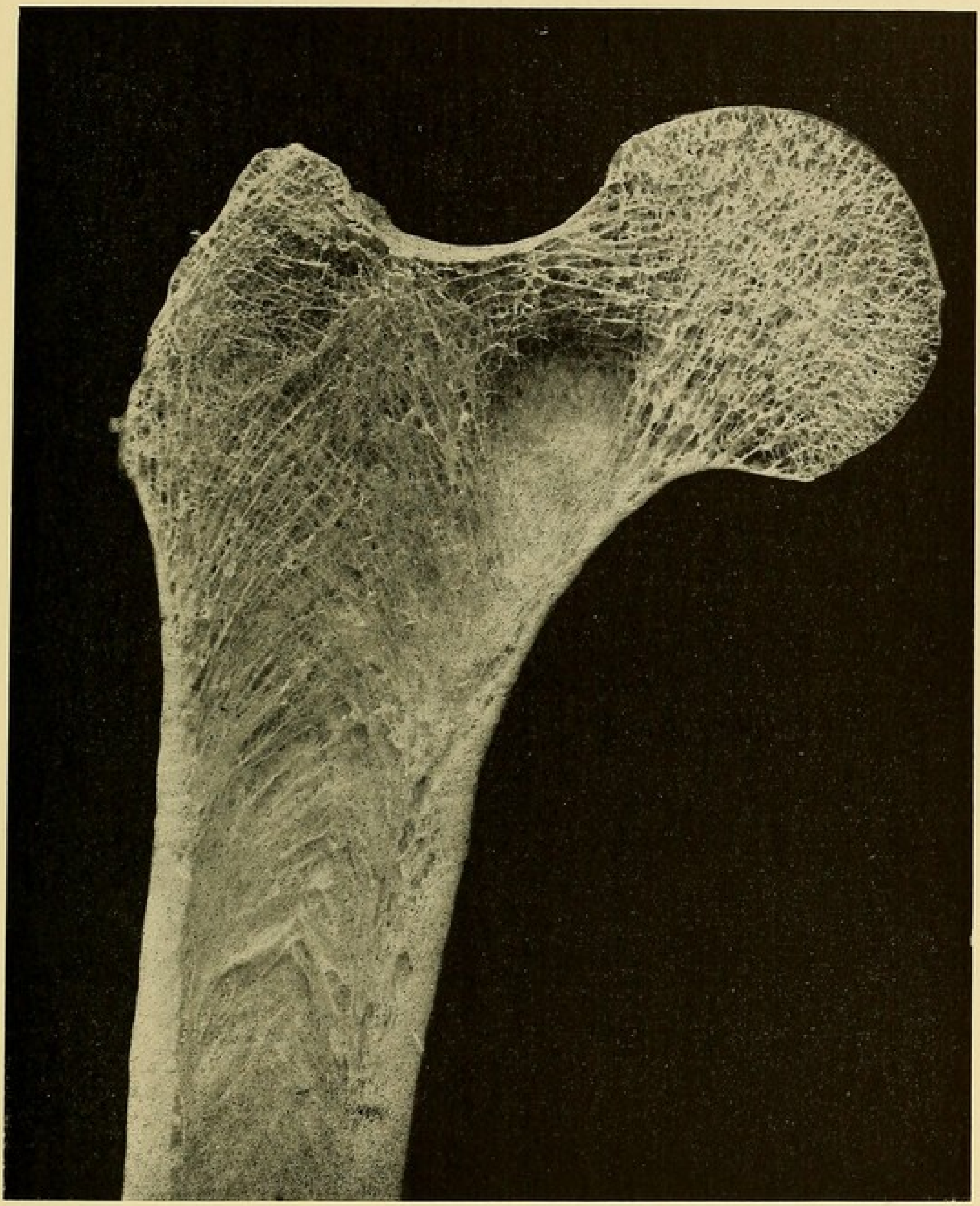

FIG. 6. SECTION OF THE HEAD OF THE THIGH BONE OF A WOMAN OF EIGHTY-TWO YEARS.—Compare with Fig. 5, and note the loss of the spongy bone in the older femur.

to the reduction in size of the single fibres. The muscle has actually lost; it is inferior, physiologically speaking, to what it was before. You remember how melancholy Jacques reminded us of this fact in speaking of the hose "a world too wide for his shrunk shank." His saying is justified by the loss of the muscles in volume and strength. The same phenomenon of atrophy shows itself in the digestive organs. Those minute structures in the wall of the stomach by which the digestive juice is produced undergo a partial atrophy, in consequence of which they are less able to act; they are not so well organised, therefore not so efficient as in earlier stages. The lungs become stiffened; the walls which divide off an air cavity from the neighbouring air cavities do not remain so thin as in youth, but become thickened and hardened, and the vital capacity of the lungs, that is to say the capacity of the lungs to take in and hold air, is by so much lessened. The heart—it seems curious at first—is in the old always enlarged; but this does not represent a gain in real power. On the contrary, if we study carefully the condition of the circulation of the blood in the old, we find that the walls of the large blood-vessels which carry the blood from the heart and distribute it over all parts of the body—vessels which we call arteries—have lost the elastic quality which is proper to them and by which they respond favourably to the pumping action of the heart. Instead they have become hard and stiff. We call this by a Greek term for hardening, sclerosis, and arterial sclerosis is one of the most marked and striking characteristics of old persons. Now when the arteries become thus stiffened, it requires a greater force and greater effort of the heart to drive the blood through them, and in response to this new necessity, the heart becomes enlarged in an effort of the organism to adapt itself to the new unfavourable condition of the circulation established by age. But the power of the heart becomes inferior along with the hypertrophy or enlargement of the organ and we see that in the old, in order to make up for the feebleness of the enlarged heart, it beats more frequently. In other words, the pulse rate in the old person increases.[1] We find, for instance, that at the time of birth the pulse is at the rate of 134 beats to a minute. It rises slightly during

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[1] My friend, Professor W. T. Porter, has had the kindness to compile the accompanying table for me, showing the pulse frequency from one to eighty years. For the first two months after birth the rate is about 130, after the third month, 140. The fœtal rate is 135 to 140.

| Age | Mean Frequency | Age | Mean Frequency | Age | Mean Frequency |
|---|---|---|---|---|---|
| 0– 1 | 134 | 13–14 | 87 | 25–30 | 72 |
| 1– 2 | 111 | 14–15 | 82 | 30–35 | 70 |
| 2– 3 | 108 | 15–16 | 83 | 35–40 | 72 |
| 3– 4 | 108 | 16–17 | 80 | 40–45 | 72 |
| 4– 5 | 103 | 17–18 | 76 | 45–50 | 72 |
| 5– 6 | 98 | 18–19 | 77 | 50–55 | 72 |
| 6– 7 | 93 | 19–20 | 74 | 55–60 | 75 |
| 7– 8 | 94 | 20–21 | 71 | 60–65 | 73 |
| 8– 9 | 89 | 21–22 | 71 | 65–70 | 75 |
| 9–10 | 91 | 22–23 | 70 | 70–75 | 75 |
| 10–11 | 87 | 23–24 | 71 | 75–80 | 72 |
| 11–12 | 89 | 24–25 | 72 | 80 and over | 79 |
| 12–13 | 88 | | | | |

the first three months of infancy until at the end of the third month it reaches some 140 beats a minute; it soon falls off, however, and at the end of the first year it has sunk to 111; at five or six years it becomes 98, and at twenty-one years it has sunk to 71 or 72. There are thereafter certain minor fluctuations in the rate of the heart-beat with advancing age, but generally it may be said that this value of 72 beats a minute is characteristic of adult life. But when a person becomes eighty years old, it has been found that upon the average the rate of the heart-beat rises and becomes 79 a minute. Hence it is clear that though the heart is larger, it has to make a greater effort, that is to say a more frequent beat, in order to maintain the necessary circulation of the blood.

Another illustration. We can demonstrate by going back to the anatomical examination of the body, that those important structures which we call the germ cells, upon which the propagation of the race depends, and which present under the microscope certain clearly recognised characteristics by which they can be distinguished from all other cells of the body,—that these germ cells cease their activity altogether in the very old, and one of the great functions of life is thus blotted out altogether from the history of the individual.

Turning now to the yet nobler organs, especially the brain, we see a curious change going on, a change of which old age presents to us the culminating record. In order to study the weight of the brain, it is necessary to compare people of the same size, for the size and weight of the brain depend somewhat upon the size of the individual. Now it has been discovered by careful examination of persons of similar size that the brain begins relatively early to diminish its weight. Thus in persons of a height of 175 centimetres, and over, of the male sex, it is found that in the period from twenty to forty years the brain weight is 1409 grams. But from forty-one to seventy years it has sunk to 1363, and in persons of from seventy-one to ninety it has shrunk to 1330. Women of equal size are not usual, and a more average height for women is 165 centimetres; a woman of such a height is likely to have—among the white races, be it understood—at twenty to forty years a brain of 1265 grams, at forty to seventy years of 1200 and at seventy-one to ninety years of only 1166 grams.[1] I give these figures because they show that there is no guessing, but a definite, positive knowledge, proving that soon after the maturity of life in the individual is reached, the shrinkage of the brain

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[1] Ernst Handmann has recently published statistics on the growth of brain, based on measurements at the Leipzig Pathological Institute. See *Archiv f. Anat. u. Entwickelungsges.*, 1906, p. 1. The following summarises his results:

| | Brain Weight in Grams | |
|---|---|---|
| Age | Male | Female |
| 4–6 | 1215 | 1194 |
| 7–14 | 1376 | 1229 |
| 15–49 | 1372 | 1249 |
| 50–84 (89) | 1332 | 1196 |

begins, and then continues almost steadily to the very end of life.[1]

It is not only the anatomist, but it is perhaps almost equally the physiologist who gives us insight into the changes which go on in the old. I spoke a few moments ago of the pulse rate, and of the change which that offers. At first sight it seems as if a greater pulse rate indicated an improvement, but if you recall the explanation given, you must acknowledge that this is by no means an acceptable interpretation, but that on the contrary the change is a clear mark of enfeeblement. In the respiration, also, we observe a like change. Here the comparison is not quite so easy as we should at first imagine, because there is a relation between the size of the individual and the respiration. The respiration, as you all know, frees the body from the products of combustion, particularly from that product which we know as carbon dioxide. The result of the combustion going on in the body (which in one of its end terms appears to us as carbon dioxide expelled from the lungs) is to produce heat, to develop the necessary warmth for the maintenance of the proper temperature of the body. Now in the very young the bulk of the body is not great, but the loss of heat is very great, and this perhaps can be most readily explained to you if you imagine that you hold in one hand a very small

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[1] For further details the reader is referred to the invaluable work by Professor H. H. Donaldson of the Wistar Institute, *The Growth of the Brain. A Study of the Nervous System in Relation to Education*, 12mo, London, 1895 (Walter Scott).

potato and in the other a very large potato, both of which have come at the same moment from the same oven, and that you have just started out for a cold winter drive. You all know, of course, that in a little while the small potato, though it was as hot as the large one at first, will have lost its heat, will no longer serve to keep the hand warm, but the other hand, in which the bulkier potato is held, in which the volume of the heat—we might so express it, perhaps—is correspondingly great, benefits by the retained heat a long time. Essentially similar to this is the difference between the child and the adult. The child loses heat with comparatively great rapidity—the old person at a comparatively slow rate. Hence it is necessary for the child to produce more warmth in order to keep up the natural normal temperature of the body. When, therefore, we find that in the old person the respiration is diminished, and that the production of carbon dioxide from the lungs is greatly lessened, we are not immediately to jump at the conclusion that the quality of physiological action has been debased—that we see here a sign of decrepitude. On the contrary, the change is the result of physiological adaptation, of suiting the performance of the body to its needs. This is one of the great wonders, one of the mysteries of life, of which we here have a sample, the constant adaptation of the means to the end. That which the body needs is done by the body. A child needs more warmth, and its body produces more; the old person needs less warmth, and his body produces less. How this is accomplished we are unable to say, but constantly we see evidence of this purposeful accommodation on the part of the body—what is called by the physiologists the teleological principle, the adaptation of the reaction of the body to its needs. There are innumerable illustrations of this, many of which are of course perfectly familiar to us, although perhaps we do not think of them as illustrations of this great law of nature; as, for instance, when we eat a meal, and the presence of food in the stomach calls into action the glands in the wall of the stomach by which the digestive juice is secreted. The juice is produced exactly at the time when it is needed. Innumerable, indeed, are the illustrations of this fundamental principle.

There is another class of phenomena characteristic of the very old which will perhaps seem a little surprising to you after the general tenor of my previous remarks. I refer to the power of repair. This, modern surgery especially has enabled us to recognise as being far greater in the old than we were wont to assume; and we know that there is a certain luxury, a certain excess reserve in the power of repair, and that we may go far beyond the ordinary necessities of our life in our demands upon our organism, and still find that our body is capable of making the necessary response.[1] Ordinarily the

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[1] A most valuable and suggestive study of the excess supply of physiological resources has been made by Dr. S. J. Meltzer, "The Factors of Safety in Animal Structure and Animal Economy," *Journal Amer. Med. Assoc.*, vol. xlviii, pp. 655–664.

amount of blood which we require is moderate in amount—moderate in the sense that the destruction of the blood continually going on in the body is not a very rapid process; but if, through some accident, a person loses a large quantity of blood, then, by one of these teleological reactions of which I have spoken, the production of new blood is increased, the loss is soon made up, and we discover that the blood, so to speak, has been repaired. Or when a little of the skin is lost, it quickly heals over. That again is due to the power of repair. Ordinarily so long as the skin remains whole that power is not called into action, but if a wound comes, then the regenerative force resident always in the skin, but inactive, comes into play and produces the mending which is such a comfort. So in old people, some of this luxury of reparative power persists, so that they can recover from wounds in a far better way than we should imagine if we judged them only by the general physiological and anatomical decline exhibited throughout all parts of the body. Some of the luxury of repair comes in usefully in old age.

Now if we consider all these changes in the most general manner, we perceive that they are clearly of one general character; they imply an alteration in the anatomical condition of the parts; but it is an alteration which does not differ fundamentally in kind from the alterations which have gone on before, but it does differ in the extent and in part in the degree to which these alterations have taken place. When the elastic cartilaginous rib becomes bony, nothing different is happening from that which happened before, for there was a stage of development when the entire rib consisted of cartilage, and in the progress of development toward the adult condition that cartilage was changed gradually into bone, thus producing the characteristic, normal, efficient bony rib of the adult. When old age intervenes, the change of the cartilage into bone goes yet further, but it progresses in such a way that it is no longer favourable, but unfavourable. We have then in this case a clear illustration of a principle of change in the very old which is, I take it, perhaps sufficiently well expressed by saying that the change which is natural in the younger stage is in the old carried to excess. But there is, in addition to this, something more, of which I have already spoken, namely the atrophy of parts, and by atrophy we mean the diminution, the lessening of the volume of the part. There is a partial atrophy of the brain in consequence of which that organ becomes smaller; there is an extensive atrophy of the muscles in consequence of which their volume is diminished, and their efficiency decreased. Atrophy is pre-eminently characteristic of the very old, and we see in very old persons that it becomes each year more and more pronounced. Indeed, it has been said recently by Professor Metchnikoff, a distinguished Russian zoölogist, now connected with the Pasteur Institute in Paris, some of whose publications many of you have doubtless read, that his conception of the nature of senility, of old age, could best be expressed in a single word, atrophy. "On résumé la senilité par un seul mot: atrophie."[1] That is his estimate of old age. But that is not the only estimate of old age which has been made up to the present time. We find one, which is much more prevalent, is that which connects it with the condition of the arteries. Indeed, Professor Osler has written this sentence: "Longevity is a vascular question, and has been well expressed in the axiom that a man is only as old as his arteries."[2] Now these are medical views, not biological, and you will find that there is a very extensive literature dealing with old age in man based upon the conception that old age is a kind of disease, a chronic disease, an incurable disease. Medical writers have put forward various conceptions giving a medical interpretation of this disease. That to which I just referred is the favourite one, the one you are most likely to hear from physicians to-day—namely, the theory of arterial sclerosis, that the hardening of the walls of the arteries is the primary thing; it interferes with the circulation, the bad circulation interferes with the proper working of every part of the body, and as the circulation becomes impeded, various accessory results are produced in the body in consequence. The body is brought to a lower or more diseased condition than before. Hence many medical writers interpret sclerosis of the arteries as

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[1] *L'Année biologique*, Tome III., p. 256, 1897.

[2] W. Osler, *The Principles and Practice of Medicine*, 1892, p. 666.

the primary factor, because they can trace so many alterations in the old which resemble diseased alterations to the natural changes in the arteries by which they acquire hardened and inelastic walls, which prevent the proper response of the artery to the heartbeat, upon which the normal healthy circulation largely depends.

Another interpretation, very curious and interesting, is that which has been recently offered by the same Professor Metchnikoff whom I have just mentioned. He has written a book upon the *Nature of Man*, translated in 1903, and published in this country. It is an interesting book. It gives a most attractive picture, incidentally, of Metchnikoff himself, a man of pleasantly optimistic temperament, but a man thoroughly imbued with the spirit which has so often been attributed to contemporary scientific men, of cold, intellectual regard towards everything, towards life, towards man, towards mystery. For him mysteries of all sorts have little interest. Those things which are mysterious are beyond the sphere of what can hold his attention. He must reside in the clear atmosphere of definite, positive fact. This mental bias is shown in his book. He reviews in a happy way various past systems of philosophy; he describes various religions; and he points out his reasons for thinking that all of these are insufficient, that there is no satisfaction to be derived from any of the ancient philosophies or from any of the great world religions. Nevertheless he is an optimist. He has noticed as a result of his meditations upon the arrangements within our bodies that we suffer very much from what he calls *disharmonies*, by which he means imperfect adaptations of structures within us to the performance of the body as a whole. He mentions various instances of such disharmonious parts. They do not seem to me quite so imposing as apparently they do to him, for many of his disharmonies are based upon the fact that we do not know that a certain structure or part has any useful rôle to play in the body. But I am inclined to suspect that in many cases it is only because we are ignorant; the list of useless structures in the human body was a few years ago very long; it has within recent years been greatly shortened, and we should learn from this experience a caution in regard to judging about these things, which, I think, Professor Metchnikoff has failed to exert duly in forming his opinions on these disharmonies. Now among the disharmonies which he recognises is that of the great size of the large intestine, which is of such a calibre that a considerable quantity of partially digested food can be retained in it at one time. When such food is retained in the intestine, it may undergo a process of fermentation. There are many sorts of fermentation, and some of them produce chemical bodies which are injurious to the human organism. Bacteria, which will cause fermentation of this sort, do actually occur in the human intestine. Metchnikoff thinks that, as we grow old, this tendency to fermentation increases.

Now the bodies produced by fermentation, the chemical bodies, I mean, get into our system and poison us. The result of the poisoning is that the native capacities of the various tissues and organs of the body are lowered, as happens in a man "intoxicated."[1] All parts of a man may be poisoned, not necessarily always with alcohol, but with many other things as well, and such a poisoning Professor Metchnikoff assumes to result from intestinal fermentation. Moreover, he has further observations, which lead him to the idea that certain cells go to work upon the poisoned parts and do further damage. The cells in question are minute microscopic structures, so small that we cannot at all see them with the naked eye, but which have a habit of feeding in the body upon the various parts thereof whenever they get a chance. Cells of this sort go by the scientific name of phagocytes, which is merely a Greek term for "eating cells." The phagocytes, for instance, devour pigment in the hair, and in old persons the production

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[1] The "poison-theory" of old age and death has recently been adopted by Prof. T. H. Montgomery, Jr., who has written: "Perhaps the best substantiated view . . . is that natural death of the individual results from self-poisoning. The waste products of metabolism, some of them toxic, accumulate in the tissues until there results a true intoxication of the latter. We may try to transcribe this into a little more definite physiological phrase: death follows on account of the insufficiency of the excretion process, therefore the limit of life is a matter of excretion" (*Transactions Texas Academy of Science*, ix, pp. 77. 78). The author gives no evidence to justify these assertions, and they are therefore hardly available for discussion. P. 79, Montgomery dissents from my views on differentiation, because I have failed to recognise "the underlying factor of senescence, which is insufficiency of the excretion process." The present volume aims to prove that the underlying factor of senescence is another than that assumed by Montgomery.

of white hair has resulted from the activity of phagocytes which have eaten the pigment which should have remained in the hair and kept its colour.[1] But the pigment of the hair is not the only thing they will attack; they will make their aggressive inroads upon any part of the body; and Professor Metchnikoff has advanced the theory that old age consists chiefly in the damage which is done by phagocytes to poisoned parts of the body, the poisoning being due to the fermentation in the large intestine. Now it has been observed by some of the German investigators[2] of these matters that the presence of lactic acid interferes with this fermentative process as it goes on in the intestine. Lactic acid, as its name implies, is the characteristic acid which occurs in milk when it becomes sour. An Italian investigator[3] tried drinking some sour milk with the idea of stopping the fermentation in the intestine, and so putting an end to the deleterious change, and he believes in the short time that he tried it that it did him good—quite, you see, in the way of a patent medicine.[4] Professor Metchnikoff, on this basis, has recommended, in his book on the *Nature of Man*, the regular drinking of sour

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[1] This interesting fact was discovered by Metchnikoff, *Annales de l'Institut Pasteur*, 1901, p. 865.

[2] Compare Bienstock, *Archiv für Hygiene*, xxxix., p. 390 (1902); also Tissier et Martelly, *Annales de l'Institut Pasteur*, 1902, p. 865.

[3] Albert Rovighi, "Die Aetherschwefelsäuren im Harn und die Darminfection," *Zeitschr. für Physiol. Chemie*, xvi., pp. 20–46; see especially p. 43.

[4] Rovighi used "kephyr," a fermented milk, in his experiments. For the mode of preparation and for the use of "kephyr," see Fischer, *Die neueren Arzneimitteln*, Berlin, 1887, p. 169.

milk,[1] in the hope apparently that it will postpone senility, and will leave us our powers in maturity long beyond that period when we at present reach the fulness of our vigour, and advance the period of time when the changes of the years put us out of court. He regards this as an optimistic substitute for the various forms of philosophy and religion which many millions of people have found helpful in life, and certainly it is the cheapest substitute which has ever been seriously proposed.

There is another writer who, though having a German name, is in reality a Russian, Professor Mühlmann.[2] He has another theory in regard to the fundamental nature of senility. He takes such instances as that which I spoke of, of respiration in connection with the production of warmth in the child's body and in the body of the adult, and finds that the diminution of the surface in proportion to the bulk of the body is characteristic of the old, and he concludes that we be come old because we do not have proportionately surface enough left. His view implies, apparently, that if

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[1] "It is plain, then, that the slow intoxications that weaken the resistance of the higher elements of the body may be arrested by the use of kephyr, or better still of soured milk" (Metchnikoff, *Nature of Man*, 1903, p. 255).

[2] Mühlmann has published several papers on old age, which contain much valuable and original matter. The following may be specially cited:

"Weitere Untersuchungen über die Veränderung der nervenzellen in verschiedenem Alter," *Arch. mikrosk. Anat.*, lviii., pp. 231–247 (1901).

"Ueber die Veränderungen der Hirngefässe in verschiedenem Alter," *Arch mikrosk. Anat.*, lix., pp. 258–269 (1901).

His general views are presented in his memoir, *Ueber die Ursache des Alters*, Wiesbaden, 1900, and in a short essay in the *Biologisches Centralblatt*, Bd. XXI, pp. 814–828.

we could keep ourselves more or less of the stature of pygmies we should be healthier and better off. I confess these theories, and many others which I might enumerate to you, seem to me to be somewhat fantastic—odd rather than valuable. Yet they all spring from this one common feeling, which is, I believe, a sinister influence upon the thought of the day in regard to the problem of age—they spring from the medical conception that age is a kind of disease, and that the problem is to explain the condition as it exists in man. Now that is precisely what I protest against. What I hope to accomplish in these lectures is to build up gradually in your minds some acquaintance with the fundamental and essential changes which are characteristic of age and in regard to which we have been learning something during the last few years—I might almost say only within recent years—and by means of this exposition to give you a broader view and a juster interpretation of the problem. I hope, before I finish, to convince you that we are already able to establish certain significant generalisations as to what is essential in the change from youth to old age, and that in consequence of these generalisations, now possible to us, new problems present themselves to our minds, which we hope really to be able to solve, and that in the solving of them we shall gain a sort of knowledge, which is likely to be not only highly interesting to the scientific biologist, but also to prove, in the end, of great practical value. Surely we cannot hope to obtain any power over age, any power over the changes which the years bring to each of us, unless we understand clearly, positively, and certainly, what these changes really are. I think you will learn, if you do me the honour to follow the lectures further, that the changes are indeed very different from what we should expect when we start out on a study of age, and that the contributions of science in this direction are novel and to some degree startling. We can begin to approach this broader view of our subject if we pass beyond the consideration of man.

If we turn from man to the animals which we are most familiar with, the common domestic quadrupeds, we see that they undergo a series of changes not very dissimilar to those which man himself must pass through. An old horse, an old dog, an old cat, shows pretty much the same sort of decrepitudes which characterise old men. But when we pass farther down in the scale to the fishes, or even to a frog, we discover great differences. Do you think you could tell a frog when it is old by the way it walks—for it never walks—or a fish by the amount of hardening of the lungs, when it has none? Yet the lack of lungs is characteristic of the fish. And what becomes of the theory of arterial sclerosis when we go still lower in the animal kingdom, towards its lowermost members, and find creatures which live and thrive and have lived and thriven for countless generations, yet have no arteries at all? They, of course, do not grow old by any change of their arteries. But when we come to study these various animals more carefully, we learn that in them the anatomical and physiological features which I have indicated to you in my description of the changes in the human being are paralleled, as it were, by similar changes; but only by similar, not by identical, changes. If we examine the insects, for instance, we see that in an old insect there is a hardening of the outer crust of the body which serves as a shell and a skeleton at once. That hardening increases with the age of the individual. We can see in the insect a lessening development of the digestive tract, and we can see—it has been demonstrated with particular nicety—a degradation of the brain.[1] Insects have a very small brain, but when a bumblebee, or a honeybee, grows old, as he does in a few weeks after he acquires his wings, we see that the brain actually becomes smaller, and not only that, but as I shall be able to demonstrate to you with the lantern in the next lecture, the elements which build up the brain have each of them become smaller and the diminution in the size of the brain is due in part to the shrinkage of the single microscopic constituents. There is another point of resemblance. We find that when one of the better parts of the body undergoes an atrophy, it becomes not only smaller, but its place is to a certain extent taken by the inferior

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[1] C. F. Hodge, "Changes in Ganglion-Cells from Birth to Senile Death. Observations on Man and Honeybee," *Journal of Physiology*, vol. xvii., pp. 129–134 (1894).

tissues—especially by those which we call comprehensively the connective tissues, which might perhaps be best described to a general audience as that which is the stuffing of the body and fills out all the gaps between the organs proper. In consequence of performing this general function, they are very properly called connective tissues, since they connect all the different organs and systems of organs in the body together. Now in every body there is a continual fighting of the parts. They battle together, they struggle, each one to get ahead, but the nobler organ, generally speaking, holds its own. There are early produced from the brain the fine bundles of fibres which we call the nerves, which run to the nose, to the tongue, and to the various parts of the body. When these appear all the parts of the body are very soft. Afterwards comes in the hard and, we should think, sturdy bone, but never, under normal conditions, does the bone grow where the nerve is. The nerve, soft and pulpy as it seems, resists absolutely the encroachment of the bone, and though the bone may grow elsewhere, and will grow elsewhere the moment it gets a free opportunity, it cannot beat the soft delicate nerve.[1] Similarly we find that the substance which forms the liver is pulpy, very

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[1] The nerve fibres of the olfactory membrane arise very early in the embryo and form numerous separate bundles. Later the bone arises between the bundles, for each of which a hole is left in the osseous tissue, so that the bone in the adult has a sieve-like structure, and hence is termed the cribriform plate. It offers a striking illustration of the inability of hard bone to disturb soft nerve fibres.

delicate. Those of you who have seen fresh liver in the butcher's shop know what a flabby organ it is, and yet though it is surrounded by the elements of connective tissue, which with great zest and eagerness produce tough fibres, it never gives way to them. The connective tissue is held back by the soft liver and kept in place by it. The liver is, so to speak, a nobler organ than the connective tissue and holds sway ordinarily; but in old age, when the nobler organs lose something of their power, then the connective tissue gets its chance, grows forward, and fills up the desired place, and acquires more and more a dominating position. We can see this process in the brain of man or the brain of the bee. That which is the nervous material proper, microscopic examination shows us to be diminished everywhere in the old bee and in the old man, and the tissue which supports it, which is of a coarser nature and cannot perform any of the nobler functions, fills up all the space thus left, so that the actual composition of the brain is by this means changed. There is, you see, therefore, during the atrophy of the brain, not only a diminution of the organ as a whole, but there is the further degradation which consists in the yielding of the nobler to the baser part, if I may so express myself. That, you recognise, necessarily implies a loss of function. The brain cannot under senile conditions do the sort of fine and efficient work which it could do before. Now if we go on from insects to yet lower organisms, we see less and less appearing of an advance in organisation, of correlated loss of parts, and when we get far enough down the scale, senescence becomes very vague. The change from youth to old age in a coral or in a sponge is at best an indefinite matter.

I should like, did the length of the course permit, to enlarge greatly upon this aspect of the question, and explain to you how it is that as the organism rises higher and higher in the scale, old age becomes more and more marked, and in no animal is old age perhaps so marked, certainly in no animal is it more marked, than in ourselves. The human species stands at the top of the scale and it also suffers most from old age. We shall learn, I hope, more clearly later on in the course of these lectures, that this fact has a deeper significance, that the connection between old age and advance in organisation, advance in anatomical structure, is indeed very close, and that they are related to one another somewhat in fashion of cause and effect; just how far each is a cause and how far each is an effect it would perhaps be premature to state very positively; but I shall show you, I think in a convincing way, that the development of the anatomical quality, or in other words of what we call organic structure, is *the* fundamental thing in the investigation of the processes of life in relation to age. We can see it illustrated again very clearly indeed when we turn to the study of plant life, for plants also grow old. Take a leaf in the spring. It is soft as the bud opens. The young leaf is delicate. It has a considerable power of growth. It expands freely, and soon becomes a leaf of full size. Then comes the further change by which the leaf gets a firmer texture; the production of anatomical quality in the leaf, so to speak, goes on through the summer, and the result of that advance in the anatomical quality is that the delicate, youthful softness and activity of the leaf is stopped. It cannot grow any more; it cannot function as a leaf properly any more. The development of its structure has gone too far and the leaf falls and is lost, and must be replaced by a new leaf the next year. When we examine the changes that go on in any flowering plant, we observe always that there is this production of structure, and then the decay, the end or death. At first structure comes as a helpful thing, increasing the usefulness of the part, and then it goes on too far and impairs the usefulness, and at last a stage is produced in which no use is possible any longer—the thing is worthless. It is cast away in the case of the plant life; and this casting away of the useless is a thing not by any means confined to plants; it occurs equally in ourselves all the time; at every period of our life we have been getting through with some portion of our body; that portion acquired a certain organisation, it worked for us awhile, and then being done with it, we threw it away because it was dead. Very early in the history of every individual there was a production of blood, and then followed the destruction of some of the blood corpuscles and their remains were used for various purposes. The pigment which is in the liver comes from the destroyed blood corpuscles, and it is believed that the pigment which colours the hair is derived from the same source. The blood corpuscles contain a material which when chemically elaborated reappears as the deposit which imparts to the hairs their colouration. You, of course, are all familiar with the loss of hair. It occurs to everybody, but did you ever think that it means that the hair which has lived has died, and that that hair which was a part of you has been cast off? That is what the loss of hair means to the biologist—the death of a part and the throwing away of it, and it is typical of what is going on through the body all the time. It occurs in the intestines, where the elements which serve for purposes of digestion are continually dying and being cast off. The outer skin is constantly falling off and being renewed, and that which goes is dead. In every part of the body we can find something which is dying. Death is an accompaniment of development; parts of us are passing off from the limbo of the living all the time, and the maintenance of the life of each individual of us depends partially upon the continual death going on in minute fragments of our body here and there.

Our next step in this course of lectures will carry us into the microscopic world, and with the aid of the lantern at the next lecture I shall hope to demonstrate to you a little of the microscopic structure of the body and of the general nature of the change which exhibits itself in the body from its earliest to its latest condition. With such knowledge in our minds, we shall be able next to study some of the laws of growth. We shall gain from our microscopic information a deeper insight into some of the secrets of the changes which age produces in the human body.

## II

## CYTOMORPHOSIS: THE CELLULAR CHANGES OF AGE

*LADIES AND GENTLEMEN:* I endeavoured in my last lecture to picture to you, so far as words could suffice to make a picture, something of the anatomical condition of old age in man, and to indicate to you further that the study merely of that anatomical condition is not enough to enable us to understand the problem we are tackling, but that we must in addition extend the scope of our inquiry so that it will include animals and plants, for since in all of these living beings the change from youth to old age goes on, it follows that we can hardly expect an adequate scientific solution of the problem of old age unless we base it on broad foundations. By such breadth we shall make our conclusion secure, and we shall know that our explanation is not of the character of those explanations which I indicated to you in the last lecture, which are so-called "medical," and are applicable only to man, but rather will our explanation have in our minds the character of a safe, sound, and trustworthy biological conclusion. The problem of age is indeed a biological problem in its broadest sense, and we cannot study, as we now know, the problem of age without including in it also the consideration of the problems of growth and the problems of death. I hope to so entice you along in the consideration of the facts which I have to present, as to lead you gently but perceptibly to the conclusion that we can with the microscope now recognise in the living parts of the body some of those characteristics which result in old age. Old age has for its foundation a condition which we can actually make visible to the human eye. As a step towards this conclusion, I desire to show you this evening something in regard to the microscopic structure of the human body.

We now know that the bodies of all animals and plants are constituted of minute units so small that they cannot be distinguished by the naked eye, although they can be readily demonstrated by the microscope.[1] These units have long been known to naturalists by the name of cells. The discovery of the cellular constitution of living bodies marks one of the great epochs in science, and every teacher who has occasion to deal in his lectures with the history of the biological sciences finds it necessary to dwell upon this great discovery. It was first shown to be true of plants, and shortly after likewise of animals. The date of the latter discovery was 1839. We owe it to Theodor Schwann, whose name will

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[1] I have estimated the average diameter of the cells in the human adult as fifteen thousandths of a millimetre (0.015 mm.). One millimetre is approximately one twenty-fifth of an inch. This estimate is probably not exact, but may serve to indicate the order of cell dimensions.

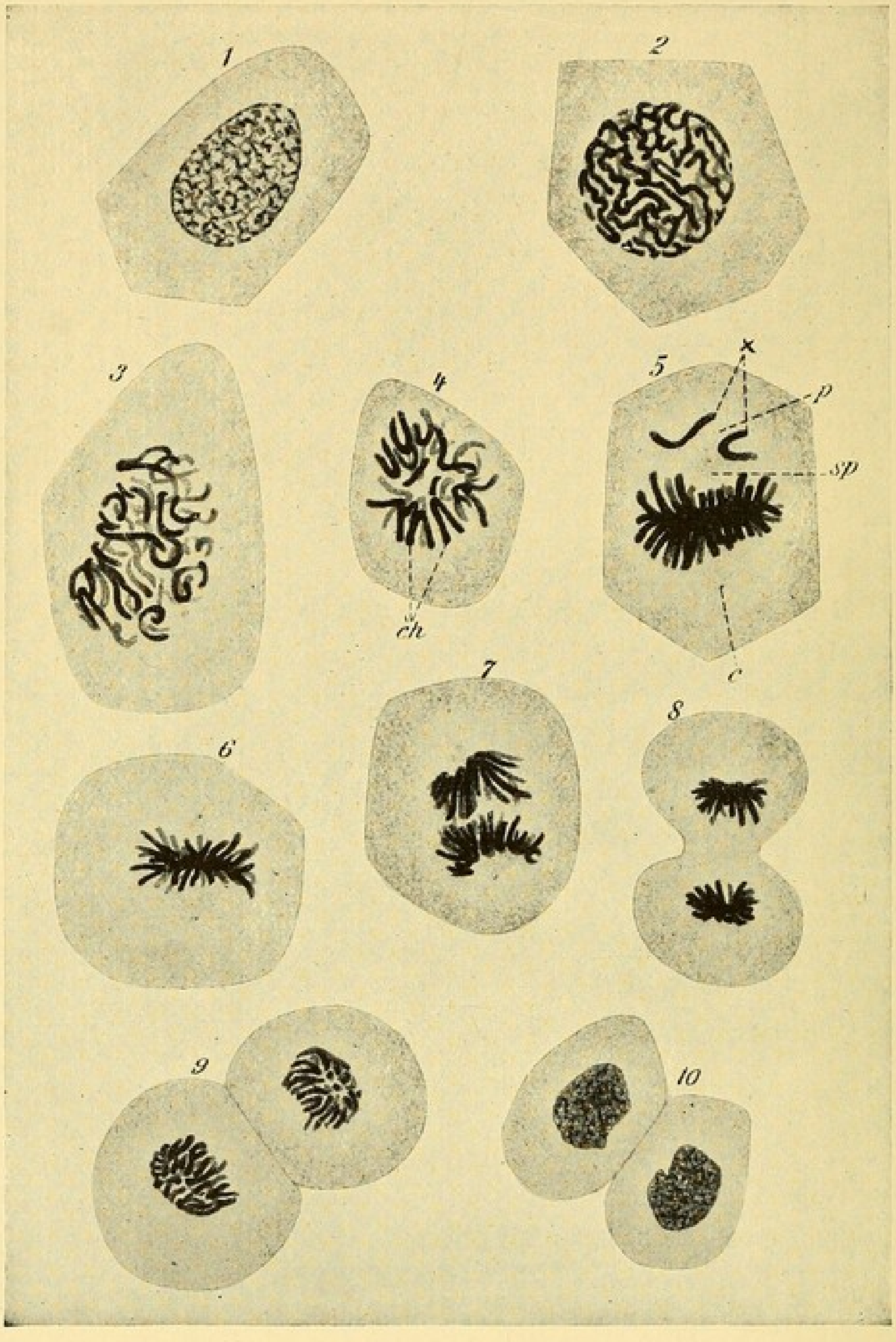

FIG. 7. CELLS FROM THE MOUTH (ORAL EPITHELIUM) OF THE SALAMANDER, to show the phases of cell division or mitosis. The cells are not represented in the living state, but artificially preserved and coloured. In the living cell there is no such marked contrast of colour between the protoplasm and the nucleus as appears in these figures.—After Sobotta.

therefore ever be honoured by all investigators of vital phenomena. What the atom has been to the chemist, the cell is to the naturalist, but with this difference, atoms are hypothetical, cells are known by direct observation. Every cell consists of two essential parts. There is an inner central kernel which is known by the technical name of *nucleus*, and a covering mass of living material which is termed the *protoplasm* and constitutes the body of the cell. I will now call for the first of our lantern slides to be thrown upon the screen. It presents to you pictures of the cells as they are found lining the mouth of the European salamander. The two figures at the top illustrate very clearly the elements of the cell. The protoplasm forms a mass, exhibiting in this view no very distinctive characteristics, and therefore offering a somewhat marked contrast with the darker oval nucleus, which presents in its interior a number of granules and threads. Every nucleus consists of a membrane by which it is separated from the protoplasm, and three internal constituents: First, a network of living material, more or less intermingled with which is a second special substance, chromatine, which owes its name to the very marked affinity which it displays for the various artificial colouring matters which are employed in microscopical research.[1] The third of the internal nuclear constitu-

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[1] It seems to me very doubtful whether the distinction drawn between the network and the chromatine of the nucleus is valid—but the distinction is usually affirmed in the text-books of to-day. There are observations which

ents we may call the sap (hyaloplasma), the fluid material which fills out the meshes of the network. Later on we shall have occasion to study somewhat more carefully the principal variations which nuclei of different kinds may present to us, and we shall learn from such study that we may derive some further insight into the rapidity of development and the nature of the changes which result in old age. While the picture is upon the screen, I wish to call your attention to the other figures, which illustrate the process of cell multiplication. As you regard them you will notice in the succession of illustrations that the nucleus has greatly changed its appearance. The substance of the nucleus has gathered into separate peculiarly elongated granules, each of which is termed a *chromosome*. The chromosomes are very conspicuous under the microscope, because they absorb artificial stains of many sorts with great avidity and stand out therefore conspicuously coloured in our microscopic preparations. They are much more conspicuous than is the substance of the resting nucleus. The fact that we can readily distinguish the dividing from the resting nucleus under the microscope,—compare Fig. 72,—we shall take advantage of later on, for it offers us a means of investigating the rate of growth in various parts of the body. I should like, therefore, to emphasise the fact at the present time sufficiently to be sure that it will remain

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render it probable that there is in the network only one constituent of which the chromatine is a functional modification, varying in extent in accordance with the alternating phases of cell-life.

in your minds until the final lecture, in which we shall make practical use of our acquaintance with it. It is unnecessary for our purposes to enter into a detailed description of the complicated processes of cell division. But let me point out to you that the end result is that where we have one cell we get as the result of division—two ; but the two divided cells are smaller than the mother cell and have smaller nuclei. They will, however, presently grow up and attain the size of their parent.

Every cell is a unit both anatomically and physiologically. It has a certain individuality of its own. In many cases cells are found to be isolated or separated completely from one another. But, on the other hand, we also find numerous instances in which the living substance of one cell is directly continuous with that of another. When the cells are thus related, we speak of the union of cells as *syncytium.* Of this I offer you an illustration in the second picture upon the screen (Fig. 8), which represents the embryonic connective tissue of man. In this you can see the prolongations of the protoplasm of a single cell body uniting with the similar prolongations from other cell bodies, the cells themselves thus forming, as it were, a continuous network with broad meshes between the connecting threads of protoplasm. The spaces or meshes are, however, not entirely vacant, but contain fine lines which correspond to the existence of fibrils, which are characteristic of connective tissue, and at the stage of development represented in this picture are beginning to appear. It is fibrils of this sort which we find as the main elements in the constitution of sinews and tendons, as, for instance, the tendon of Achilles, at the heel. In a very young body we find there are but few fibrils; in the adult body an immense number.

If we are to be scientifically exact we must note

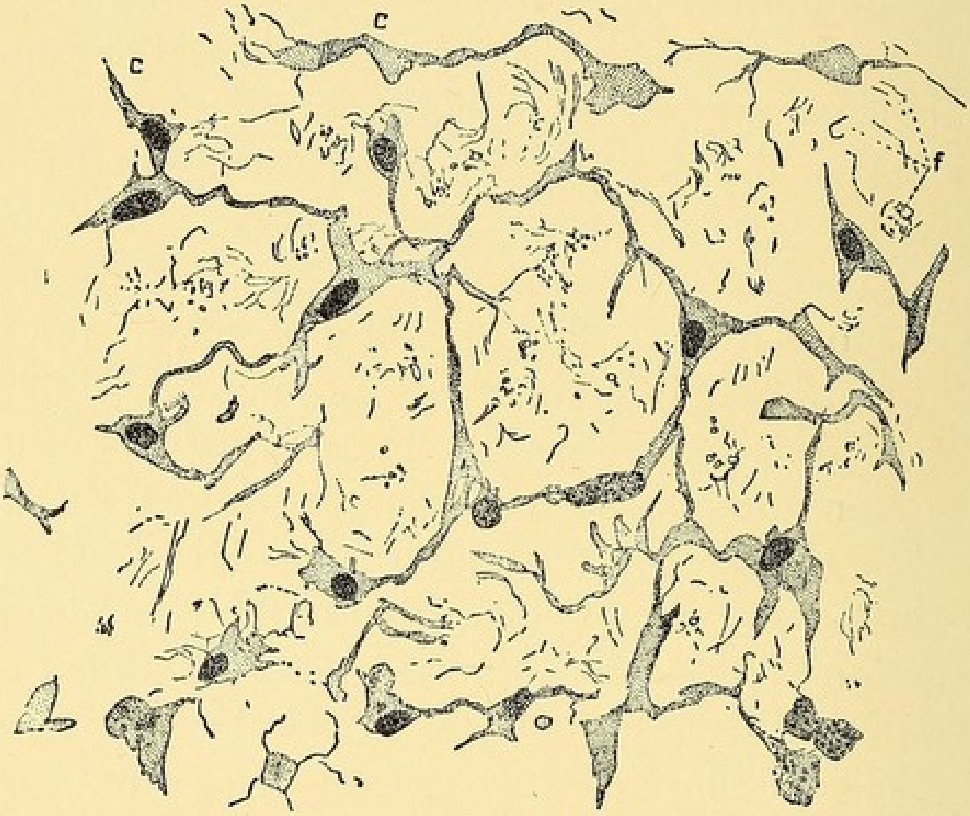

Fig. 8. **Example of a Syncytium.** Embryonic connective tissue from the umbilical cord of a human embryo of about three months, magnified about 400 diameters; *c*, *c*, cells; *f*, intercellular fibrils.

that in the early stages of vertebrates, the germ or embryo is not constituted of discrete cells. There are nuclei, and each nucleus is surrounded by protoplasm. Each nucleus is perfectly individualised, but its protoplasm merges into that about the neighbouring nuclei. All the primitive parts are then true *syncytia.* Thus it happens that in Fig. 9, which represents sections of a very young rabbit germ, the single cells are not marked off. Nevertheless it is customary and convenient to speak of the cells even at such a stage. The actual delimitation of the cells occurs in older stages in nearly every part of the body. The blood corpuscles are always the first cells in vertebrates to become definitely individualised.

There is, in fact, as you probably all know, a constant growth of cells; and this growth implies also, naturally, their multiplication. There has been in each of us an immense number of successive cell generations, and at the present time a multiplication of cells is going on in every one of us. It never entirely ceases as long as life continues. The development of the body, however, does not consist only of the growth and multiplication of cells, but also involves changes in the very nature of the cells, alterations in their structure. Cells in us are of many different sorts, but in early stages of development they are of few sorts. Moreover, in the earliest stages we find the cells all more or less alike. They do not differ from one another. Hence comes the technical term of *differentiation*, to designate the modifications which cells undergo with advancing age. Some authorities use *specification* as a technical synonym for differentiation. At first cells are alike; in older individuals the cells have become of different sorts, they have been differentiated into various classes. This whole phenomenon of cell change is comprehensively designated by the single word, *cytomorphosis*, which is derived from two Greek words meaning *cell* and *form*, respectively.

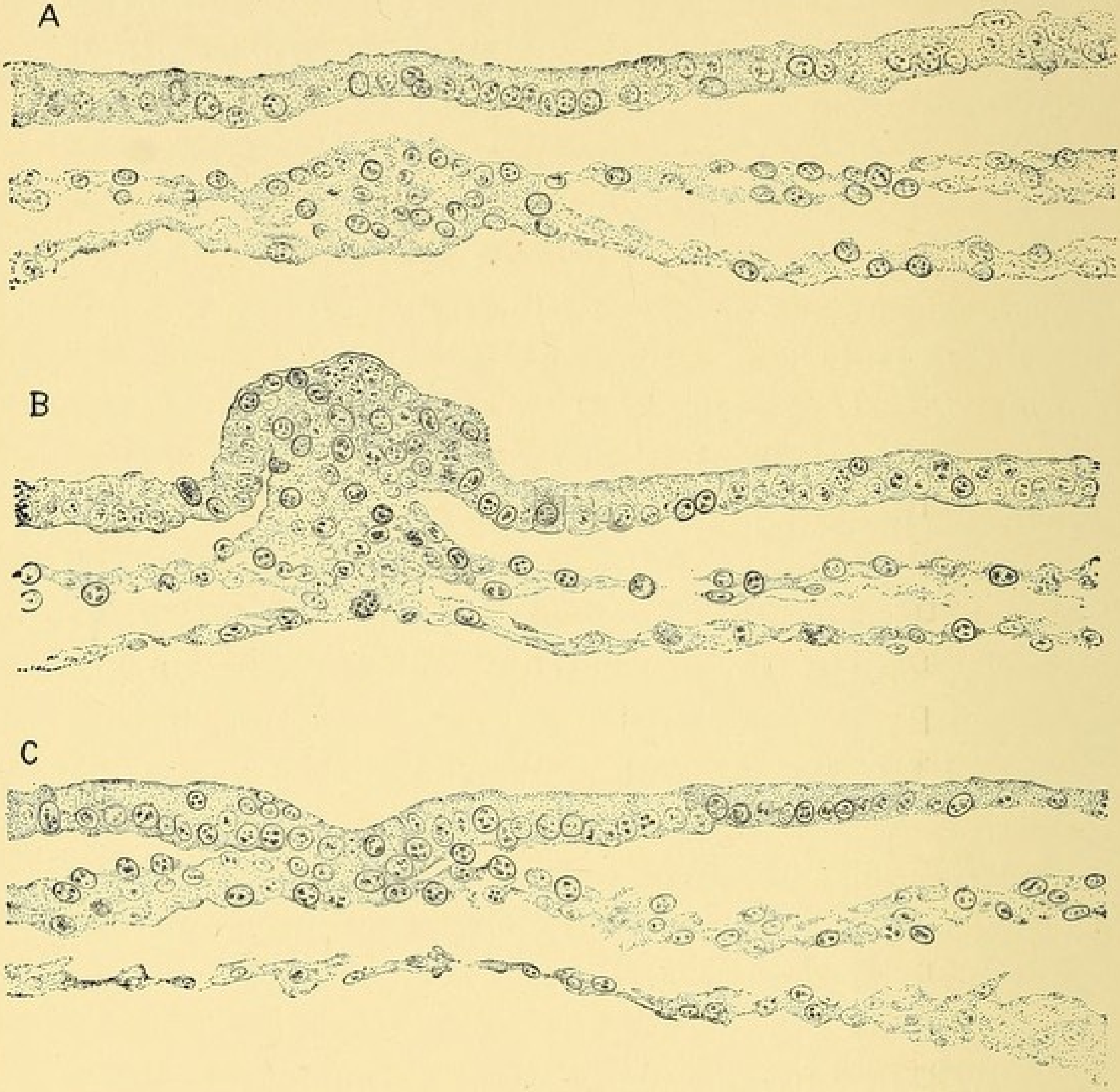

Fig. 9. Three Transverse Sections through a Rabbit Embryo of Seven and One Half Days, from series 622 of the Harvard Embryological Collection. *A*, section 247 across the anterior part of the germinal area. *B*, section 260 across the middle region of the germinal area. *C*, section 381 through the posterior part of the germinal area. Magnified 300 diameters.

A correct understanding of the conception cytomorphosis is an indispensable preliminary to any comprehension of the phenomena of development of animal or plant structure. I shall endeavour, therefore, now to give you some insight into the phenomena of cytomorphosis as regarded by the scientific biologist. The first cells which are produced are those which form the young embryo. We speak of them on that account as embryonic cells, or cells of the embryonic type. Our next picture illustrates the actual character of such cells as seen with the microscope, for it represents a series of sections through the body of a rabbit embryo, the development of which has lasted only seven and one half days. You will notice at once the simplicity of the structure. There are not yet present any of those parts which we can properly designate as organs. The cells have been produced by their own multiplication, and are not yet so numerous but that they could be readily actually counted. They are spread out in somewhat definite layers or sheets,[1] but beyond that they show no definite arrangement which is likely to attract your attention. That which I wish you particularly to observe is that in every part of each of these sec-

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[1] The layers are three in number, and are known as the *germ-layers;* the outer layer (uppermost in each of the three sections in Fig. 9) is the *ectoderm*, the middle the *mesoderm*, and the inner one the *entoderm*. The science of embryology has for its chief task to trace the numerous modifications and often very complicated metamorphoses which the three simple germ-layers pass through in order to produce the complex organs of the adult. Our present conceptions of the structure of multicellular animals are based on two great discoveries, first of the germ-layers, second of cells.

tions the cells appear very much alike. The nuclei are all similar in character, and for each of them there is more or less protoplasm; but the protoplasm in all parts of these young rabbits is found to be very similar; and indeed if we should pick out one of these cells and place it by itself under the microscope, it would be impossible to tell what part of the rabbit embryo it had been taken from, so much do all the cells of all the parts resemble one another. We learn from this picture that the embryonic cells are all very much alike, simple in character, have relatively large nuclei, and only a moderate amount of protoplasm for each nucleus to complete the cell.

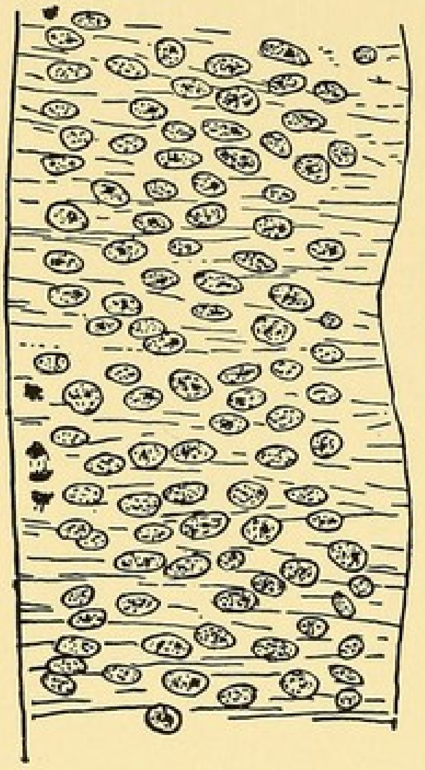

FIG. 10. PORTION OF A TRANSVERSE SECTION OF THE SPINAL CORD OF A HUMAN EMBRYO OF FOUR MILLIMETRES. Harvard Embryological Collection, series 714. The spinal cord at this stage is a tubular structure. The figure shows a portion of the wall of the tube; the left-hand boundary of the figure corresponds to the inner surface of the tube.

Very different is the condition of affairs which we find when we turn to the microscopic examination of the adult. Did time permit it would be possible to study a succession of stages and show you that the condition which we are about to study as existing actually in the adult is the result of a gradual progress and that in successive stages of the individual we can find successive stages of cell change; but it will suffice for our immediate purpose to consider the results of differentiation as they are shown to us by the study of the cells of the adult. I will have thrown upon the screen for you a succession of pictures illustrating various adult structures. The first is, however, a part of a cross-section of the embryonic spinal cord in which you can see that much of the simple character of the embryonic cells is still kept. All parts of the spinal cord, as the picture shows, are very much alike, and the nuclei of the cells composing the spinal cord at this stage are all essentially similar in appearance. What a contrast this forms with our next picture, which shows us an isolated so-called motor nerve cell from the adult spinal cord. It owes its name motor to the fact that it produces a nerve fibre by which motor impulses are conveyed from the spinal cord to the muscles of the body. The cell has numerous elongated branching processes stretching out in various directions, but all leading back towards the central body in which the nucleus is situated. These are the processes which serve to carry in the nervous impulses from the periphery towards the centre of the cell, impulses which in large part, if not exclusively, are gathered up from other nerve cells which act on the motor element. At one point there runs out a single process of a different character. It is the true nerve fibre, and forms the axis, as it was formerly termed, or axon, as it is at present more

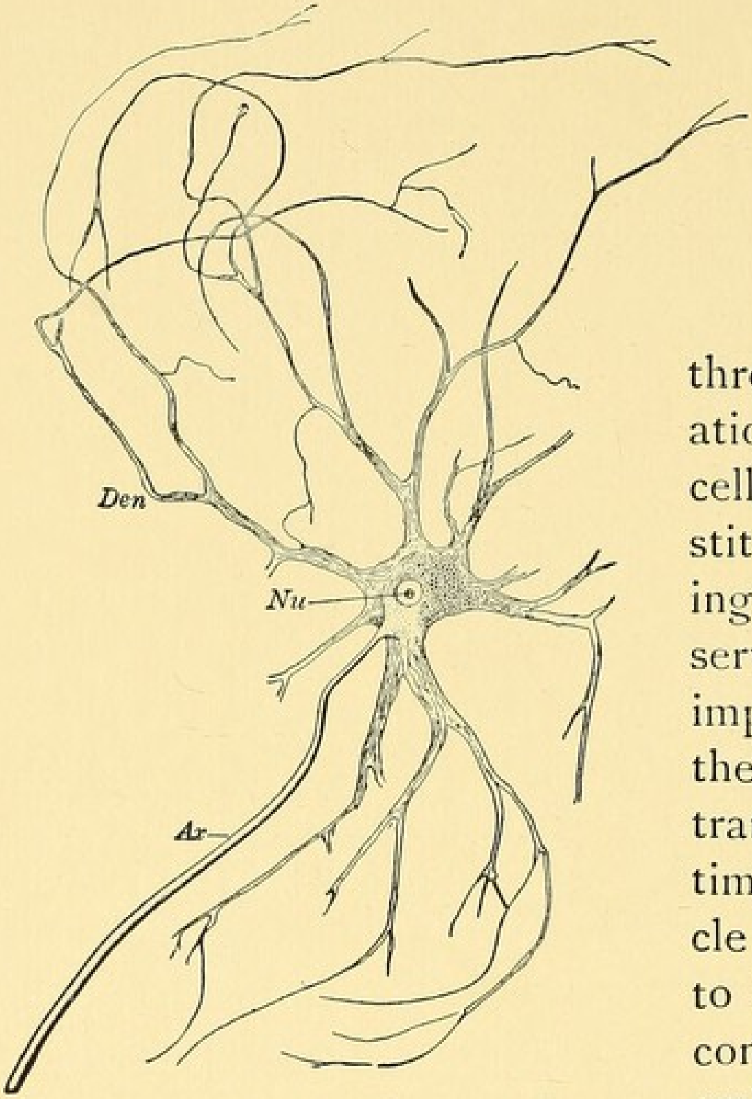

FIG. 11. COPY OF THE ORIGINAL FIGURE FROM THE MEMOIR OF DEITERS, in which the proof of the origin of the nerve fibres directly from the nerve cells was first published. The memoir is one of the classics of anatomy. It was issued posthumously, for the author died young, to the great loss of science. The figure represents a single isolated motor nerve cell from the spinal cord of an ox. The single unbranched axon, *Ax*, is readily distinguished from the multiple branching dendrites, *Den*. *Nu* is the spherical nucleus with its characteristic central dot.

usually named, of the nerve fibre as we encounter it in an ordinary nerve. This single thread-like prolongation of the nerve cell is likewise constituted by the living protoplasm and serves to carry the impulses away from the cell body and transmit them ultimately to the muscle fibres which are to be stimulated to contraction. In the embryonic spinal cord none of these processes existed, and the amount of the protoplasm in the nerve cell was very much smaller. As development progressed, not only did the protoplasm body grow, but the processes gradually grew out. Some of them branched so as to better receive and collect the impulses; one of them remained single and very much elongated, and acquired a somewhat different structure in order to serve to carry the nervous impulses away. The third picture[1] shows us a section through the

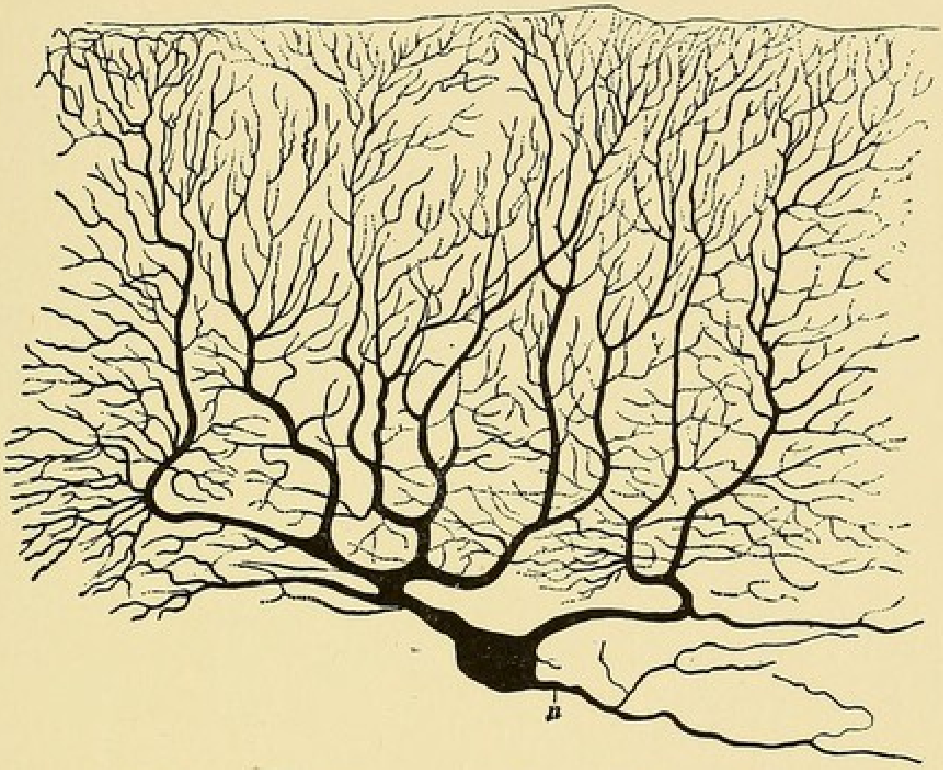

Fig. 12. A Large Cell from the Small Brain (Cerebellum) of a Man. It is usually called a Purkinje's cell. It was stained black throughout by what is known as the Golgi silver method, hence shows nothing of its internal structure.—After von Kölliker.

spinal cord of an adult fish. It has been treated by a special stain in order to show how certain elements of the spinal cord acquire a modification of their organisation by which they are adapted to serve as supports for the nervous elements proper. They play in the

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[1] The illustration referred to is not reproduced in the text.

microscopic structure the same supporting rôle which the skeleton performs in the gross anatomy of the body as a whole. They do not take an active part in the nervous functions proper. None of the appearances which this figure offers for our consideration can be recognised in any similar preparation of the embryonic cord. Obviously, then, from the embryonic to the adult state in the spinal cord there occurs a great differentiation. That which was alike in all its parts has been so changed that we can readily see that it consists of many different parts. A striking illustration of this is afforded by the next picture, which represents one of the large nerve cells which occur in the small brain, or cerebellum, that portion of the central nervous system which the physiologists have demonstrated to be particularly concerned in the regulation and co-ordination of movements. These large cells occur only in this portion of the brain, and as you see, differ greatly in appearance from the motor cells of the type which we were considering a few moments ago. And, again, another picture illustrates yet other peculiarities of the adult nerve cells. The upper figures in this plate are taken from cells which have been coloured uniformly of a very dark hue, in consequence of which they are rendered so opaque that the nucleus which they really contain is hidden from our view. But the deep artificial colour makes it easy to follow out the form of the cells and the ramifications of their long processes. In the middle figures we have cells which have been stained

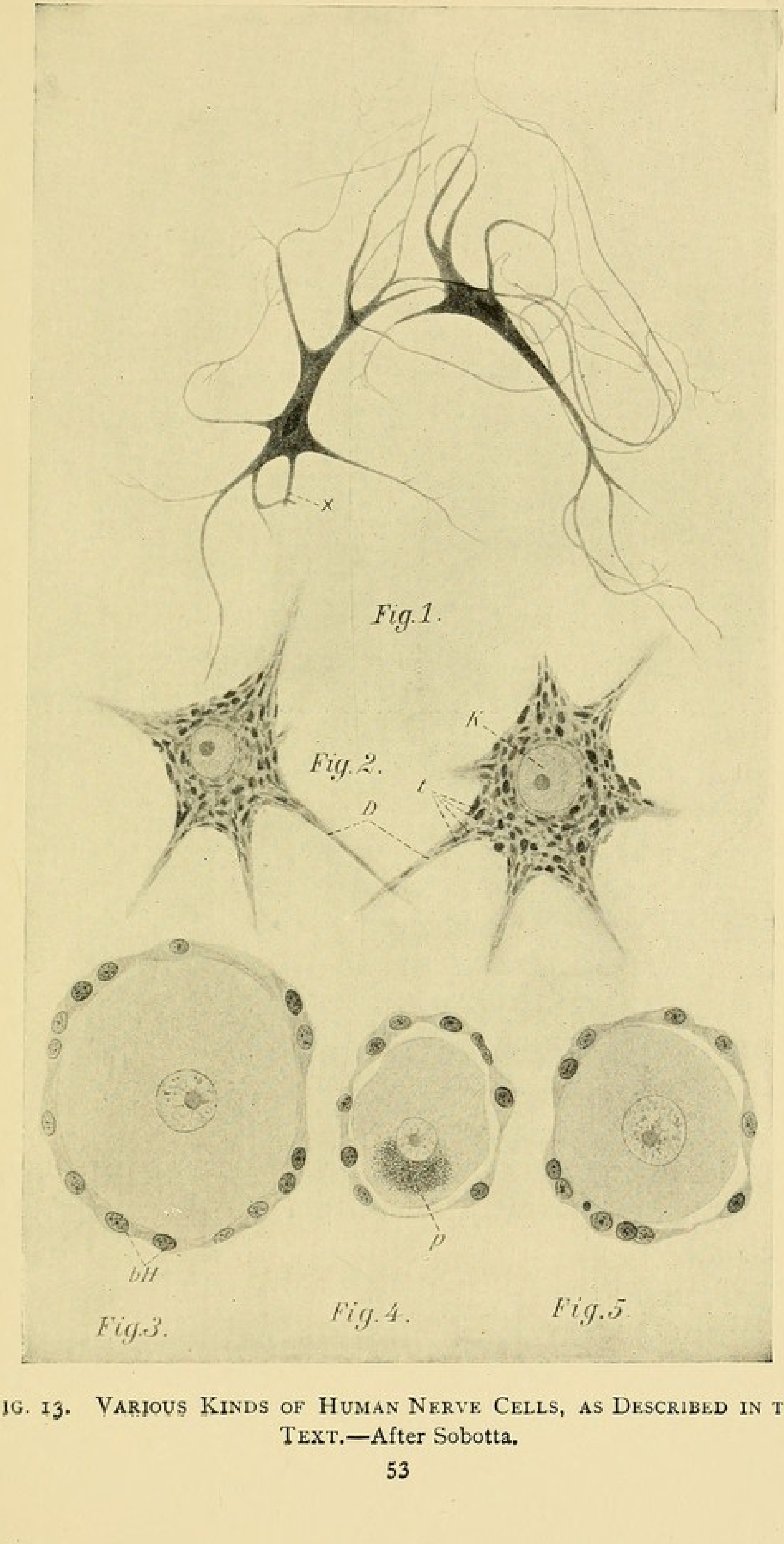

FIG. 13. Various Kinds of Human Nerve Cells, as Described in the Text.—After Sobotta.

by another method which brings out very clearly to the eye the fact that in the protoplasm of the cell there are scattered spots of substance of a special sort. No such spots can be demonstrated in the elements of the young embryonic nerve cells. To some fanciful observers the spots, thus microscopically demonstrable in the nerve cells, recall the spots which appear on the skin of leopards, and hence they have bestowed upon these minute particles the term tigroid substance. The bottom figures represent the kind of nerve cells which occur upon the roots of the spinal nerves, and each of which is surrounded by a special protective envelope of small non-nervous cells. It is unnecessary to dwell upon their appearance, as the mere inspection of the figures shows at once that they differ very much indeed from the other nerve cells we have considered.

We pass now to another group of structures, the tissues which are known by the technical name of *epithelia*. You can notice immediately in the figures on the plate (Fig. 14) that the appearances are very different from those we have encountered in contemplating the cells of the nervous system, and you can readily satisfy yourselves, by the comparison of the various figures now before you, of the further fact that these epithelia are unlike one another. The figures represent epithelium, respectively, first from the human ureter; second, from the respiratory division of the human nose; third, from the human ductus epididymidis; and, fourth, from the pigment layer of the retina of the cat.

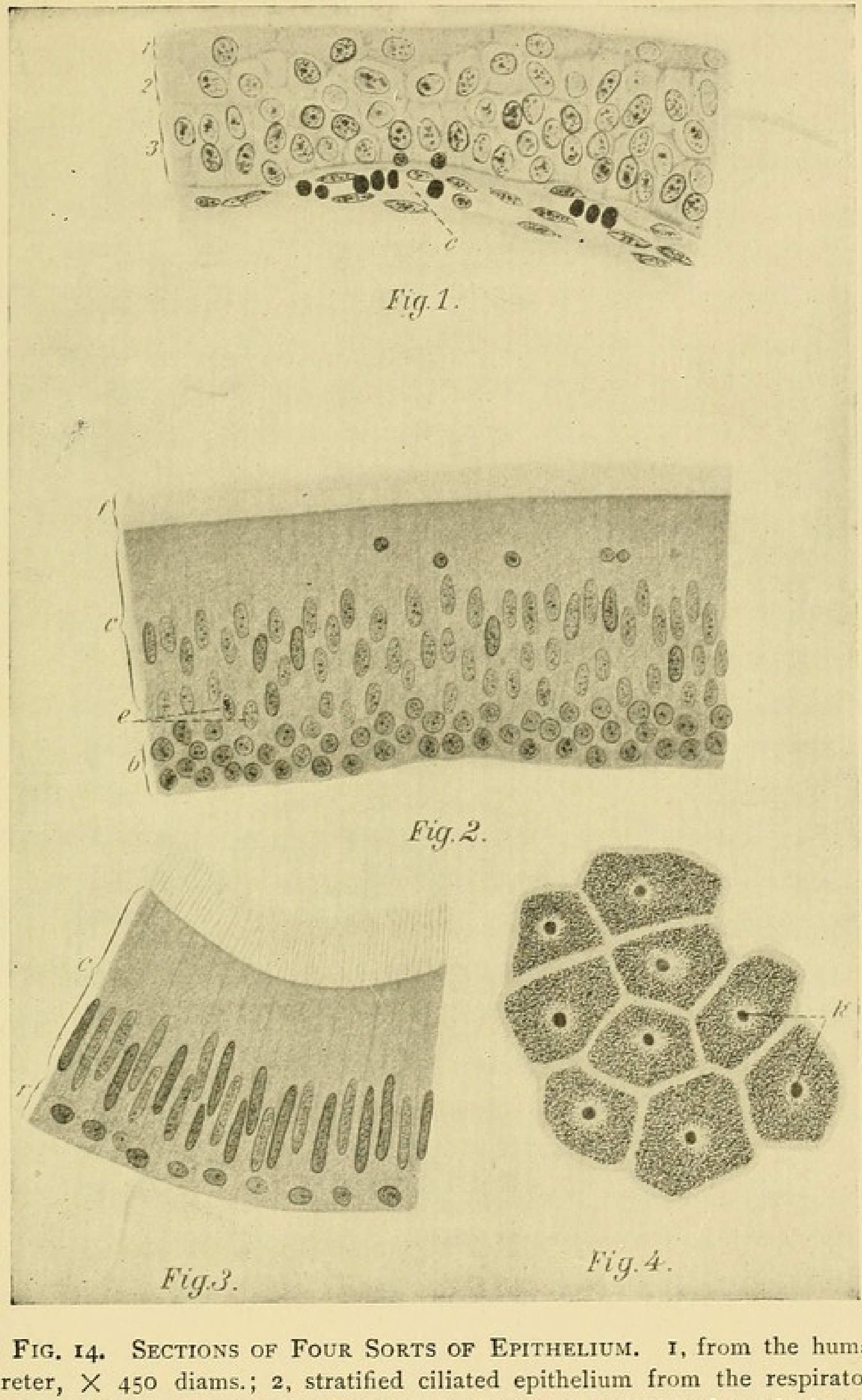

Fig. 1.

Fig. 2.

Fig. 3.

Fig. 4.

FIG. 14. SECTIONS OF FOUR SORTS OF EPITHELIUM. 1, from the human ureter, × 450 diams.; 2, stratified ciliated epithelium from the respiratory region of the human nose, × 500 diams.; 3, ciliated epithelium from the human ductus epididymidis, × 420 diams.; 4, surface view of the pigmented epithelium from the retina of a cat's eye, × 280 diams.—After Sobotta.

We turn now to a representation of a section of one of the orbital glands. This is very instructive because we see not only that the cells which compose the gland have acquired a special character of their own, but also that they are not uniform in their appearances. This lack of uniformity is due chiefly to the fact that the cells change their appearance according to their functional state. We can actually see in these cells under the microscope the material imbedded in their protoplasmic bodies out of which the secretion, which is to be poured forth by the cells, is to be manufactured. So long as that material for the secretion is contained in the cells, the cells appear

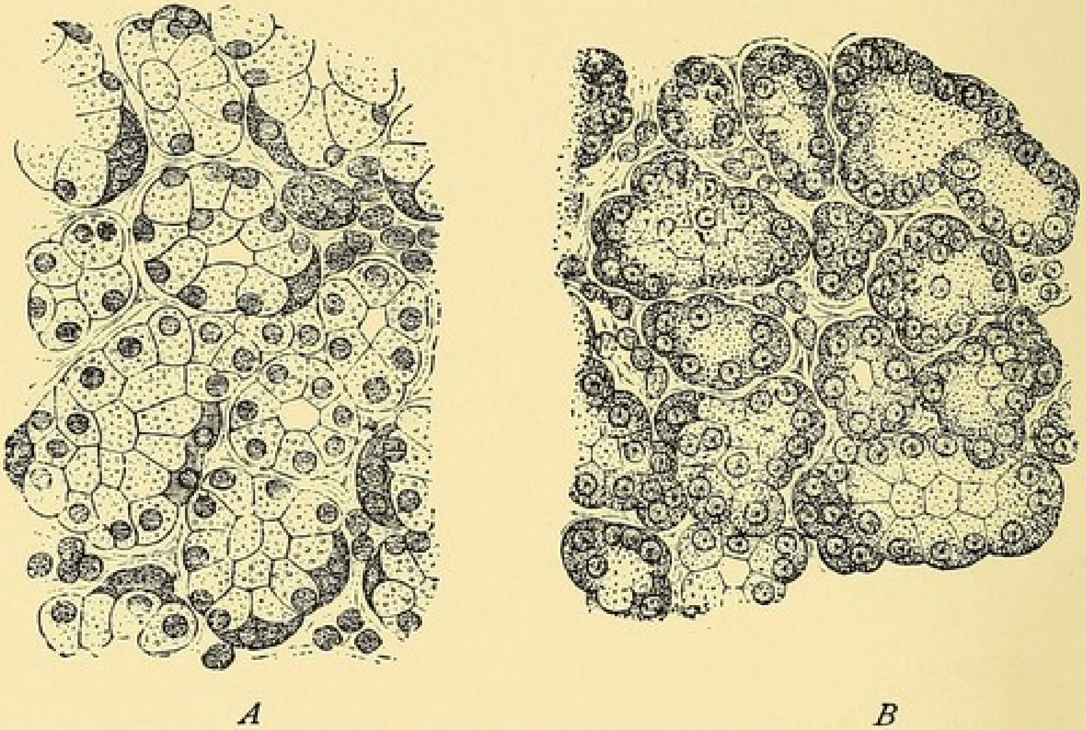

FIG. 15. TO SHOW THE ORBITAL GLAND OF A DOG. *A*, with the material to form the secretion accumulated within the cells. *B*, after loss of the material through prolonged secretion.—From R. Heidenhain after Lavdowsky.

large, and their protoplasmic bodies do not readily absorb certain of the staining matters which the microscopist is likely to apply to them (Fig. 15, *A*). When, however, the accumulated raw material has been changed into the secretion and discharged from the gland, the cell is correspondingly reduced in bulk, and as you see (Fig. 15, *B*), it then takes up the stain with considerable avidity, as does also the nucleus, which has likewise become reduced in size. These facts are very instructive for us, since they prove conclusively that with the microscope we can see at least part of the peculiarities in cells which are correlated with their functions. We can actually observe that the cells of the orbital, and, it might be added, of the salivary, glands are able to produce their peculiar secretion because they contain a kind of substance which in the embryonic cell does not appear at all. There is a visible differentiation of the orbital-gland cells from the simple stage of the embryonic cells. Something similar to this can be recognised in the next of our pictures representing sections of the gland properly known as the pancreas but which is sometimes termed the abdominal salivary gland for the reason that it somewhat resembles the true salivary. In the cells of the pancreas also we can see the material which is to produce the secretion accumulated in the inner portion of the cell, and when it is so accumulated the cell appears enlarged in size and the nucleus is driven back towards the outer end of the cell where some unaltered protoplasm is also accumulated (Fig. 16, *A*). When this raw material is turned over into secretion by a chemical change, it is discharged from the cell, the cell loses in volume, and in its shrunken state presents a very different appearance, as is shown at *B* in the figure. It is necessary for the cells to again elaborate the material for secretion before they can a second time become functionally active. Here we have something of the secret of the production of the various juices in the body revealed to us.

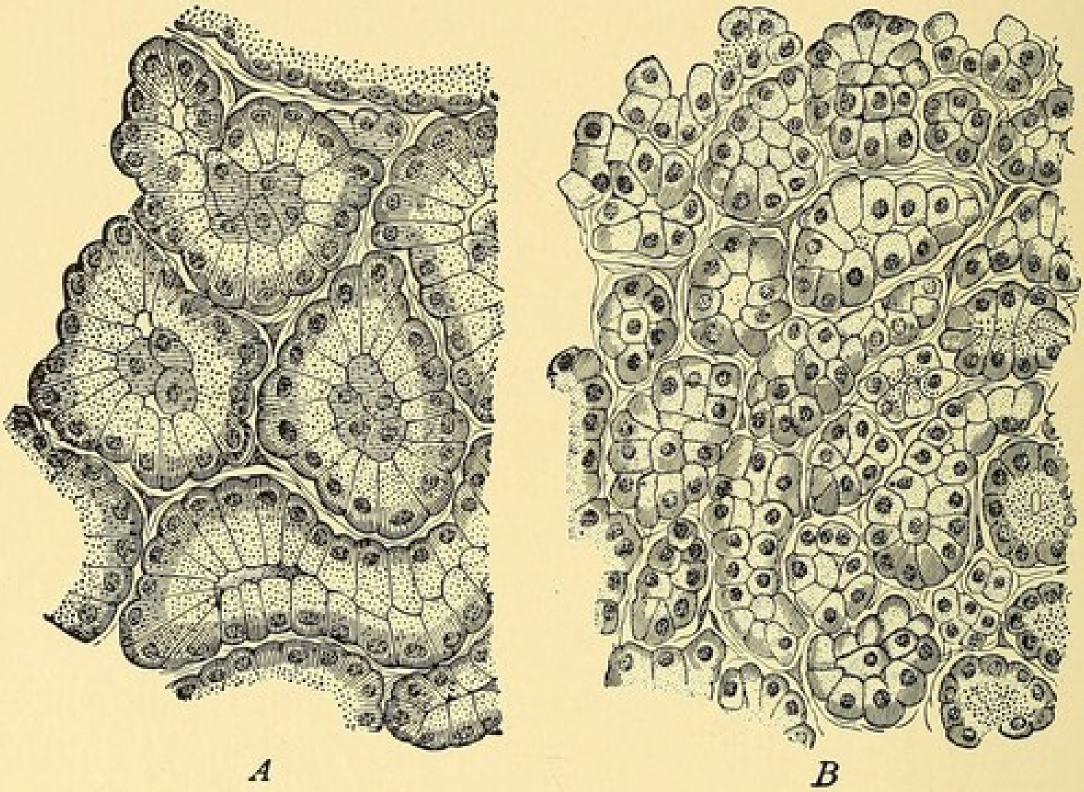

FIG. 16. TWO SECTIONS OF THE PANCREATIC GLAND OF A DOG. *A*, the cells are enlarged by the accumulation of material to form the secretion. *B*, the cells are shrunk because there has been prolonged secretion and part of their substance is lost.—From R. Heidenhain.

Other excellent examples of the differentiated condition of the cells are afforded us by the examination of hairs, of which I will show you two pictures. The first represents a section through the human skin taken in such a way that the hairs are themselves cut

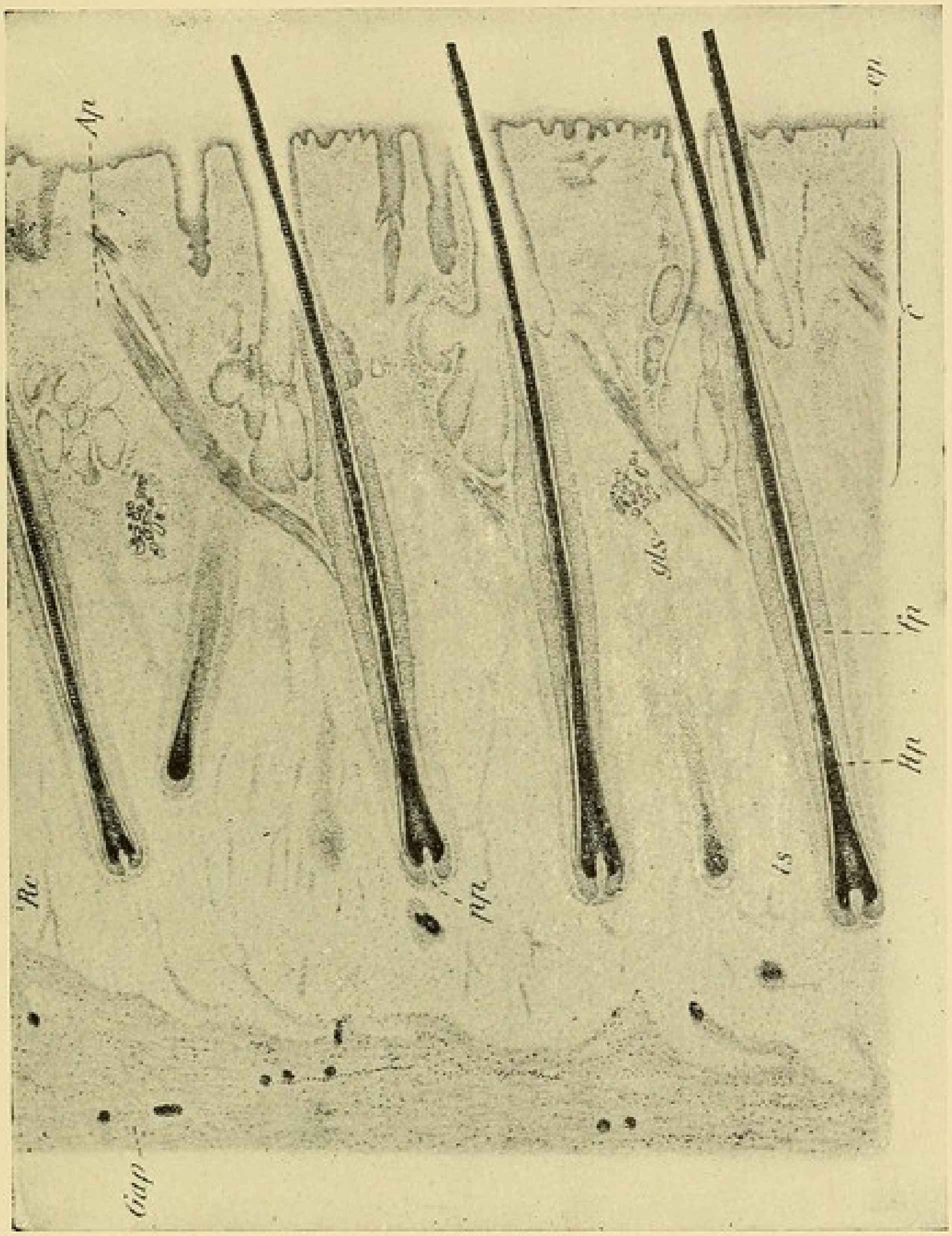

Fig. 17. Section of the Human Skin, Made so that the Hairs are Cut Lengthwise. *Ap*, erector muscle of the hair; *ep*, epidermis; *c*, deep skin or dermis; *fp*, hair follicle; *Rp*, root of hair; *Rc*, subdermal tissue; *gls*, sweat glands; *Gap*, fibrous layer (aponeurosis). × 15 diameters.—After Sobotta.

lengthwise and you see not only that each hair consists of various parts, but also that the cells in these parts are unlike. The follicles within the skin in which the hair is lodged likewise have walls with cells of various sorts. It may interest you also to point out in the figure the little muscle, *Ap*, which runs from each hair to the overlying skin, so disposed that when the muscle contracts the "particular hair will stand up on end." Still more clearly does the variety of cells which actually exists in a hair show in the following picture (Fig. 18), which represents a cross-section of a hair, and its follicle, but more highly magnified than were the hairs in the previous figure.

The adult body consists of numerous organs. These are joined together and kept in place by intervening substance. The organs themselves consist of many separate parts which are also joined by a substance which keeps them in place. This substance has received the appropriate name of connective tissue. We find in the adult that it consists of a considerable number of structures. There are cells and fibres of more than one kind, which have been produced by the cells themselves. There is more or less substance secreted by the cell which helps to give consistency to the tissue. In some cases this substance, which is secreted by the cells, becomes tougher and acquires a new chemical character. Such is the case, for instance, with cartilage. Or, again, you may see a still greater chemical metamorphosis going on in the material secreted by the cells in the case of bone, where the substance is made tougher and stronger by the deposit of calcareous material. Nothing like cartilage, nothing like bone, exists in the

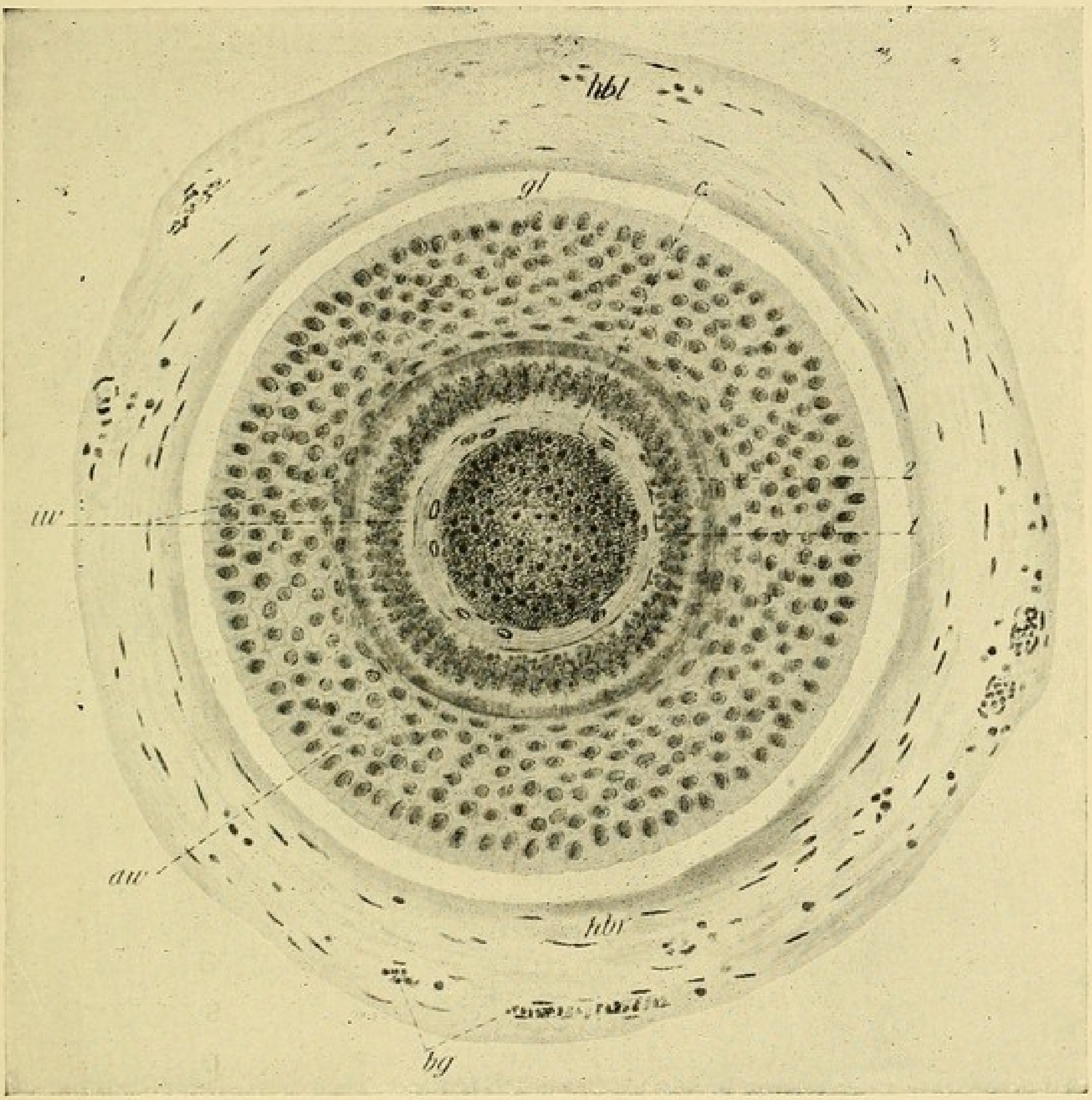

FIG. 18. CROSS SECTION OF THE ROOT OF A HAIR. *hbl*, longitudinal, *hbr*, circular fibres of the hair sheath; *bg*, blood-vessels; *gl*, hyaline sheath; *aw*, outer layer of follicle; *iw*, inner layer of follicle; *c*, outer cuticle of the hair; *1*, Huxley's layer of the follicle; *2*, Henle's layer of the follicle. × 300 diameters.—After Sobotta.

early state of the embryo. They represent something different and new.

The next of our illustrations, Figs. 19 and 20, show us muscle fibres of the sort which serve for our voluntary motions and are connected typically with some part of the skeleton. These muscle fibres are elongated structures. Each fibre contains a contractile substance different from protoplasm, and which exists in the form of delicate fibrils which run lengthwise in the muscle fibres (Fig. 19), and is so disposed, further, that a series of fine lines are produced across the fibre itself (Fig. 20), each line corresponding with a special sort of material different from the original protoplasm. These cross lines give to the voluntary

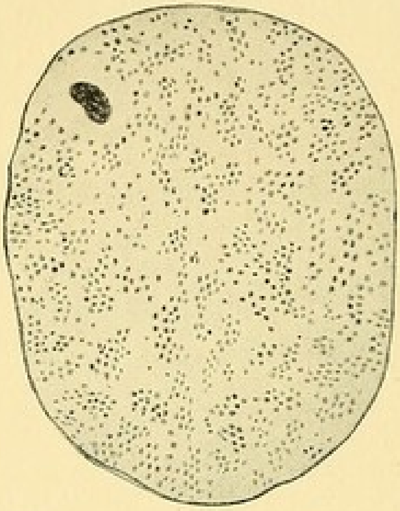

FIG. 19. CROSS SECTION OF A LINGUAL MUSCLE FIBRE OF THE MOCASSIN SNAKE, ANCISTRODON PISCIVORUS. The single large dark spot represents a nucleus. Each small dot represents a cross section of a muscle fibril. There are several hundred in each fibre.

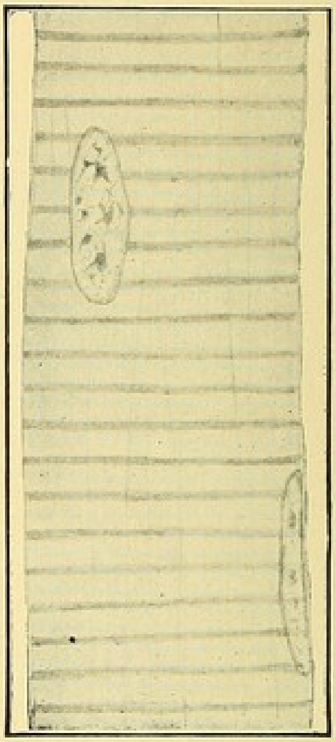

FIG. 20. PART OF A MUSCLE FIBRE OF THE HUMAN TONGUE TO SHOW THE CROSS STRIATIONS. Two nuclei are included, one of which is shown at the edge of the fibre, the other in surface view. In the adult striated muscle fibres of mammals the nuclei are superficially placed.

muscle fibres a very characteristic appearance, in consequence of which they are commonly designated in scientific treatises by the term *striated.* A striated muscle fibre is that which is under the control of our will. It should perhaps be mentioned that the muscle fibres of the heart are also striated, though they differ very much in other respects from the true voluntary muscles.

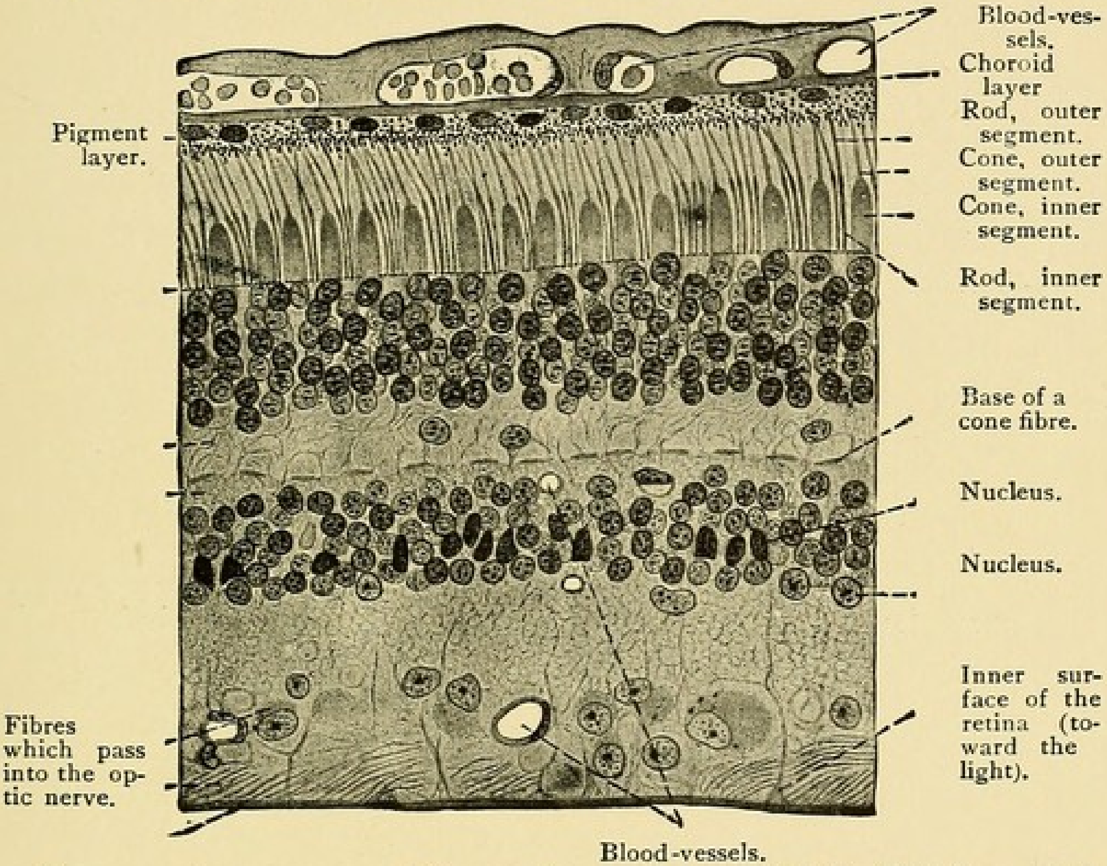

FIG. 21. SECTION OF A HUMAN RETINA, from Stöhr's *Histology*, sixth American edition. Although the retina is very thin it comprises no less than twelve distinct layers; the outermost layer is highly vascular. The pigment layer prevents the escape of light. The rods and cones convert the light waves into a sensory impulse, which is transmitted through the remaining layers of the retina to the optic nerve. The total structure is extremely complicated.

Last of all for this series of demonstrations, I have chosen a section of the retina (Fig. 21). One can see near the top of the figure the peculiar cylindrical and tapering projections (rods and cones) which are characteristic of a retina, projections which are of especial interest because they represent the apparatus by which the rays of light are transformed into an actual sensory perception. After this has been accomplished, the perception is transmitted into the interior substance of the retina, and by the complication of the figure you may judge a little of the complication of the arrangements by which the transmission through this sensory organ is achieved, until the perception is given off to a nerve fibre and carried to the brain. There is not time to analyse all I might present to you of our present knowledge concerning the structure of the retina. But it will, I think, suffice for purposes of illustration to call your attention to the complicated appearance of the section as a whole and to assure you that nothing of the sort exists in the early stage of the embryo.

To recapitulate, then, what we have learned from the consideration of these pictures, we may say that in place of uniformity we now have diversity. It should be added, to make the story complete, that the establishment of this diversity has been gradually brought about, and that what we call development is in reality nothing more than the making of diversity out of uniformity. It is a process of differentiation. Differentiation is indeed the fundamental phenomenon of life; it is the central problem of all biological research, and if we understood fully the nature of differentiation and the cause of it, we should have probably got far along towards the solution of the final problem of the nature of life itself.

The size of animals deserves a few moments of our time, for it is intimately connected with our problem of growth and differentiation. Cells do not differ greatly from one another in size. The range of their dimensions is very limited. This is particularly true of the cells of any given individual animal. Recent careful investigations have been made upon the relation of the size of cells to the size of animals, and it has been found that animals are not larger, one than another, because their cells are larger, but because they have more of them.[1] This statement must be understood with certain necessary reservations. There are some kinds of animals, like the star-fish, which have very small cells; others, like frogs and toads, which have large cells; so that a star-fish of the same bulk as a given frog would contain a great many more cells. Our statement is true of allied animals. For example, a large frog differs from a small frog or a large dog from a small dog by the number of the cells. An important exception to this law is offered for our consideration by the cells of the central nervous system, the nerve cells properly

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[1] G. Levi, "Vergleichende Untersuchungen ueber die Grösse der Zellen," *Verhandl. Anat. Ges.*, xix., 156–158.

G. Levi, "Studî sulla Grandezza delle cellule," *Archivio ital. anat. embriol.*, v., pp. 291–358. This paper is important and suggestive.

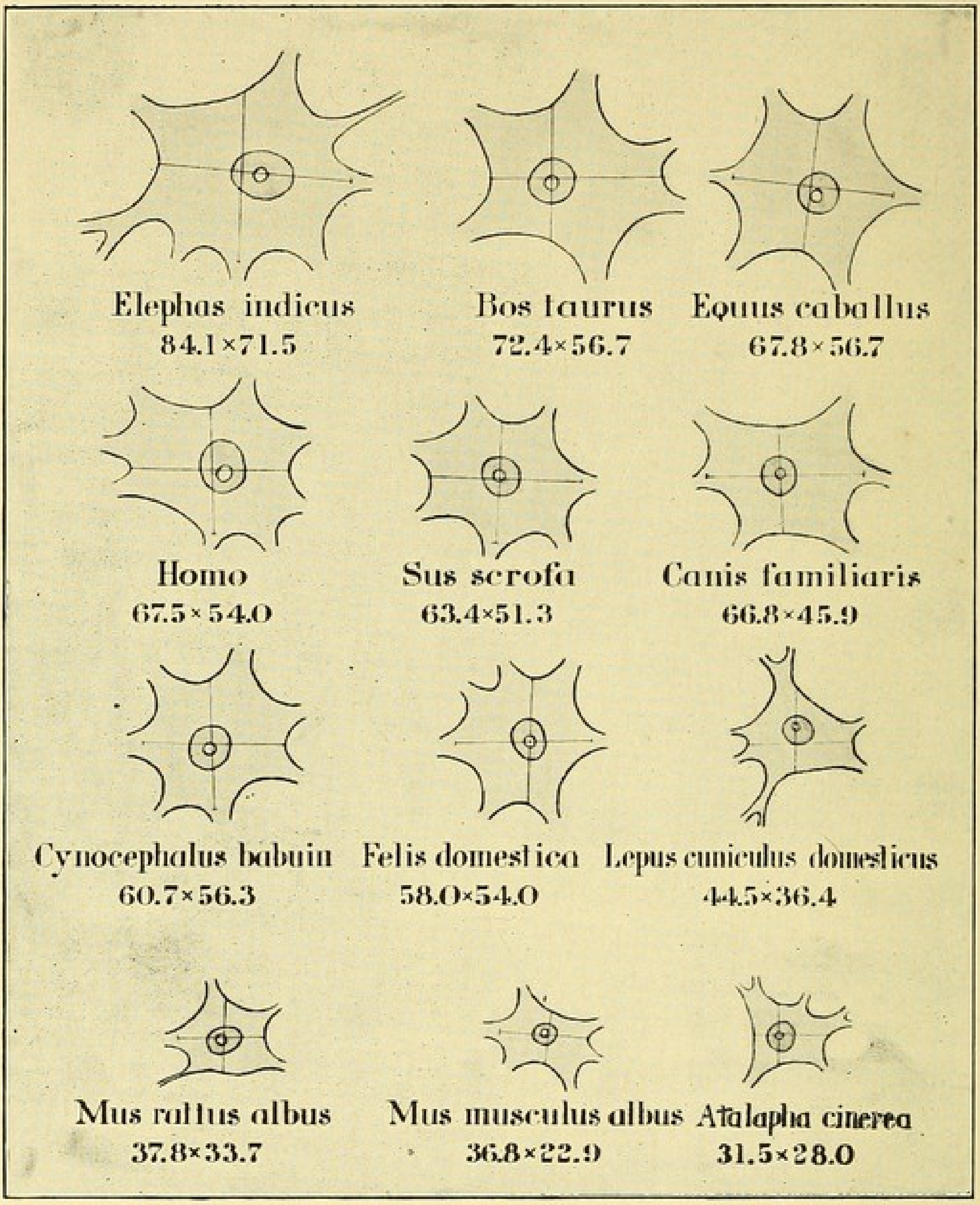

FIG. 22. MOTOR NERVE CELLS OF VARIOUS MAMMALS, all from the cervical region of the spinal cord. The cells are represented all uniformly magnified. The cross lines on each figure indicate the directions in which the original cells have been measured.—After Irving Hardesty.

so called.[1] This is demonstrated by the slide now before us (Fig. 22), which shows corresponding motor nerve cells from the spinal cords of twelve different mammals arranged in the order of their size—the elephant, the cow, the horse, man, the pig, the dog, the baboon, the cat, the rabbit, the rat, the mouse, and a small bat. You recognise immediately that there is a proportion between the size of these cells and the size of the respective species of animals. To a minor degree, but much less markedly, there is a difference in the calibre and length of the striated or voluntary muscle fibres. But with these exceptions our statement is very nearly exactly true, that the difference in size of animals does not involve a difference in the size of their cells. For the purpose of the study of development, which we are to make in these lectures, this uniformity in the size of cells is a great advantage, and enables us to speak in general terms in regard to the growth of cells, and renders it superfluous to stop and discuss for each part of the body the size of the cells which compose it, or to seek to establish different principles for different animals because their cells are not alike in size.

Now we pass to a totally different aspect of cell development, that which is concerned with the degeneration of cells. For we find that, after the differentiation has been accomplished, there is a tendency

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[1] Irving Hardesty, "Observations on the Medulla Spinalis of the Elephant, with Some Comparative Studies of the Intumescentia Cervicalis and the Neurones of the Columna Anterior," *Journ. Comp. Neurol.*, xii, 125–182, pls. ix–xiii.

to carry the change yet further and to make it so great that it goes beyond perfection of structure, so far that the deterioration of the cell comes as a consequence. Such cases of differentiation we speak of as a degeneration, and it may occur in a very great number of ways. Very frequently it comes about that the alteration in the structure of the cell goes so far in adapting it to a special function that it is unable to maintain itself in good physiological condition, and failing to keep up its own nourishment it undergoes a gradual shrinkage which we call atrophy. A very good illustration of this, and a most important

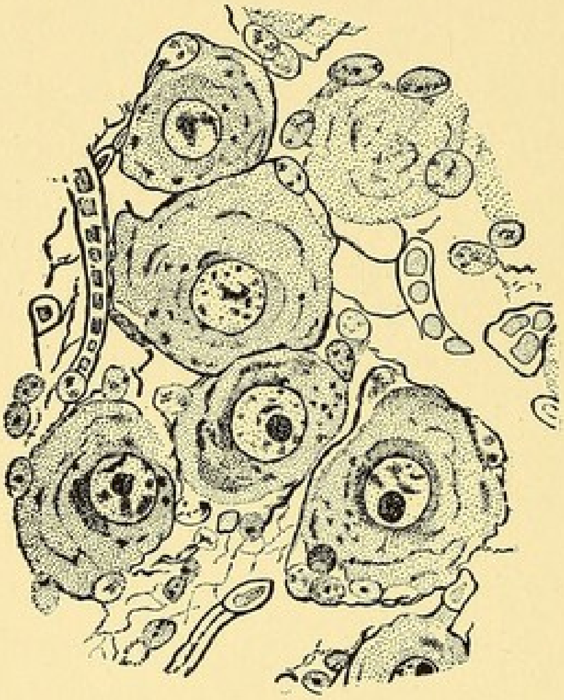

Fig. 23. Group of Five Nerve Cells from the First Cervical Ganglion of a Child at Birth. Specimen preserved with osmic acid. × 500 diams.—After C. F. Hodge.

one, is offered us by the changes which go on in the nerve cells in extreme old age. This is beautifully illustrated by the two pictures which are now before us, copied from investigations[1] of Professor Hodge, of Clark University. The two figures represent human nerve cells taken from the root of a spinal

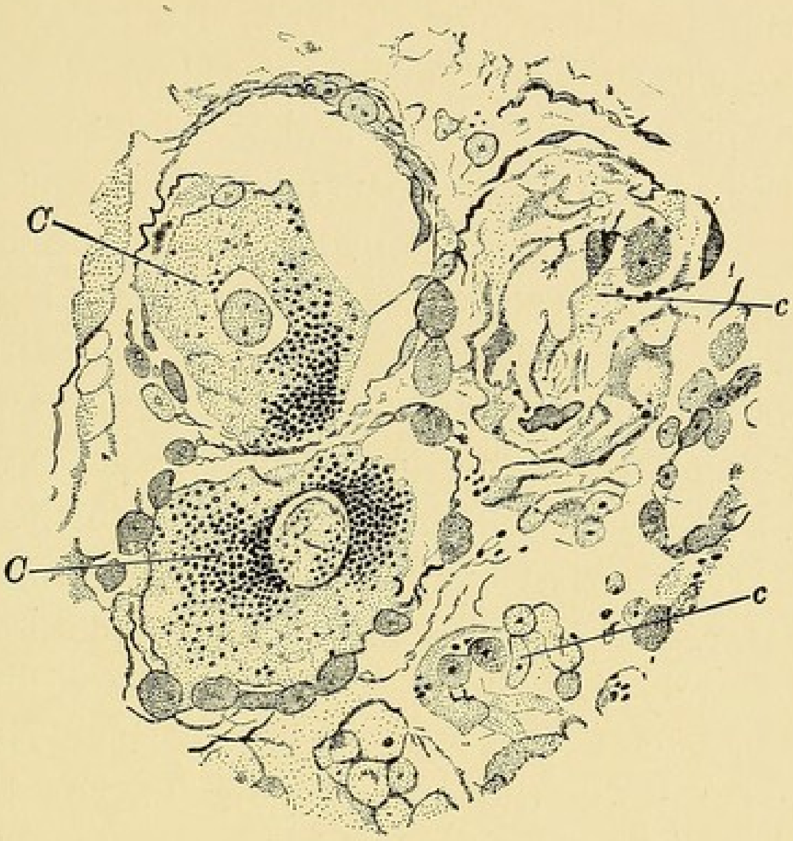

FIG. 24. GROUP OF FOUR NERVE CELLS FROM THE FIRST CERVICAL GANGLION OF A MAN DYING OF OLD AGE AT NINETY-TWO YEARS. Specimen preserved with osmic acid. *C*, *C*, two cells still intact, but loaded with pigment granules; *c*, *c*, two cells which have disintegrated. × 500 diams.—After C. F. Hodge.

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[1] C. F. Hodge, "Changes in Ganglion Cells from Birth to Senile Death," *Journal of Physiol.*, vol. xvii., pp. 129–134.

nerve. The first figure shows these cells as they exist in their first maturity; the second figure, as they appear in a person of extreme old age. In the latter you will readily notice that the cells, C, have shrunk and no longer fill the spaces allotted to them, the nuclei have become small, and have lost their conspicuous granules, and the protoplasm has changed its appearance very strikingly because there have been deposited in it granules of the pigment which impart to these cells an appearance very different from that which they had in their maturity when their functional powers were at their maximum. You will notice also in other parts of the second figure that the atrophy of the cells has led on to their disintegration (*c*, *c*), that they are breaking down, being destroyed, and that the result of their breaking down will ultimately be their disappearance. Thus the atrophy of a cell may lead to its death. The other two figures[1] upon the screen show us the brain of the humblebee. On the left is the brain of the bee in the condition in which we find it when the bee first emerges from the pupa or chrysalis. The cells are then in a fine physiological condition, but in a few weeks at most the bee becomes old and in the space which belongs to each cell we find only its shrunken and atrophied remnants, the nucleus greatly reduced in volume, and an irregular mass of protoplasm shrunk together around it. These cells have likewise undergone an atrophy and are on their way to death.

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[1] The two figures of the bee's brain are not reproduced in the text.

In other cases we find that there is a change going on which we call *necrobiosis*, which means that the cells continue to live, but change their chemical organisation so that their substance passes from a living to a dead state. No more perfect illustration of this sort of change can be found than that which is afforded by the skin. In the deep layer of the outer skin are the living and growing parts, which we all know from experience are sensitive. As these multiply some of them move up towards the surface ; and they are continually shoved nearer and nearer the surface by the growth of the cells underneath. They finally become exposed at the surface by the loss of the superficial cells which preceded them. During this migration the protoplasm of each cell, which was alive, is changed chemically into a new substance which we call keratin, or in common language, horny substance. Ultimately the cell protoplasm becomes nothing but horny substance and is absolutely dead. Here life and death play together and go hand in hand. Hence the term necrobiosis, death and life in one.

Another form of degeneration which occurs in many cases is of great interest because it seems as if the cells were making a last great effort ; and their final performance is one of enlargement. They become greater in size than before ; but there will follow a disintegration of these cells also ; and they break down and are lost. This form of degeneration is termed *hypertrophy*, and represents a third type, as I have stated.

In all parts of the body degenerative changes are going on, and they represent collectively a third phase in the cytomorphic cycle. But there is yet one more phase, which is needed to complete the story, namely the phase of the death and final removal of the cells. The degenerative change, when complete, always results in the death of the cell. In many cases the dead material is removed merely by being cast off, as is the case with the skin. All the scales which peal off from the outer surface of our body represent little scraps or clusters of cells which are entirely dead; and in the interior of the body, in the intestinal canal, and in the glands of the stomach, we find cells continually dying, dropping off from their place upon the walls, and being cast away. Or if we examine the saliva which comes from the mouth, we detect that that also is full of cells which have died and fallen off from their connection with the body and are thus removed.[1] An even more important method of the removal of cells is by a chemical process in consequence of which the cells are dissolved and disappear before our eyes, very much as marble may disappear from sight under the corrosive action of an acid. Indeed, we know that all the parts of the body, so far as they are alive, produce within themselves a ferment which has a tendency to

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[1] Two kinds of cells are commonly found in the saliva, the first are cornified cells sloughed off the lining epithelium of the mouth, the second are salivary corpuscles, which are really white blood corpuscles (leucocytes) that have migrated into the saliva and died. Being dead they have enlarged themselves by the imbibition of water.

destroy the living substance itself.[1] The production of these destructive agents is going on at all times, apparently, in all parts of the body which are alive. A striking illustration of this is offered in the stomach. The digestive juice which is produced in the stomach is capable of attacking and destroying living substance, and any organic material suitable for food which is placed in the stomach will, as we know, be attacked by the gastric juices, dissolved to a certain extent by them, and so destroyed. Why then does the gastric juice not attack the stomach itself? This is but one phase of the problem why the body does not continually destroy itself. It has lately been ascertained by some ingenious physiological investigations that the body not only produces the destructive agents, but also antagonists thereto, anti-compounds which tend to prevent the activity of the destroying factors. The whole problem is one of great interest and importance which calls for very much further investigation before we can be said to have arrived at a clear understanding of it. But it helps us much in our conception of cytomorphosis to know that all portions of the body are endowed with this faculty of destroying themselves, for it enables us to understand how it is possible that after the degeneration of a cell it will be dissolved away. It is merely that the agents of solution which are ordinarily held at bay

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[1] This remarkable phenomenon is known by the name of *autolysis*. An excellent general exposition of the subject has been made by Dr. P. A. Levene of the Rockefeller Institute in the *Harvey Lectures*, 1905–6, p. 73.

are no longer restrained, and they at once do their work.

There is another, but comparatively rare, mode of cell destruction. The cells break up into separate fragments,[3] which are then dissolved by chemical means and disappear, by the method of histolysis above described, or else are devoured by the cells to which reference was made in the first lecture and which are known by the name of *phagocytes*, and to which Metchnikoff has attributed so great an importance. It is unquestionable that phagocytes do eat up fragments of cells and of tissues, and may even attack whole cells. But to me it seems probable that their rôle is entirely secondary. They do not cause the death of cells, but they feed presumably only upon cells which are already dead or at least dying. Their activity is to be regarded, so far as the problem of the death of cells is concerned, not as indicating the cause of death, but as a phenomenon for the display of which the death of the cell offers an opportunity. A word of caution! Let me state explicitly that the death of cells does not depend always upon their completing the cytomorphic cycle. Death may befall a young cell just as it may befall a young child. I think it probable in all such cases,

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[3] The best known case of fragmentation is that of the red-blood corpuscles. Vast numbers of them are constantly destroyed at the close of their cytomorphosis by this process, which has been studied by numerous investigators chiefly in the spleen and the liver. Another noteworthy illustration of this method of cell destruction was discovered by Ranvier ("Des clasmatocytes," *Archives l'anatomie microsc.*, iii., 122–139) among wandering cells which occur in the connective tissue of mammals.

even when the death of the cells is normal and occurs in the regular course of development, that the cause of the cells' death is extraneous to them, not intrinsic. The subject of the death and disintegration of cells is an exceedingly complex one, and might well occupy our attention for a long time. But it is not permissible to depart from the strict theme which we have before us, and I will content myself, therefore, with throwing upon the screen two tables[1] which illustrate

[1] I. DEATH OF CELLS

First. Causes of death.
  *A.* External to the organism:
    (1) Physical (mechanical, chemical, thermal, etc.).
    (2) Parasites.
  *B.* Changes in intercellular substances (probably primarily due to cells):
    (1) Hypertrophy.
    (2) Induration.
    (3) Calcification.
    (4) Amyloid degeneration (infiltration).
  *C.* Changes inherent in cells.
Second. Morphological changes of dying cells.
  *A.* Direct death of cells:
    (1) Atrophy.
    (2) Disintegration and resorption.
  *B.* Indirect death of cells:
    (1) Necrobiosis (structural change precedes final death).
    (2) Hypertrophic degeneration (growth and structural change often with nuclear proliferation precede final death).
Third. Removal of cells.
  *A.* By mechanical means (sloughing or shedding).
  *B.* By chemical means (solution).
  *C.* By phagocytes.

II. INDIRECT DEATH OF CELLS.

*A.* Necrobiosis.
  (1) Cytoplasmic changes:
    (*a*) Granulation.
    (*b*) Hyaline transformation.

to us the variations in the death of cells and in their modes of removal which are known at the present time. These tables are taken from a lecture which I delivered in New York a few years ago, and which was subsequently published.[1] If any of you should care to make a closer acquaintance with them they are therefore readily accessible to you.

In order to render the nature of cytomorphosis clearer to you let me ask your attention for a concrete example, the biological history of the red blood corpuscles, minute bodies, which in man are normally cup-shaped,[2] as they are in various other mammals also. It

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        (*c*) Imbibition.
        (*d*) Desiccation.
        (*e*) Clasmatosis.
    (2) Nuclear changes :
        (*a*) Karyorhexis.
        (*b*) Karyolysis.
*B*. Hypertrophic degeneration.
    (1) Cytoplasmic :
        (*a*) Granular.
        (*b*) Cornifying.
        (*c*) Hyaline.
    (2) Paraplasmic :
        (*a*) Fatty.
        (*b*) Pigmentary.
        (*c*) Mucoid.
        (*d*) Colloid, etc.
    (3) Nuclear (increase of chromatin).

[1] "The Embryological Basis of Pathology," the Middleton Goldsmith Lecture delivered before the New York Pathological Society, March 26, 1901, *Science*, xiii., 481–498, and *Boston Med. Sur. Journal*, cxliv., 295–305.

It was in the course of this lecture that the law of cytomorphosis was first publicly announced and formulated.

[2] The form usually ascribed to them is that of a biconcave disc, a shape which appears to be a post-mortem artefact. The true shape was first proven by

may interest you to know that it was not until 1902 that the actual shape was correctly recognised. The corpuscles are so small that about 5,000,000 occur in a cubic millimetre of blood. The picture now before us illustrates the life history of these cells.[1] In the earliest stage of their cytomorphosis the cells have each a well formed nucleus, Fig. 25, No. 1, with a minimal amount of protoplasm around it, indeed the protoplasmic envelope is so exceedingly thin that earlier observers thought the corpuscles began as naked nuclei without a cell body.[2] In the next stage, No. 2, the cell body has grown so that there is more protoplasm than before in proportion to the volume of the nucleus. The cell body around the nucleus is at this time loading itself with hæmoglobin, the red substance which plays, as you all know, so important a part in respiration. The enlargement of the cell soon reaches

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Weidenreich (*Archiv f. mikrosk. Anat.*, LXI., p. 61), whose observations have been confirmed in my laboratory, especially by Professor F. T. Lewis (*Journ. Med. Research*, x., 513, 1904).

[1] As regards the drawings in Figure 25, it should be stated that from each embryo a single corpuscle was selected by me as typical. In the specimens corpuscles in many different stages of development are found together and the selection of a typical corpuscle is difficult. The choice is necessarily somewhat arbitrary. The drawings illustrate the progress of development correctly, except that the transition from the last nucleated stage, No. 6, to the final cup-shaped stage, No. 8, is still subject to discussion, but No. 7 was drawn from an actual corpuscle, which had certainly lost its nucleus and become smaller, and apparently was just beginning to assume the cup-shape. How the nucleus disappears is not known with certainty; there are two principal views, the first that the nucleus is extruded, the second that it is dissolved by the rest of the cell. The problem of the disappearance of the nucleus, though very important cytologically, is of secondary interest for the main purpose of the present lecture.

[2] For example, F. M. Balfour, Works, vol. i., p. 50.

its maximum, No. 3, and the corpuscle is in the Ichthyopsidan stage,[1] which means the stage which

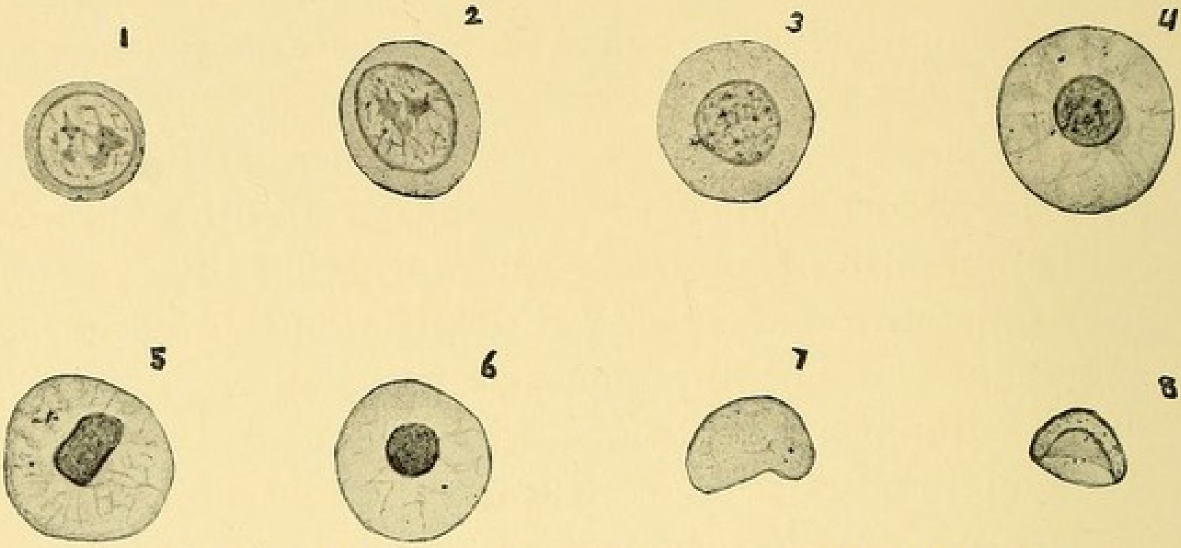

Fig. 25. Life History of Blood Corpuscles, Rabbit Embryos.

No. 1. Embryo of 8 days, 6 hours, No. 883. No. 2. Embryo of 9 days, No. 621. No. 3. Embryo of 9 days, 12 hours, No. 567. No. 4. Embryo of 10 days, No. 940. No. 5. Embryo of 11 days, No. 556. No. 6. Embryo of 14 days, 18 hours, No. 143. No. 7. Embryo of 16 days, 12 hours, No. 1229. No. 8. Embryo of 18 days, No. 167.

is permanent and the highest attained in fishes and amphibians. The next stage, No. 4, is characterised by a shrinkage of the nucleus, a degenerative change, but bringing the physiological advantage of more room for hæmoglobin in the corpuscles. When the nucleus shrinks it loses the granular appearance it had before and also stains more deeply with the microscopists' dyes, Nos. 5 and 6. This is called the Sauropsidan stage,[1] because it is that which is permanent and the highest attained in reptiles and birds.

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[1] C. S. Minot, "Morphology of the Blood Corpuscles," *Proc. Amer. Assoc. Adv. Science*, xxxix. (1890), p. 341, and *Anatomischer Anzeiger*, v., p. 601.

Next the nucleus disappears, No. 7, probably by being completely expelledt from the cell, and by further contraction the enucleate cell assumes the cup-shape, thus evolving the true mammalian non-nucleated red corpuscle, No. 8. The cells have been differentiated and are now degenerating. The last stage of all is their death and removal.[1] Their usual end is breaking up into small fragments, which are then eaten by phagocytes and so disposed of. Sometimes, however, corpuscles are devoured whole by phagocytes. It is possible that corpuscles are normally destroyed by imbibing fluid until they burst, as is said to occur under pathological conditions. To recapitulate: 1, the cells have little protoplasm; 2, the protoplasm grows; 3, differentiation occurs; 4, degeneration; 5, disintegration of the cells; 6, removal of their remains.

Let us turn from the study of details and illustrations, to the examination of general considerations. Our first endeavour must be to answer the question: How, from the standpoint of cytomorphosis, ought we to look upon old age? Cytomorphosis, the succession of cellular changes which goes on in the body, is always progressive. It begins with the earliest development, continues through youth, is still perpetually occurring at maturity and in old age. The rôle of the last stage of cytomorphosis, that is, of death in life, is very important, and its importance has only lately become clear to us. I doubt very much if the conception is at all familiar to the members of this audi-

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[1] Compare Weidenreich, *Anatom. Anzeiger*, xxiv., pp. 186–192.

ence. Nevertheless the constant death of cells is one of the essential factors of development, and much of the progress which our bodies have made during the years we have lived has been conditional upon the death of cells. As we have seen, cytomorphosis, when it goes through to the end, involves not only the differentiation but the degeneration and death of the parts. There are many illustrations of this which I might cite to you as examples of the great importance of the destruction of parts. Thus there is in the embryo before any spinal column is formed an easily visible structural axis which is termed the notochord. In the young mammalian embryo this structure is clearly present and plays an important part, but in the adult it has almost disappeared, and its disappearance begins very early during embryonic life. There are numerous blood-vessels which we find to occur in the embyro, both those which carry the blood away from the heart and those which bring blood to the heart, which during the progress of development are entirely destroyed, and disappear for ever. Knowledge of these is to the practical anatomist and surgeon often of great importance. Vast numbers of the smaller blood-vessels which we know commonly by the name of capillaries exist only for a time and are then destroyed. There is in the young frog, while he is in the tadpole stage, a kidney-like organ, which on account of its position is called the head-kidney, but it exists only during the young stage of the tadpole. There is later produced another kidney which, from its position, is called the middle-kidney, and which is the only renal organ found in the adult, for the head-kidney disappears in these animals long before the adult condition is reached. In the mammal there is yet a third kidney. We have during the embryonic stage of the mammal always a well-developed excretory organ which corresponds to the middle or permanent kidney of the frog, yet during embryonic life the greater part of this temporary structure is entirely destroyed. It is dissolved away and vanishes, leaving only a few remnants of comparatively little importance in the adult. The new structure, the permanent kidney which we have, takes its place functionally. Large portions of the tissues which arise in the embryo are destroyed at the time of birth, and take no share in the subsequent development of the child.[1] If we follow out with the microscope the various changes which go on in the developing body we see revealed to us a very large number of cases of death of tissues, followed by their removal. Thus the cartilage which exists in the early stages dies and is dissolved away, and its place is taken by bone. Many of the bony elements of the skeleton in the adult, in the embryo exist merely as cartilage, yet the cartilage is not converted into bone but is destroyed and *pari passu* its place taken by bone.[2] There is overlying the heart of a child at

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[1] Reference is made to the after-birth, which includes the structures known anatomically as the umbilical cord, the amnion (the "caul" of the midwife), the chorion læve, and the fetal placenta.

[2] The conversion of cartilage into bone was studied by many investigators especially between 1845 and 1870, and was the subject of prolonged and ani-

birth a well-developed gland known as the thymus. After childhood this undergoes a retrograde development; it becomes gradually absorbed and persists only in a rudimentary condition. With the loss of the teeth occurring during infancy, you are familiar, and know that the first set of teeth are but for a short period, and are to be replaced by the permanent set. In very old persons we see a great deal of the bony material absorbed, and this absorption of the bone is a phenomenon which occurs at almost every period of the development. Portions of the epidermis or outer skin are constantly shed, as is well known, and the loss of hair and the loss of portions of our nails are so familiar to us that we hardly heed them. Of the constant destruction of the cells which are found in the lining of the intestine, I have already spoken. At all times in the body there is a vast amount of destruction of blood corpuscles going on, a destruction which is physiologically indispensable, for the material which the blood corpuscles furnish is used in many ways. For instance, the pigment which occurs in the hair is supposed to be derived from the chemical substances the use of which the body obtains by destroying blood

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mated debates, one might almost say of constant controversy. This need not be wondered at for the changes involved are very complicated, owing to the fact that the formation and destruction of cartilage, the formation of new and the removal of old bone, and the development of a new tissue (marrow) all go along together, and often may all be seen at once, each in various phases, within the limits of a single microscopic field of view. Our present knowledge renders it certain that the cartilage degenerates, dies, and disappears and takes no share in the production of bone. That certain rare exceptions to this rule occur has been maintained, but the evidence is, in my opinion, unconvincing.

corpuscles. One of the most familiar instances of destruction is that of the tail of the tadpole. The young frog and the young toad during their larval stages live in the water and each of them is furnished with a nice tail for swimming purposes. As the time approaches for the metamorphosis of the tadpole into the adult, the tail is gradually dissolved away. It is not cast off, but it is literally dissolved, resorbed, and vanishes ultimately altogether.

It is evident that such a vast amount of destruction of living cells could not be maintained in the body without the body going entirely to destruction itself, were there not some device for making good the losses which are thus brought about. We find in fact that there is always a reserve of cells kept to make good the loss which it is essential should be made good. Some losses apparently do not have to be repaired, but the majority of them must be compensated for, and this is done by having in the body a reserve supply of cells which can produce new cells of the sort required. This leads us to consideration of the phenomenon of regeneration and of the repair of parts. These phenomena we can better take up later in our course, after we shall have dealt with the general processes of development and growth. From the study of regeneration we shall be able to confirm the explanation of old age, which I want to lay before you. This confirmation is so important that it will be better taken up in a separate lecture, than slipped in now when the hour is nearly by.

Old age, after what I have said, I think you will all recognise as merely the advanced and final stage of cytomorphosis. Old age differs but little in its cytomorphosis from maturity; maturity differs much from infancy; infancy differs very much indeed from the embryo; but the embryo differs enormously from the germ in its cytomorphic constitution. We know that in the early time comes the great change, and this fact we shall apply for purposes of interpretation later on. Cytomorphosis is then a fundamental notion. It gives us in a general law, a comprehensive statement of all the changes which occur in the body. None, in fact, are produced at any period in any of us except in accordance with this general cytomorphic law. There is, first, the undifferentiated stage, then the progressive differentiation; next there follows the degenerative change ending in death, and last of all, the removal of the dead cells. Such we may conveniently designate as the four essential stages of cytomorphosis. This cytomorphosis is at first very rapid; afterwards it becomes slower. That is a significant thing. The young change fast; the old change slowly. We shall be able, when we get a little farther along in our study, to see that in differentiation lies the explanation of a great many of the known phenomena of biology, lies the explanation of our conception of cell structures; and in it also lies not only the explanation of the death of cells, but also, as it seems to me—and this is one of the points that I shall want particularly to bring forward before the close of the course,—of general death, that which we mean by death in common parlance, when the continuation of the life of the individual ceases, and is thereafter bodily impossible. The explanation of death is one of the points at which we shall be aiming in the subsequent lectures of the course.

Now we know that in connection with age there is always growth. I propose, therefore, in the next lecture to take up the subject of growth. We shall arrive at some paradoxical conclusions, for it can be shown by merely statistical reckonings that our notion that man passes through a period of development and a period of decline is misleading, in that in reality we begin with a period of extremely rapid decline, and then end life with a decline which is very slow and very slight. The period of most rapid decline is youth; the period of slowest decline is old age, and that this statement is correct I shall hope to prove to you with the aid of tables and lantern illustrations at the next lecture.

# III

## THE RATE OF GROWTH

LADIES AND GENTLEMEN: In the first of the lectures, I described those grosser characteristics of old age, which we ourselves can readily distinguish, or which an anatomical study of the body reveals to us. In the second lecture I spoke of the microscopic alterations which occur in the body as it changes from youth to old age. But besides the changes which we have already reviewed, there are those others, very conspicuous and somewhat known to us all, which we gather together under the comprehensive term of *growth*. It is growth which I shall ask you to study with me this evening, and I shall hope, by the aid of our study, to reinforce in your minds the conclusion which I have already indicated, that the early period of life is a period of rapid decline, and that the late period of life is one of slow decline.

In order to study growth accurately, it is desirable, of course, to measure it, but since we are concerned with the general problem of growth, we wish no partial measure, such as that of the height alone would be. And indeed, if we take any such partial measure, how could we compare different forms with one another? The height of a horse is not comparable to that of a man; the height of a caterpillar is not comparable to that of any vertebrate. Naturally, therefore, we take to measuring the weight, which represents the total mass of the living body, and enables us at least with some degree of accuracy to compare animals of different sorts with one another. Now in studying this question of the increase of weight in animals, as their age increases, it is obviously desirable to eliminate from our experiments all disturbing factors which might affect the rate of growth or cause it to assume irregularities which are not inherent either in the organisation of the animal or in the changes age produces. The animals which belong to the vertebrate sub-kingdom, of which we ourselves are members, can be grouped in two large divisions according to the natural temperature of their bodies. The lower vertebrates, the fishes, frogs, and their kin, are animals which depend for their body temperature more or less on the medium in which they live. The other division of vertebrate animals, which includes all the higher forms, are so organised that they have within certain limits the power of regulating their own body temperature. Now it is easily to be observed—and any one who has made observations upon the growth of animals can confirm this—that animals otherwise alike will grow at different speeds at different temperatures.

There are animals, like the frogs and salamanders, which will live at a very considerable range of temperature and thrive, apparently. No ultimate injury is done to them by a change of their bodily temperature. Here we have four young tadpoles, (Fig. 26), all of which are exactly three days old. The first of these has been kept at a temperature not much above freezing; the fourth at a temperature of about twenty-

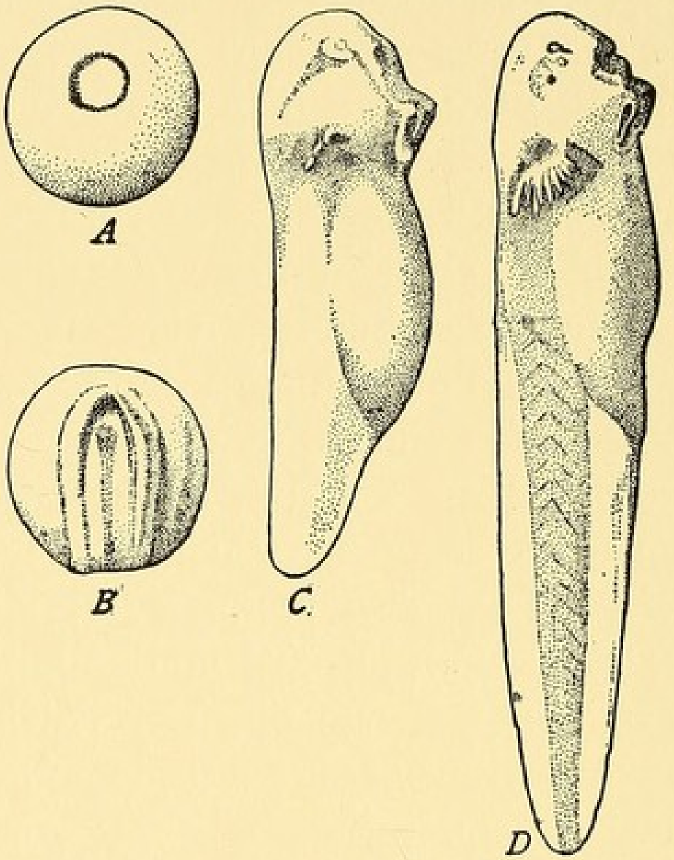

FIG. 26. FOUR TADPOLES OF THE EUROPEAN FROG *Rana fusca*. After Oskar Hertwig. The four animals are all of the same age (three days) and raised from the same batch of eggs, but have been kept at different temperatures.

*A* at 11.5° centigrade. *B* at 15.0° centigrade
*C* " 20.0° " *D* " 24.0° "

four degrees centigrade; the other two at temperatures between. They are all descendants from the same batch of frogs' eggs, and you can see readily that the first one is still essentially nothing but an egg. The second one, which has had a little higher temperature, already shows some traces of organisation, and those familiar with the development of these animals can see in the markings upon the surface the first indications of the differentiation of the nervous system. The third has been kept at a considerably warmer temperature, and is now obviously a young tadpole; here are the eyes, the rudimentary gills, the tail, etc. While the fourth tadpole, which was maintained at the best temperature for the growth of these animals, has advanced enormously in its development. Obviously, should we make experiments upon animals of this class it would be necessary to keep them at a uniform temperature, if we wished to study their rate of development, and that is, for very practical reasons, extremely difficult and unsatisfactory. Far better it has seemed for our study of growth to turn to those animals which regulate their own temperature. This, accordingly, I have done, and the animal chosen for these studies was the guinea-pig, a creature which offers for such investigations certain definite advantages. It is easily kept; it is apt to remain, with proper care, in good health. Its food is obtainable at all seasons of the year, in great abundance, and at small expense. The animals themselves being of moderate size do not, of course, require such extraordinary amounts of food as the large animals, should we experiment with them. Accordingly with guinea-pigs I began making, years ago, a long series of records, taking from day to day, later from week to week, and then, as the animals grew older, month by month, the weight of recorded individuals. There was thus obtained a body of statistics which rendered it possible to form some idea of the rapidity of growth of this species of mammal.

Now in regard to the rapidity of growth, it is encessary that we form clearer notions than perhaps you started out with when you came into the hall this evening. I will ask for the next of our pictures on the screen, where we shall see illustrated to us older methods of recording the progressive growth of animals. Fig. 27 is a chart taken from the records of my friend, Dr. Henry P. Bowditch, showing the growth of school children in Boston. Here we have, in the lower part of the figure, the two curves of growth in weight. The upper curve is the weight of boys. We can follow it back through the succession of years down to the age of five and one half years, when the records begin. The child weighs, as you see, a little under forty pounds at that time. When the boy reaches the age of eighteen and one half years, he approaches the adult size, and weighs well over 130 pounds. Here then we see growth represented to us in the old way, the progressive increase of the animal as it goes along through the succession of years. Now this is a way which records the actual facts satisfactorily. It shows the progressive changes of weight as they really occur; but it does not give

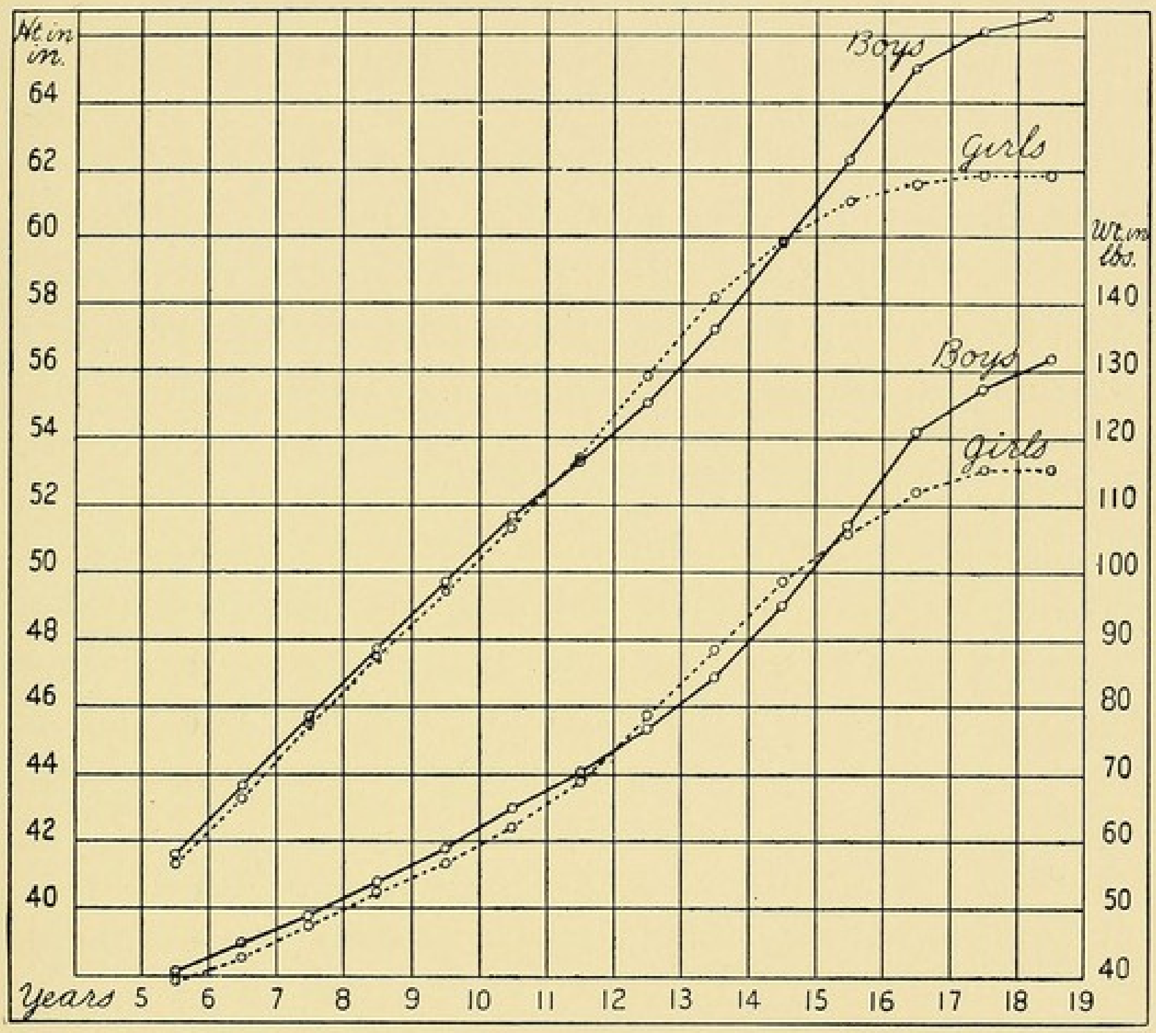

FIG. 27. CURVES SHOWING THE GROWTH OF BOSTON SCHOOL CHILDREN IN HEIGHT AND WEIGHT.— After H. P. Bowditch.

us a correct impression of the *rate* of growth. Concerning the rate of growth, some more definite notion must be established in our minds before we can be said to have an adequate conception of the meaning of that term.[1] It is from the study of the statistics

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[1] The method described in the text of determining the rate of growth was

of the guinea-pigs, and of other animals which I have since had an opportunity of experimenting with, that we get indeed a clearer insight as to what the rate of growth really is and really means.

I should like to pause a moment to say that when I first published a paper upon the subject of growth, it, fortunately for me, interested the late Dr. Benjamin A. Gould. The experiments which I had made and recorded in that first publication came to a sudden end, owing to a disaster for which I myself was personally not responsible, by which practically my entire stock of animals was suddenly destroyed. Dr. Gould, after consulting with me, proposed that I should have further aid from the National Academy of Sciences, and through his intervention I obtained a grant from the Bache fund of the Academy. That liberal grant enabled me to continue these researches, and this is the first comprehensive presentation of my results which I have attempted. In this and the subsequent lectures, I hope that enough of what is new in scientific conclusions may appear to make those to whose generosity I am indebted feel that it has been worthily applied. I cannot let such an occasion as this pass by without expressing publicly my gratitude to Dr. Gould for his encouragement and support at a time when I most keenly appreciated it.

If animals grow, that which grows is of course the actual substance of the animal. Now we might say

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first defined and advocated by me in my article, " Senescence and Rejuvenation," *Journ. of Physiol.*, vol. xii., pp. 97–153 (1891).

that given so much substance there should be equal speed of growth, and we should expect, possibly, to find that the speed would be more or less constant. I can perhaps illustrate my meaning more clearly, and briefly render it distinct in your minds, by saying that if the rate of growth, as I conceive it, should remain constant, it would take an animal at every age just the same length of time to add ten per cent. to its weight; it would not be a question whether a baby grew an ounce in a certain length of time, and a boy a pound in the same time, for the pound might not be the same percentage of advance to the boy that the ounce would be to the baby. In reality with an advance of an ounce the baby might be growing faster than the older boy with the addition of the pound.

To determine the rate I devised the following method.[1] Take the weight at a given age, and the weight at the next older age for which there are observations. From these data calculate the average daily increase in weight for the period between the two determinations of the weight, then express the daily increase as a percentage of the weight at the beginning of the period. From a series of determinations the daily percentage increments are readily calculated for successive ages. Subsequently the method was modified for the study of the rate of growth in man by substituting the monthly, or even yearly, percentage increments for the daily. This method is not mathematically exact, since the grow-

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[1] *L. c.*

ing weight is a variable function of the age, but it is sufficiently exact for our present needs, and has the advantages of simplicity and rapidity in its practical application.

In the next slide (Fig. 28) which we are to see upon the screen we have my method of measuring the rate of growth illustrated graphically. There is here a curve which represents the rate of growth of male guinea-pigs. The figures at the bottom indicate the age of the animals in days. When guinea-pigs are born they are very far advanced in development, and the act of birth seems to be a physiological shock from which the organism suffers, and there is a lessening of the power of growth immediately after birth. But in two or three days the young are fully re-

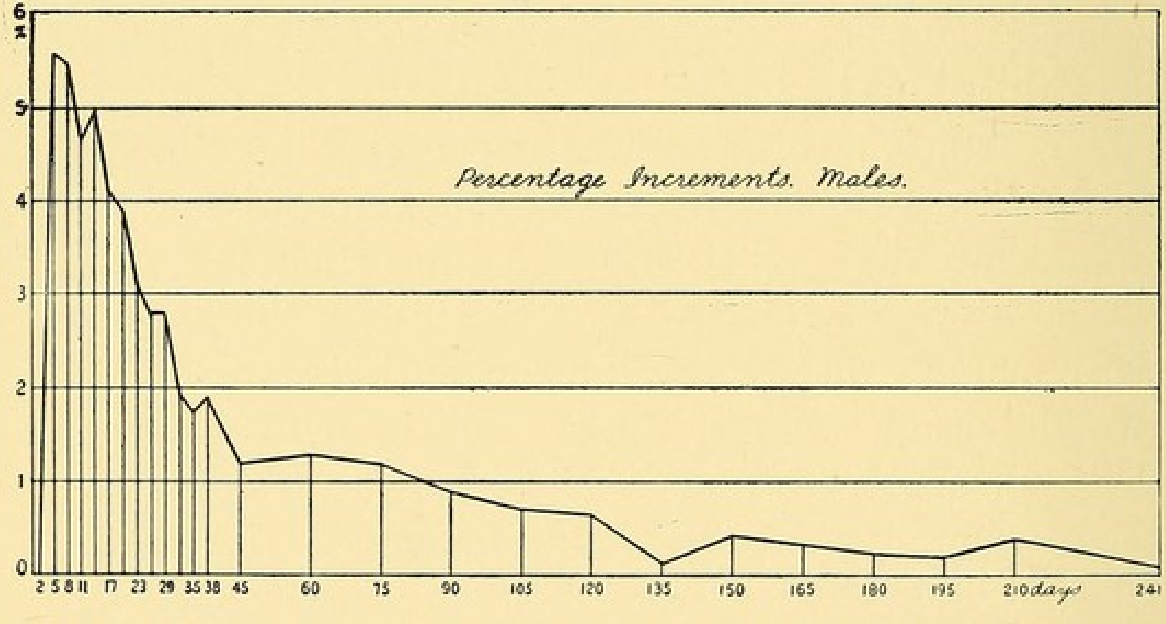

FIG. 28. CURVE SHOWING THE DAILY PERCENTAGE INCREMENTS IN WEIGHT OF MALE GUINEA-PIGS.

covered, and after that restoration they can add over five per cent. to their weight in a single day. But by the time they are 17 days old, as represented by this line, they can add only four per cent., and by the time they are 24 days old, less than two per cent.; at 45 barely over one per cent.; at 70 still over one per cent.; at 90 less; at 160 less; and towards the end the curve continues dropping off, coming gradually nearer and nearer to zero, to which it closely approximates at the age of 240 days. In about a year, the guinea-pig attains nearly its full size. You notice that this curve is somewhat irregular. Such is very apt to be the result from statistics when the number of observations is not very large. It means simply that there was not a sufficiently large number of animals measured to give an absolutely even and regular set of averages. But the general course of the curve is very instructive. In the earlier condition of the young guinea-pig there is a rapid decline; in the later, a slow decline. The change from rapid to slow decline is not sudden, but gradual, as you see by the general character of this curve.

In the next slide (Fig. 29) we can see immediately that what I have asserted as true of the male is equally true of the female, although the values which we have differ slightly in the two sexes, and there are accidental but not significant variations in this curve as in the first. Here also we observe at once an early period of rapid decline in which the rate of growth is going down and down—a period of slight decline in which, to be sure, it is going down still, but with diminished rapidity.

There is another method by which we can represent

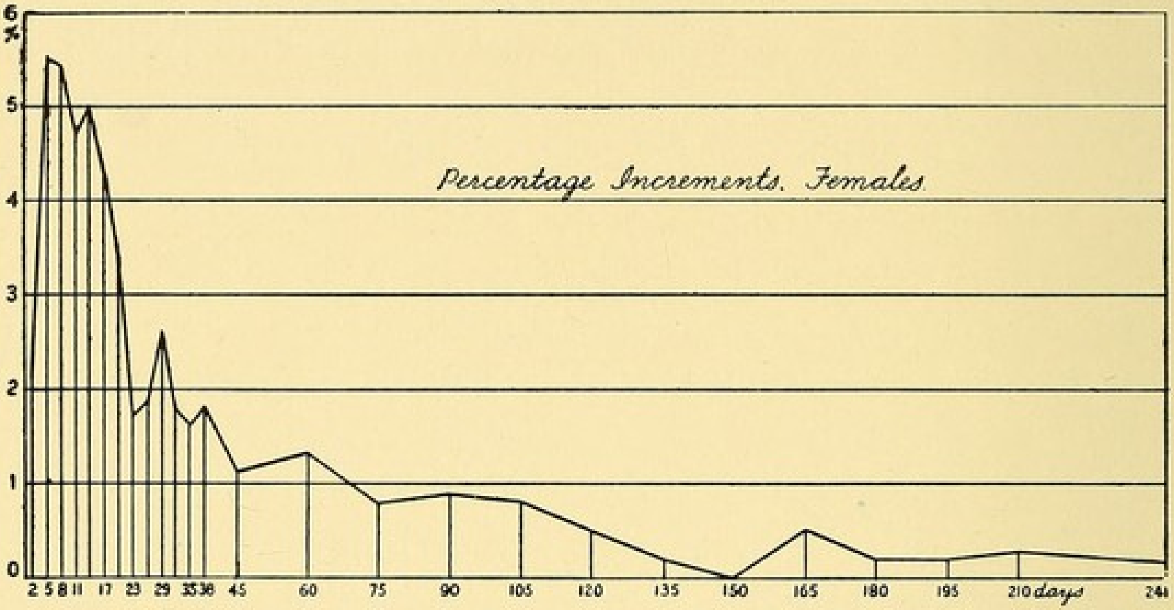

Fig. 29. Curve Showing the Daily Percentage Increments in Weight of Female Guinea-pigs.

this change in the rate of growth which will perhaps help to illustrate it; and in the next of our pictures (Fig. 30) we see this other form of representation. The first vertical line represents the length of time which it takes a young male guinea-pig to add ten per cent. to its weight the first time. Here the third time—the fourth—the fifth—and you see as it is growing older and older it takes the animal longer and longer to add ten per cent. to its weight. Finally we get to the nineteenth addition, and we see that the period is very long indeed. How long that period is we can judge by the figures upon the left, which represent the length of the periods in days.

From the base line to the one marked "ten" is a period of ten days, and you see that the guinea-pig in adding to its weight ten per cent. for the nineteenth time does it so slowly that it requires ten days and more; for the twenty-first time, nearly twenty; for the twenty-second time, nearly forty days. At last the number of observations becomes small, and the curve grows irregular. Thus we demonstrate that as the animal grows older it takes longer and longer to add ten per cent. to its weight. In the other sex, as the next slide shows, (Fig. 31), the same phenomena can be clearly demonstrated; here are the periods as

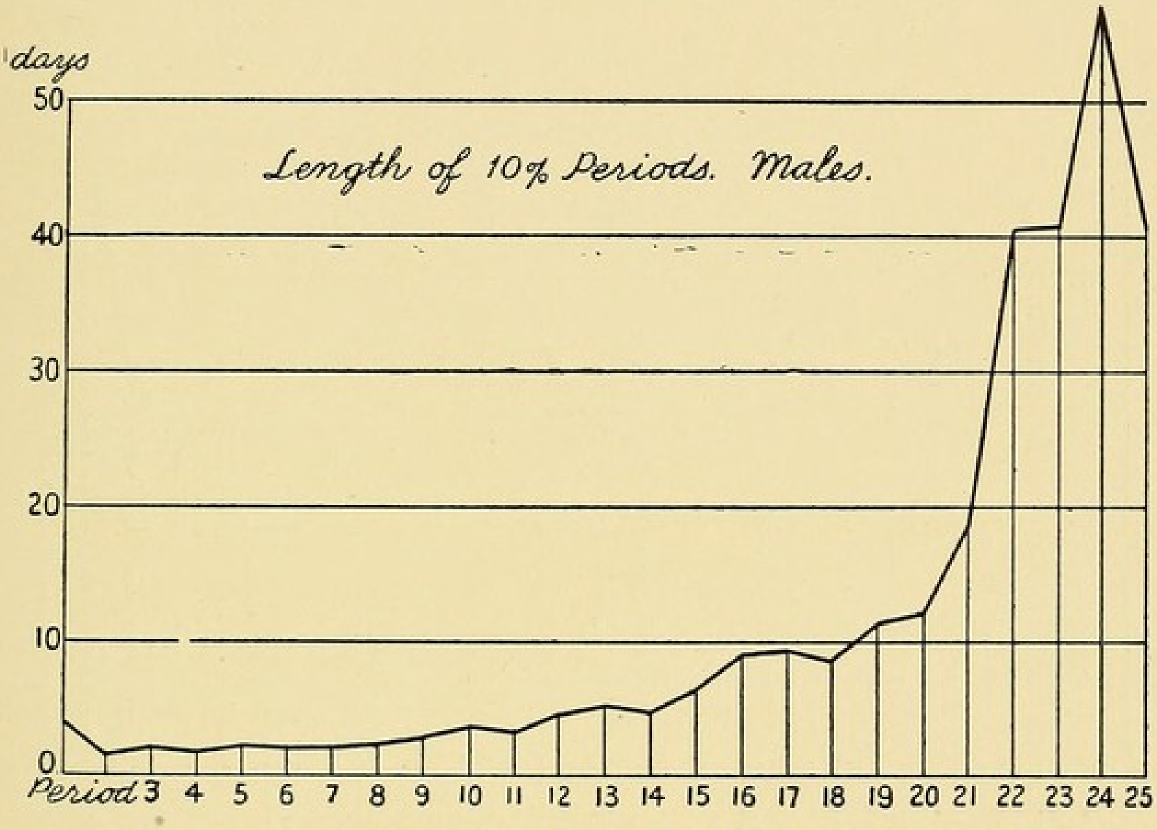

FIG. 30. CURVE SHOWING THE LENGTH OF TIME REQUIRED TO MAKE EACH SUCCESSIVE INCREASE OF 10 PER CENT. IN WEIGHT BY MALE GUINEA-PIGS.

before, lengthening out, as you see, at first; then becoming very long indeed. In the following slide I have another form of representation of this same phe-

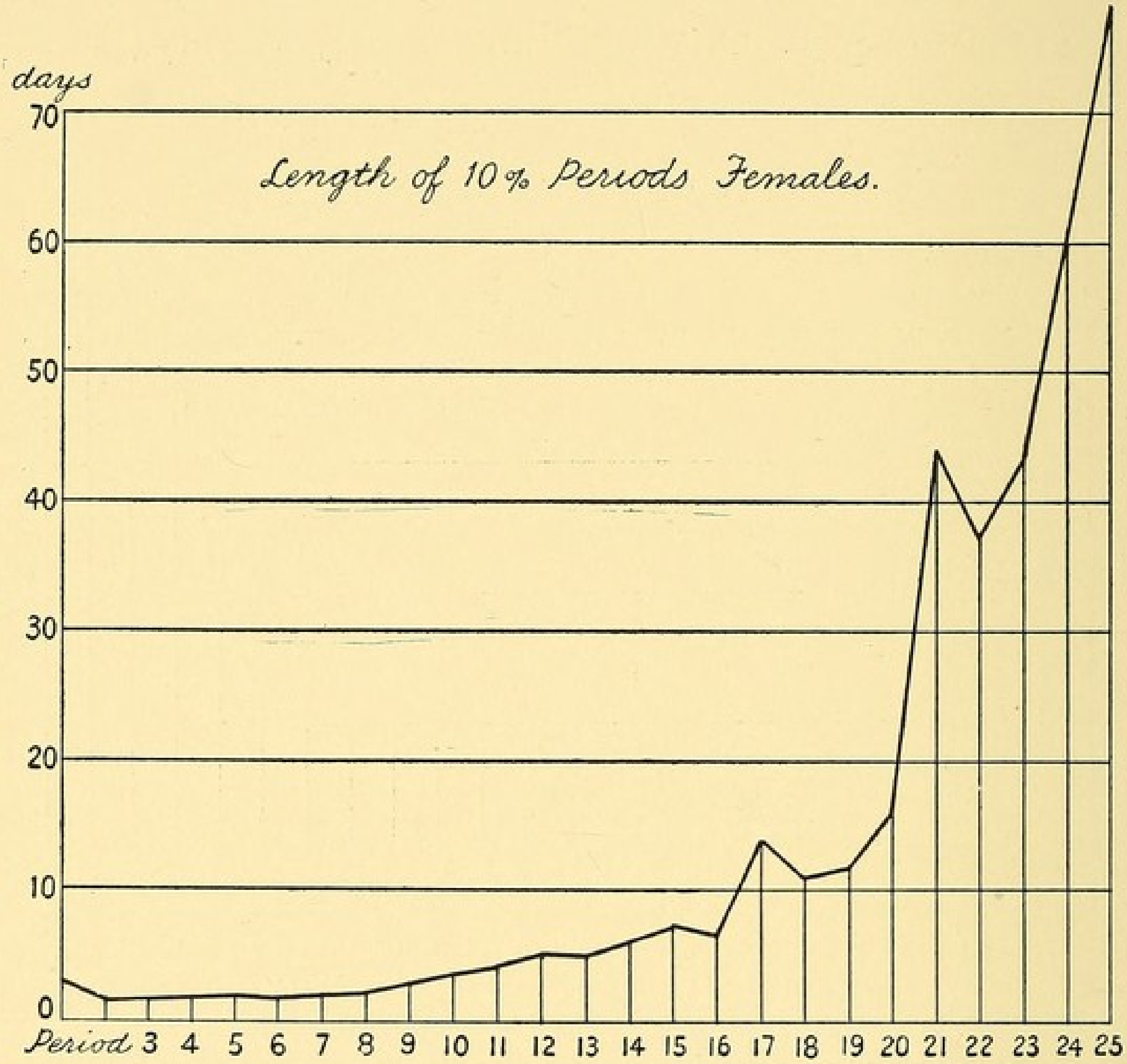

FIG. 31. CURVE SHOWING THE LENGTH OF TIME REQUIRED TO MAKE EACH SUCCESSIVE INCREASE OF 10 PER CENT. IN WEIGHT BY FEMALE GUINEA-PIGS.

nomenon as it occurs in the human subject. Here is a diagram of growth, (Fig. 32), which represents, as accurately as I could determine it, the curve complete for man from birth up to the age of forty years.

It has been calculated by a simple mathematical process where these ten-per-cent. increments fall, and from each point in this curve where there has been such an increment, a vertical line has been drawn, as you see here. These lines are very close together at the start. One ten per cent. after another follows in a short interval of time, but gradually the time, as indicated by the space between two of these vertical lines, increases, and when the individual is three years old, you can see there has been a very great lengthening out of the period which is necessary for it to add

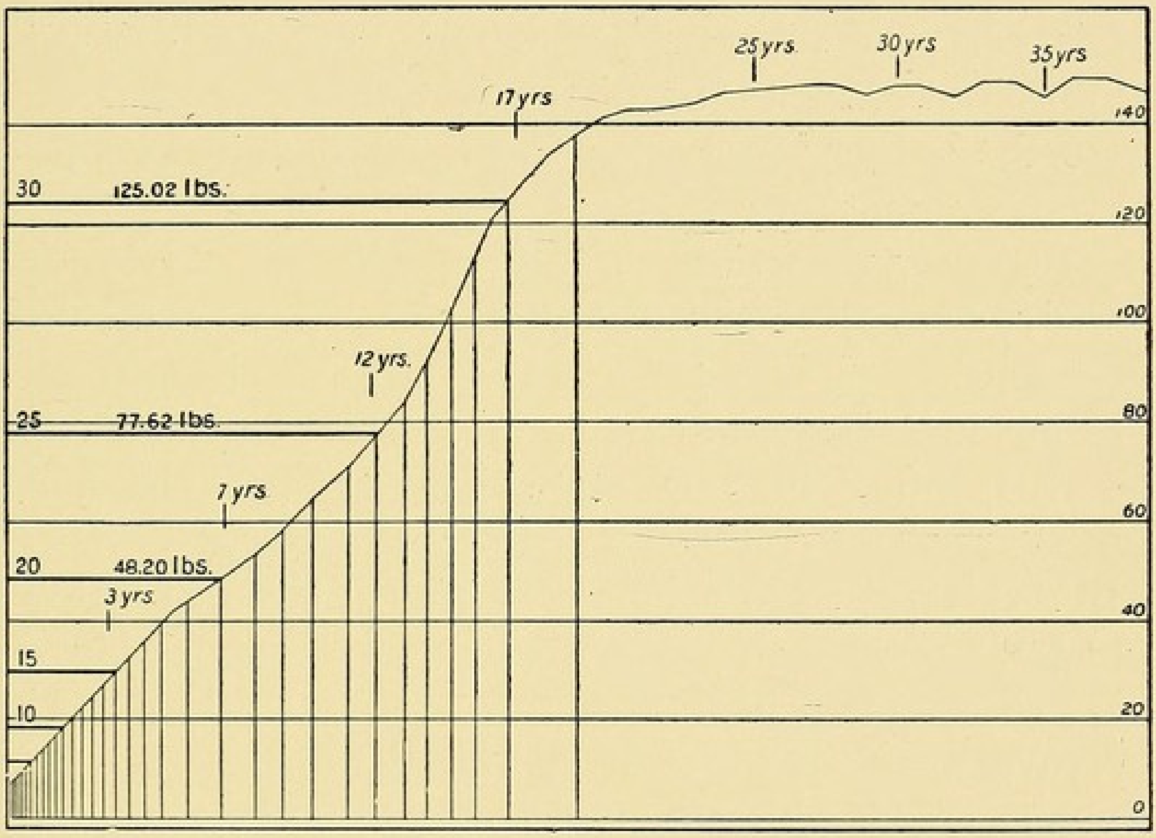

FIG. 32. CURVE SHOWING THE GROWTH OF MAN FROM BIRTH TO MATURITY, with vertical lines added to mark the duration of the periods for each 10 per cent. addition to the weight.

ten per cent. to its weight. Then it comes at the age of twelve to a period of slightly more rapid growth, a fluctuation which is characteristic of man, but does not appear in the majority of animals. After that comes very rapidly the enormous lengthening of the period. I have not added the last ten per cent. because the curve here at the top, you see, is not very regular, and it could not be calculated with certainty. Our diagram is merely another form of graphic representation of the fact that the older we are the longer it takes us to grow a definite proportional amount.

Figure 33 carries us into another part of our study, away from the mammals which we have thus far considered, into the class of birds. The growth of chickens is represented here. Now a chicken is born in a less matured state than a guinea-pig, and has a good deal higher efficiency of growth at first. In a chicken, as in a guinea-pig, birth is a disturbing factor, and growth immediately after the hatching of the chicken is a little impeded, but the chick quickly recovers and, as we see, the first time when the rate can be distinctly measured we get a nine-per-cent. addition to the weight in a single day. In a chicken, as in the guinea-pig, the rate gradually diminishes. The change from the rapid decline at first to the later slower decline is more gradual; the curve is more distinctly marked in the chicken as a round curve. There is not in the bird so distinct a separation of the preliminary rapid decline and the later slower decline as we find in the guinea-pig. The curve again is very irregular because I had only a very limited number of observations upon the weight of chicks.[1] The other sex, as the next slide will show, presents similar phenomena, though the female chickens do not grow quite as fast as their brothers. Here we notice an initial increase of almost, but not quite, nine per cent., which rapidly diminishes. After the chick is two months old it never adds as much as 3% per diem to its weight. It loses in the first two months from a capacity to add nine per cent., down to a capacity of adding less than three daily. It loses in two months two thirds of its power of growth, for from nine to zero is divisible into two parts, of

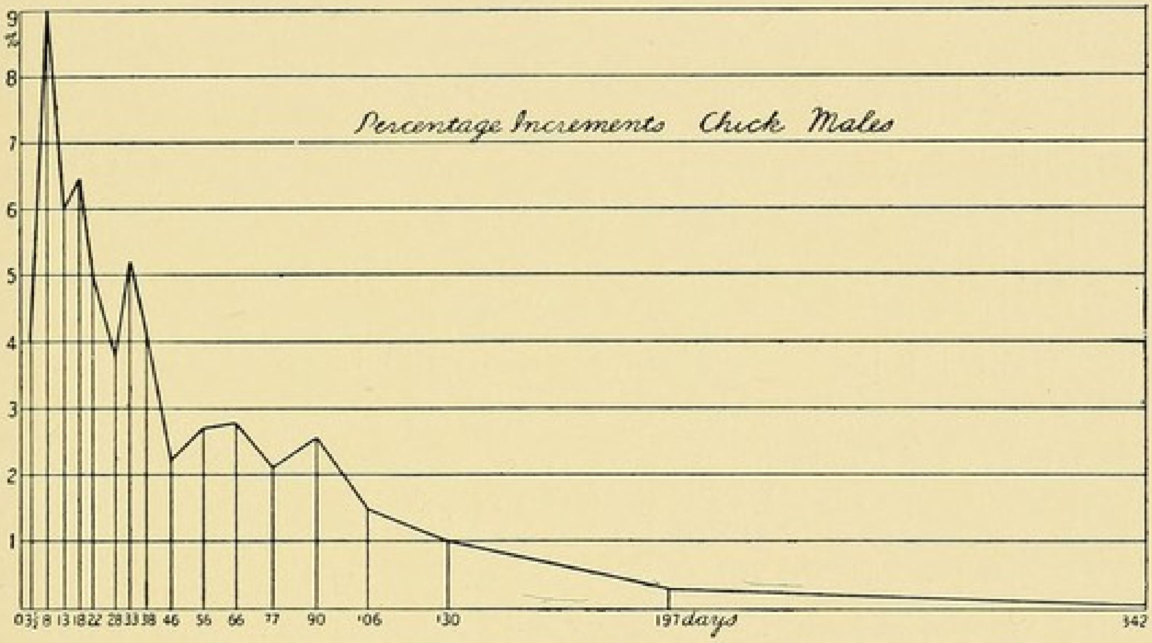

FIG. 33. CURVE SHOWING THE DAILY PERCENTAGE INCREMENTS IN WEIGHT BY MALE CHICKENS.

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[1] See Appendix No. II.

which the first, from nine down to three, would be two thirds, and the second, from three to zero, would be one third. Here then we learn that two thirds of the decline which occurs in the life of a chick takes place in two months, and for the rest of the life of the bird there is a decline of one third. That, you must acknowledge, is an extraordinary and most impressive difference.

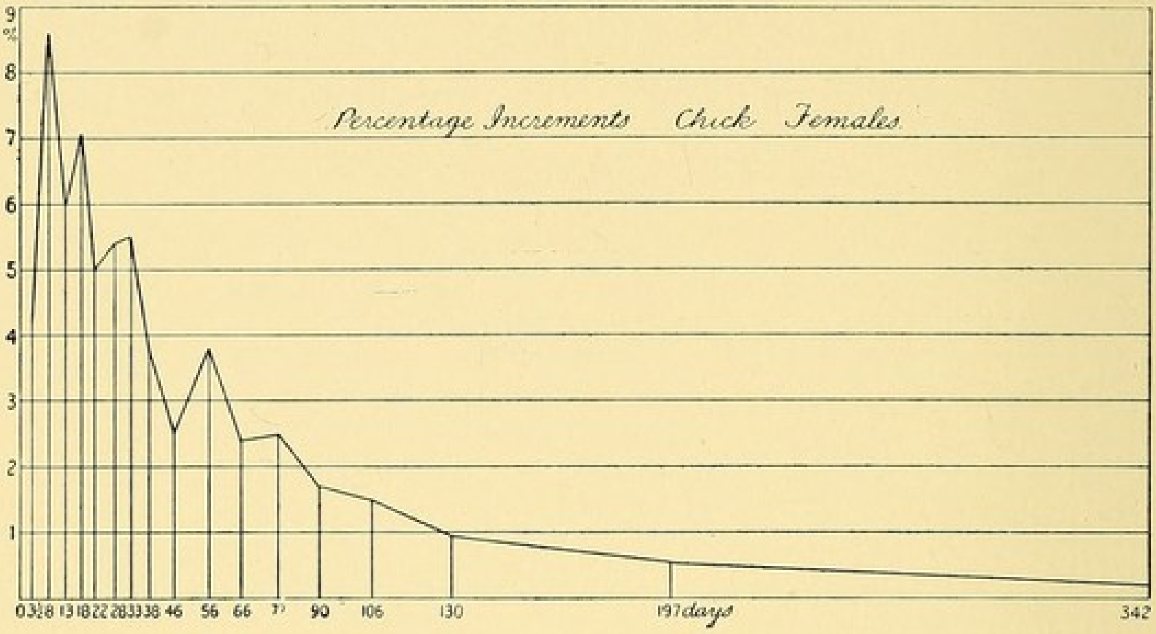

Fig 34. Curve Showing the Daily Percentage Increments in Weight by Female Chickens.

If it be true that the more rapid growth depends upon the youth of the individual, — its small distance in time from its procreation,—then we may perhaps, by turning to other animals which are born in a more immature state, get some further insight into these changes; and that I have attempted to do by my observations upon the development of rabbits.[1] Rabbits,

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[1] See Appendix No. I.

as you know, are born in an exceedingly immature state. They are blind, they are naked, they are almost incapable of definite movements, quite incapable of locomotion, and are hardly more than little imperfect creatures lying in the nest and dependent utterly upon the care of the mother, quite unable to do anything for themselves except take the milk which is their nourishment. They are indeed animals born in a much less advanced stage than are the guinea-pigs, which appear clothed with hair, having open eyes and sight, and able to run about, although rather wobbly the first day or two. Upon the screen we see this interesting result demonstrated to us, that a male rabbit, the fourth day after its birth, is able to add over seventeen per cent. to its weight in one day. From that the curve drops down, as you see, with amazing rapidity, so that here at an age of twenty-three days the rabbit is no longer able to add nearly eighteen per cent. daily, but only a little over six. At the end of two months from its birth, the growth power of the rabbit has dropped to less than two per cent., and at two months and a half it has dropped to one. The drop in two and a half months has been from nearly eighteen per cent. down to one per cent., and the rest of the loss of one per cent. is extended over the remaining growing period of the rabbit. Could we have a more definite and certain demonstration of the fact that the decline is most rapid in the young, most slow in the old? It is not in this case any more than in the others the one sex that

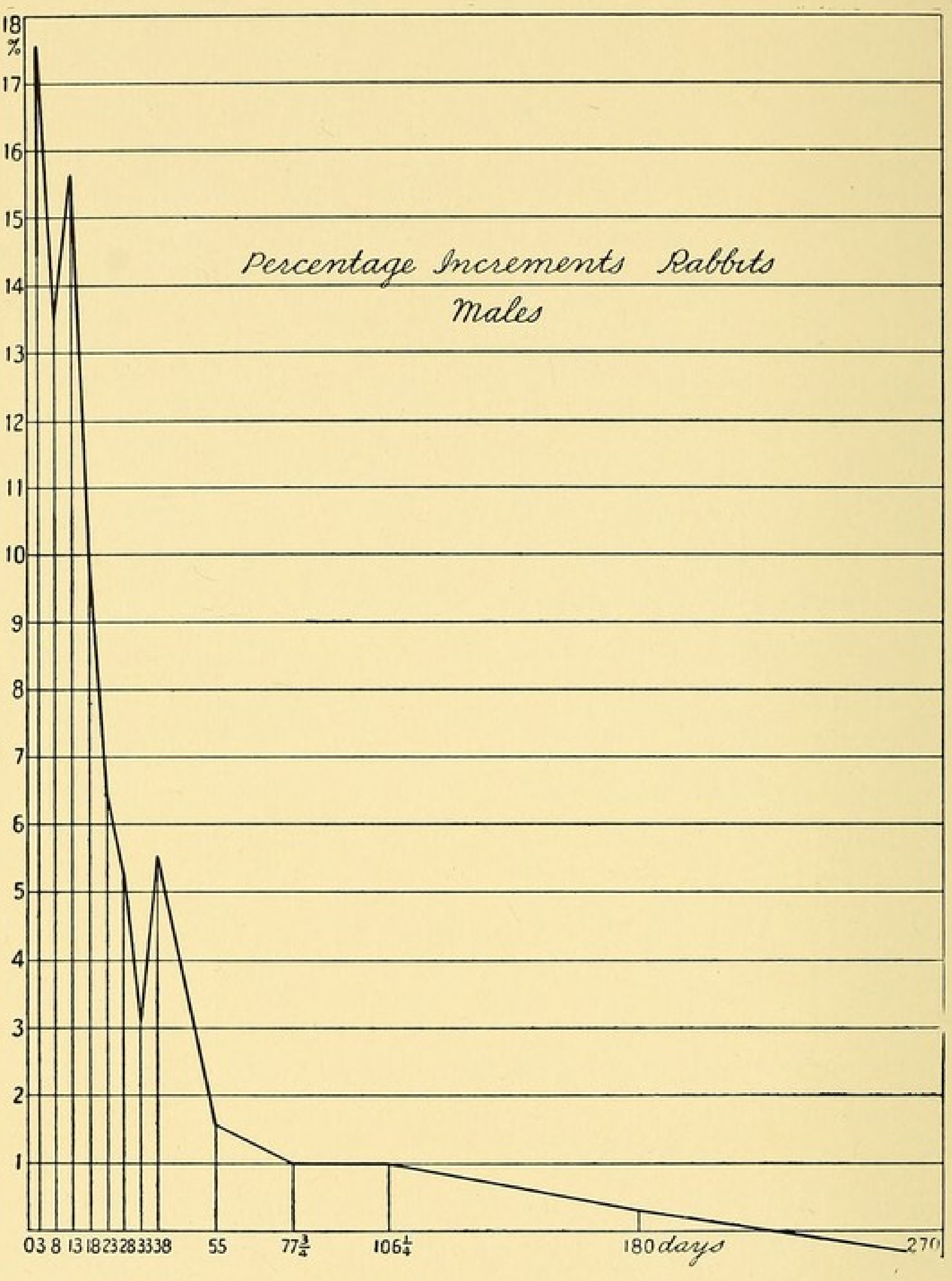

Fig. 35. Curve Showing the Daily Percentage Increments in Weight by Male Rabbits.

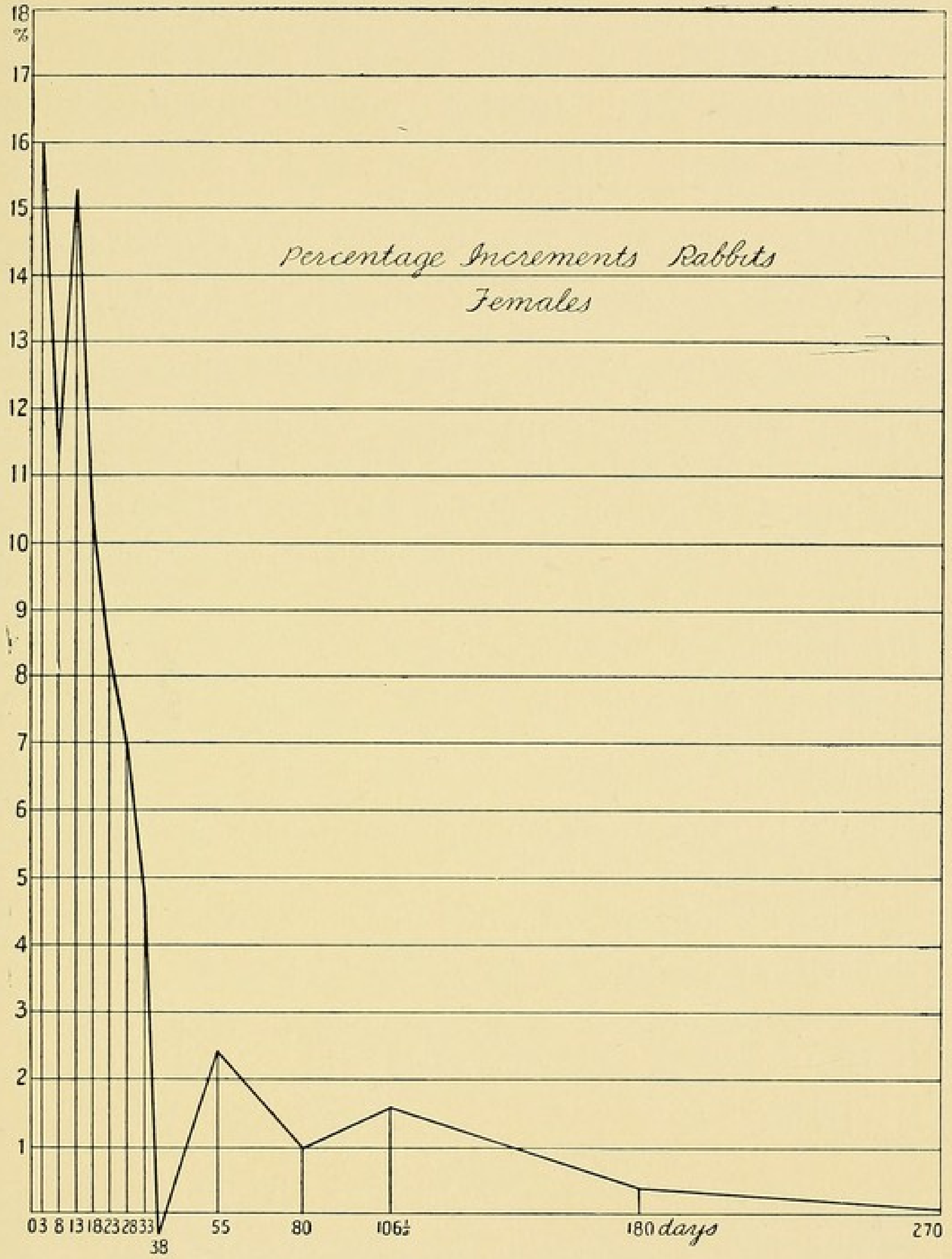

FIG. 36. CURVE SHOWING THE DAILY PERCENTAGE INCREMENTS IN WEIGHT BY FEMALE RABBITS.

demonstrates this fact, for in the female we find exactly the same phenomena, as the next slide will show. The irregularities are not significant. The strange dip at thirty-eight days, for instance, corresponds to an illness of some of the rabbits which were measured, but they rapidly recovered from it and grew up to be fine, nice rabbits. If instead of measuring half a dozen rabbits, we had measured two hundred or five hundred, these irregularities would certainly have disappeared. The females in the case of the rabbits, as in the case of the guinea-pigs, are not able to grow quite so fast at first. We see here sixteen instead of over seventeen per cent. as the initial value, but the general character of the drop is the same, enormously rapid at first and very slow afterwards. All of our cases, then, show the same fundamental phenomena appearing with different values.

Now in regard to man, we do not possess any such adequate series of statistics of growth as is desirable. We have many records of the weight of babies, by which I mean children from the date of birth up to one year of age. We have also very numerous records of school children, which will extend perhaps from five and one half up to say seventeen, eighteen, or even nineteen years. There are records of boys at universities, and a still more limited number of weighings of girls at colleges. But all these statistics piled together do not give us one comprehensive set of data including all ages. This is very much to be regretted, and it would be an important addition to our scientific knowledge could statistics of the growth of man be gathered with due precautions. It would fill one of the gaps in our knowledge which is lamentable. We have, however, some rough, imperfect data which for our present purposes it seems to me are adequate, and the results of the study of these will be shown by the next series of pictures.

But let us pause for a moment to consider this singular table. It shows in the second column the number of days required for each species of animal indicated at the left to double its weight after birth. A man takes 180 days to double his weight; a horse, 60; a cow, 47; a goat, 19; a pig, 18; a sheep, 10; a cat, 9½; a dog, 8; a rabbit, 6 (or possibly 7 days). Now here are analyses of the milk. The main point of interest is to be found in the figures in the third column, which represent the amount of albu-

TABLE I[1]

| Species. | Days Needed to Double Weight. | 100 Parts Mother's Milk Contain | | | |
|---|---|---|---|---|---|
| | | Proteid. | Ash. | Lime. | Phosphoric Acid. |
| Man | 180 | 1.6 | 0.2 | 0.0328 | 0.0473 |
| Horse | 60 | 2.0 | 0.4 | 0.124 | 0.131 |
| Cow | 47 | 3.5 | 0.7 | 0.160 | 0.197 |
| Goat | 19 | 4.3 | 0.8 | 0.210 | 0.322 |
| Pig | 18 | 5.9 | — | — | — |
| Sheep | 10 | 6.5 | 0.9 | 0.272 | 0.412 |
| Cat | 9½ | 7.0 | 1.0 | — | — |
| Dog | 8 | 7.3 | 1.3 | 0.453 | 0.493 |
| Rabbit | 7 | 10.4 | 2.4 | 0.8914 | 0.9967 |

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[1] After Abderhalden, *Zeitschrift für Physiologische Chemie*, Band XXVI., p. 497.

minoid, or proteid material contained in the milk. You will observe that for man the proportion is lowest, 1.6 per hundred parts; the horse has a little more—2; cattle—3.5; and so the values run. In other words, it is obvious that the less the proteid in the milk, the longer does the species require to double its weight. This looks at first sight as if there were a relation between the composition of the milk and the period of growth of the animal; but you know very well that if you take the milk of a cow, which is very much richer in proteid material, and feed it to a baby, a human baby, that baby does not grow at the same rate as the young cow, but grows at the human rate. It is obvious, therefore, that it is somewhat more complicated than a mere question of food supply. We have here in fact one of the beautiful illustrations of the teleological mechanism of the body. These various species have their characteristic rates of growth, and by an exquisite adaptation, the composition of the mother's milk has become such that it supplies the young of the species each with the proper quantum of proteid material which is needed for the rate of growth that the young offspring is capable of. It is a beautiful adjustment, but there is not a causal relation between the proteid matter of the mother's milk and the rate of growth of the young. It is an example of correlation, not of causation.

We pass now to the next of our slides (Fig. 37), which carries us to the study of our own species. It is not possible at the present time to represent in any form of curve, which I have seen, the daily percentages of increment for man covering the whole period of growth. In order to get the results together, I have confined myself here to the representation of the yearly percentages. Now from the age of zero to the age of one year, you see according to Table II., a child is able to increase its weight 200 per cent.; but from the end of the first to the end of the second year, only 20 per cent., and thereafter it fluctuates in the neighbourhood of 10 per cent. a year until the age of thirteen. At fourteen or fifteen there is a

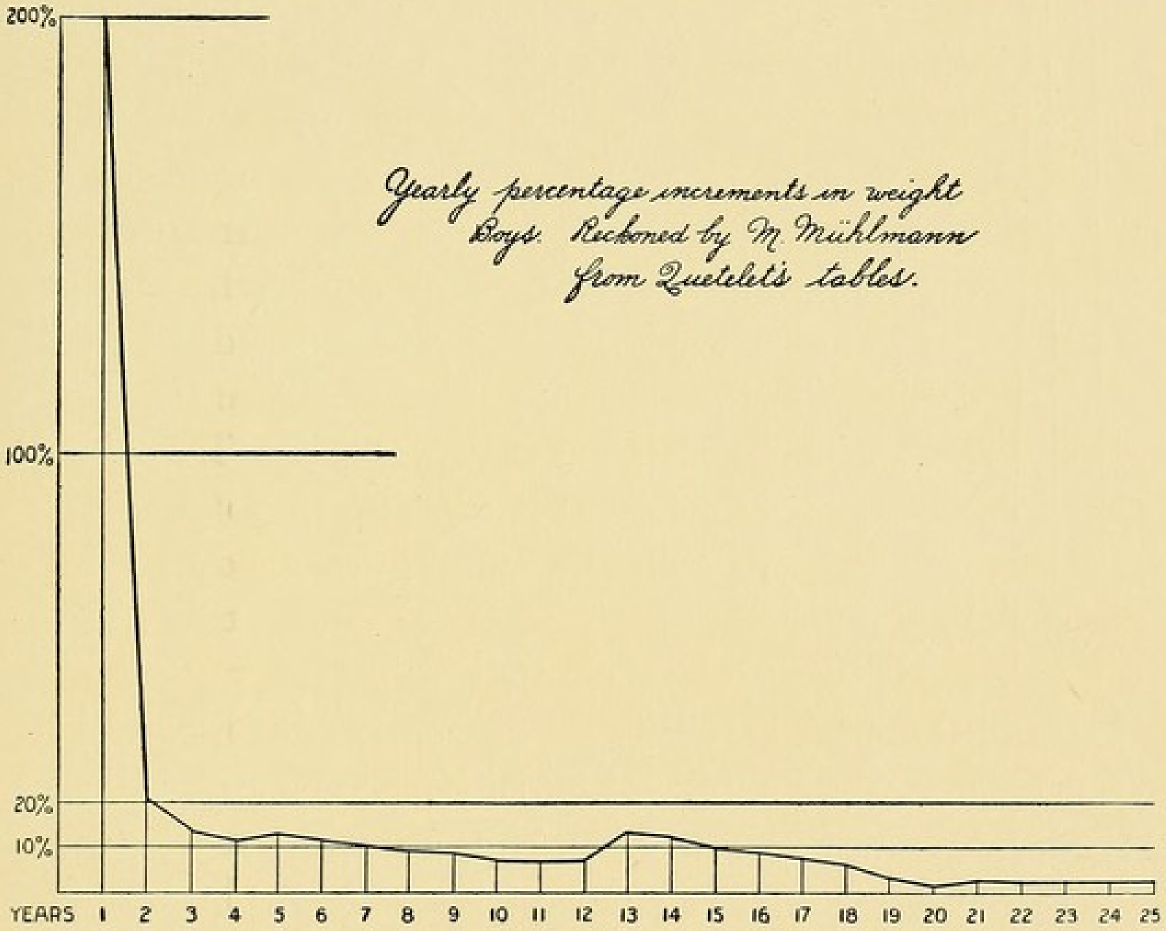

Fig. 37.

fluctuation, an increase, and then the decline goes on again, and slowly we see the growth power fading out.[1] Authors are not agreed as to the exact statistical value, and so I will ask to have thrown upon the screen another curve (Fig. 38), also representing the percentage increase of boys, and based chiefly upon

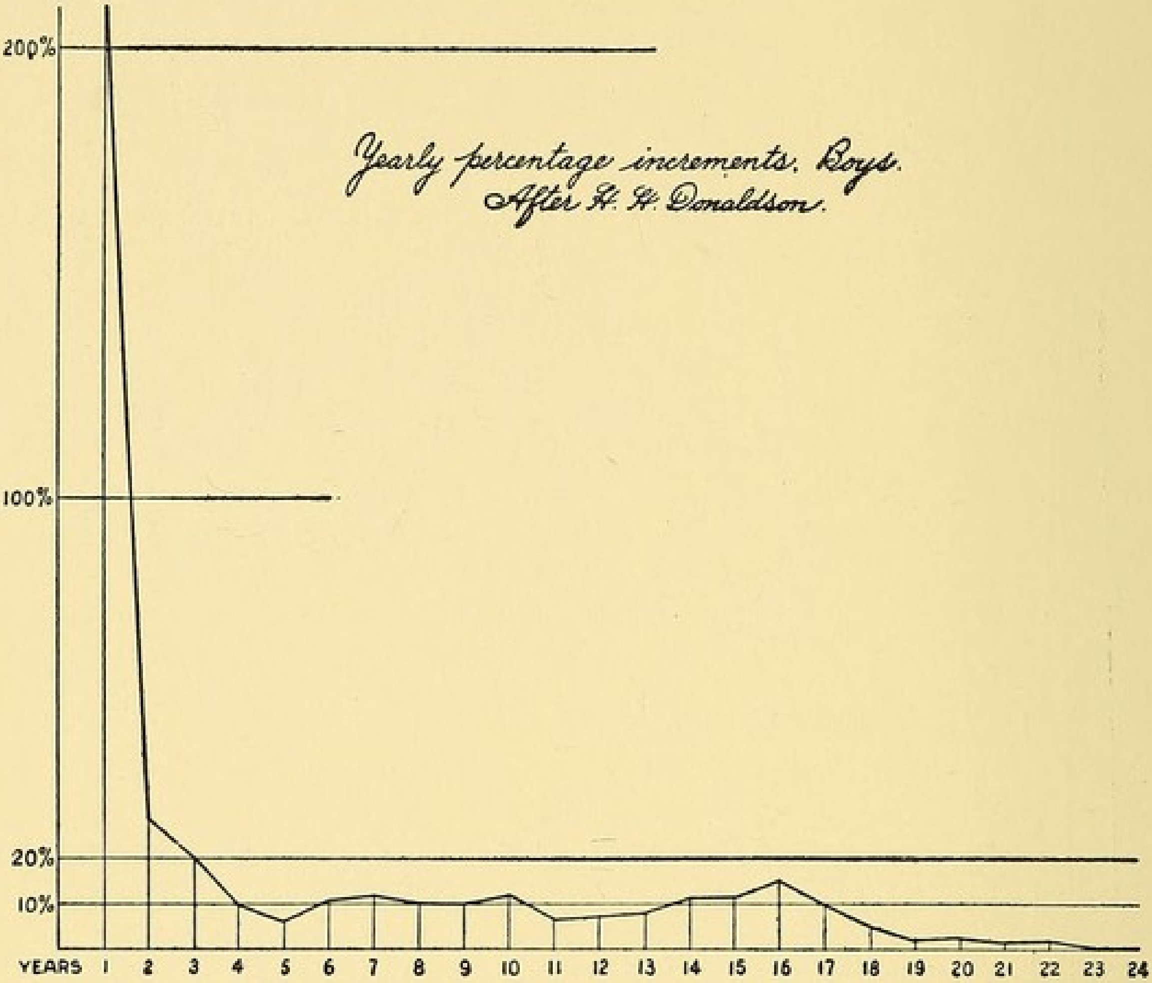

FIG. 38.

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[1] The curves credited to Mühlmann are taken from his very excellent memoir, *Ueber die Ursache des Alters*, 8vo, Wiesbaden (Bergmann), 1900; see specially p. 114. His tables are particularly available in this connection because he has adopted my method of calculating the rate of growth, but he does not present his results in graphic form.

English tables. For Tables II. and III., I am indebted to my friend Professor Donaldson, of the Wistar Institute in Philadelphia.[1] He finds in these

### TABLE II

### Growth of English Boys

(Compiled by H. H. Donaldson)

| Years. | Weight in Kilos. | | | | | | | | Yearly Percentage Increments. |
|---|---|---|---|---|---|---|---|---|---|
| 0 | 3.2 | | | | | | | | |
| 1 | 9.9 | — | 3.2 | = | 6.7 | ÷ | 3.2 | = | 209.0 % |
| 2 | 12.8 | — | 9.9 | = | 2.9 | ÷ | 9.9 | = | 29.0 % |
| 3 | 15.4 | — | 12.8 | = | 2.6 | ÷ | 12.8 | = | 20.0 % |
| 4 | 16.9 | — | 15.4 | = | 1.5 | ÷ | 15.4 | = | 9.7 % |
| 5 | 18.1 | — | 16.9 | = | 1.2 | ÷ | 16.9 | = | 5.9 % |
| 6 | 20.1 | — | 18 1 | = | 2.0 | ÷ | 18.1 | = | 11.0 % |
| 7 | 22.6 | — | 20.1 | = | 2.5 | ÷ | 20.1 | = | 12.0 % |
| 8 | 24.9 | — | 22.6 | = | 2.3 | ÷ | 22.6 | = | 10.0 % |
| 9 | 27.4 | — | 24.9 | = | 2.5 | ÷ | 24.9 | = | 10.0 % |
| 10 | 30.6 | — | 27.4 | = | 3.2 | ÷ | 27.4 | = | 11.6 % |
| 11 | 32.6 | — | 30.6 | = | 2.0 | ÷ | 30.6 | = | 6.5 % |
| 12 | 34.9 | — | 32.6 | = | 2.3 | ÷ | 32.6 | = | 7.1 % |
| 13 | 37.6 | — | 34.9 | = | 2.7 | ÷ | 34.9 | = | 7.9% |
| 14 | 41.7 | — | 37.6 | = | 4.1 | ÷ | 37.6 | = | 11.0 % |
| 15 | 46.6 | — | 41.7 | = | 4.9 | ÷ | 41.7 | = | 11.7 % |
| 16 | 53.9 | — | 46.6 | = | 7.3 | ÷ | 46.6 | = | 15.7 % |
| 17 | 59.3 | — | 53.9 | = | 5.4 | ÷ | 53.9 | = | 10.0 % |
| 18 | 62.2 | — | 59.3 | = | 2.9 | ÷ | 59.3 | = | 4.9 % |
| 19 | 63.4 | — | 62.2 | = | 1.2 | ÷ | 62.2 | = | 1.9 % |
| 20 | 64.9 | — | 63.4 | = | 1.5 | ÷ | 63.4 | = | 2.3 % |
| 21 | 65.7 | — | 64.9 | = | 0.8 | ÷ | 64.9 | = | 1.2 % |
| 22 | 67.0 | — | 65.7 | = | 1.3 | ÷ | 65.7 | = | 1.9 % |
| 23 | 67. | — | 67. | = | .0 | ÷ | 67.0 | = | .0 % |
| 24 | 67. | — | 67. | = | .0 | ÷ | 67.0 | = | .0 % |

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[1] Compare Donaldson, *The Growth of the Brain*, London, 1895, pp. 51 and 63. Professor Donaldson has had the kindness to revise his tables and allow me to use them. They are given in the text. The following extract from his letter of January 23, 1907, refers to the tables as herewith printed:

"I shall be very glad to let you make any use of tables or diagrams in *The Growth of the Brain*, and, to facilitate this, I enclose the calculations for the records an increment of a little more than 200 in the first year, but the drop comes during the second year

### TABLE III

### GROWTH OF ENGLISH GIRLS

(Compiled by H. H. Donaldson)

| Years. | Weight in Kilos. | | | | | | | | Yearly Percentage Increments. |
|---|---|---|---|---|---|---|---|---|---|
| 0 | 3.1 | | | | | | | | |
| 1 | 9.1 | — | 3.1 | = | 6.0 | ÷ | 3.1 | = | 193 % |
| 2 | 11.5 | — | 9.1 | = | 2.4 | ÷ | 9.1 | = | 26 % |
| 3 | 14.4 | — | 11.5 | = | 2.9 | ÷ | 11.5 | = | 25 % |
| 4 | 16.4 | — | 14.4 | = | 2.0 | ÷ | 14.4 | = | 14 % |
| 5 | 17.8 | — | 16.4 | = | 1.4 | ÷ | 16.4 | = | 8.5 % |
| 6 | 19.0 | — | 17.8 | = | 1.2 | ÷ | 17.8 | = | 6.7 % |
| 7 | 21.6 | — | 19.0 | = | 2.6 | ÷ | 19.0 | = | 13.7 % |
| 8 | 23.7 | — | 21.6 | = | 2.1 | ÷ | 21.6 | = | 9.7 % |
| 9 | 25.3 | — | 23.7 | = | 1.6 | ÷ | 23.7 | = | 6.9 % |
| 10 | 28.2 | — | 25.3 | = | 2.9 | ÷ | 25.3 | = | 11.4 % |
| 11 | 31.0 | — | 28.2 | = | 2.8 | ÷ | 28.2 | = | 9.9 % |
| 12 | 34.7 | — | 31.0 | = | 3.7 | ÷ | 31.0 | = | 11.9 % |
| 13 | 39.7 | — | 34.7 | = | 5.0 | ÷ | 34.7 | = | 14.4 % |
| 14 | 44.0 | — | 39.7 | = | 4.3 | ÷ | 39.7 | = | 10.8 % |
| 15 | 48.3 | — | 44.0 | = | 4.3 | ÷ | 44.0 | = | 9.8 % |
| 16 | 51.4 | — | 48.3 | = | 3.1 | ÷ | 48.3 | = | 6.4 % |
| 17 | 52.5 | — | 51.4 | = | 1.1 | ÷ | 51.4 | = | 2.1 % |
| 18 | 55.1 | — | 52.5 | = | 2.6 | ÷ | 52.5 | = | 4.9 % |
| 19 | 56.4 | — | 55.1 | = | 1.3 | ÷ | 55.1 | = | 2.3 % |
| 20 | *56.1 | — | 56.4 | = | .3 | ÷ | 56.4 | = | .5 %* |
| 21 | *55.5 | — | 56.1 | = | .6 | ÷ | 56.1 | = | 1.0 %* |
| 22 | 56.1 | — | 55.5 | = | .6 | ÷ | 55.5 | = | 1.0 % |
| 23 | 56.4 | — | 56.1 | = | .3 | ÷ | 56.1 | = | 0.5 % |

* Decrease.

and is startling in its enormous extent and is contrasted

---

percentages. These have been recently revised in the first part, in the following way. In place of the values given in Roberts' Tables, I have introduced, in the males, first year, where he leaves a blank, the following, 9.9 kilos, and in place of his entry for the second year, which figures 14.5 kilos, I have used the value 12.8. These two values, 9.9 and 12.8, are taken from Camerer. They are based on three cases in each instance (Camerer, W., '9[illegible], ' Untersuchungen with the later less decline. The phenomena may well arouse our attention and convince us that we are approaching a most important scientific question, the question of why the drop comes in this way. In the case of girls, as the next of our slides will show,

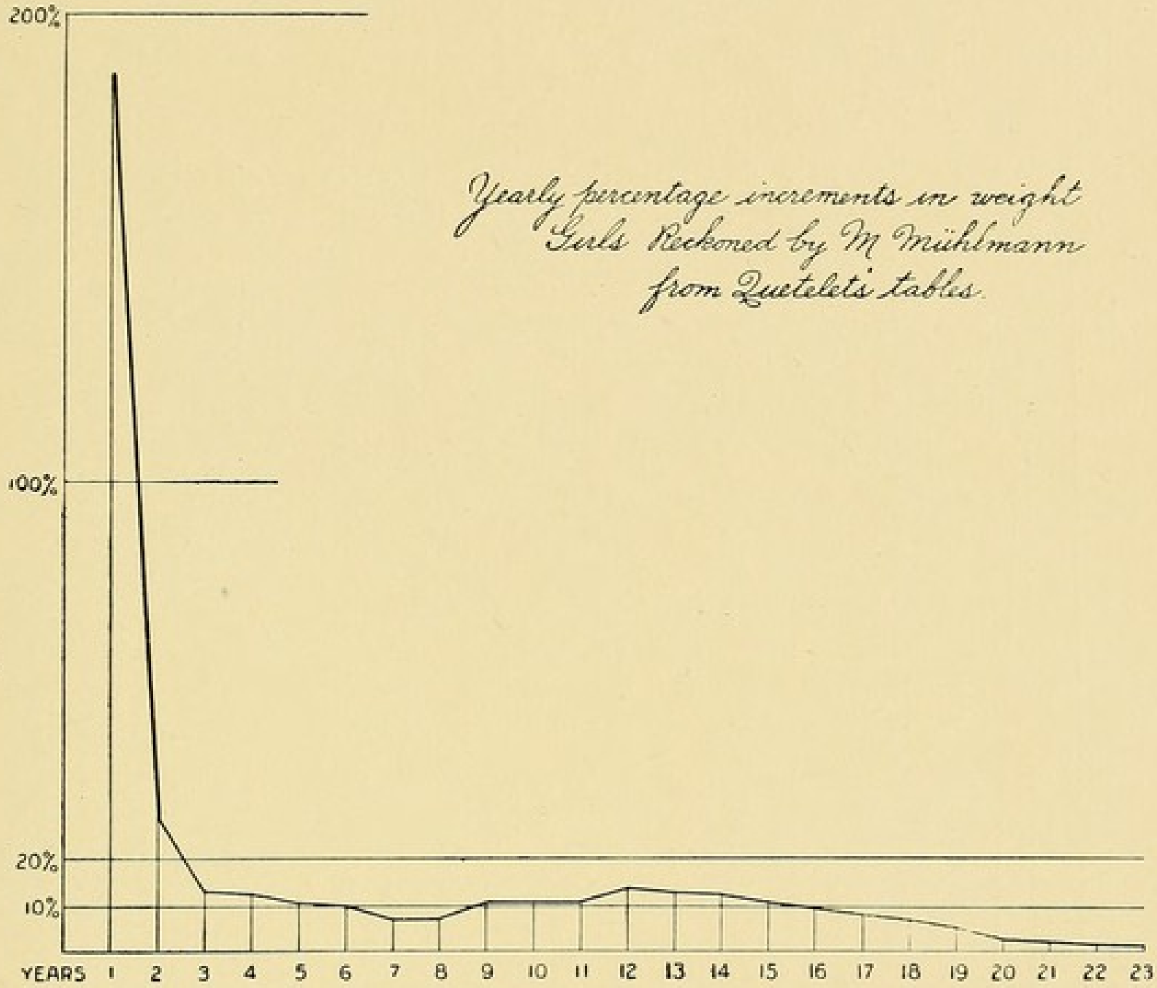

FIG. 39.

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ueber Massenwachsthum und Laengenwachsthum,' *Jahrbuch f. Kinderheilkunde*, Bd. XXXVI., pp. 249–293, 1893).

"These calculations represent weights without clothing, whereas my understanding of Roberts' Tables is that, with the exception of the weight at birth, his values represent weights with clothing; although I imagine the statement would not bear very careful investigation. I have not attempted in turn to correct Camerer's records by adding the amount due for clothing, which, however, could be done by the use of Bowditch's Tables."

we can prove the same phenomena with slightly different values. Girls, like the females of other species, grow a little less forcibly (Fig. 39) than boys. They do not quite attain a 200 per cent. value for the first year, but they too drop in a similar manner to the boys to about 30 per cent., and away down towards 10 per cent. in the third year. Then comes the long slow gradual decline up to the period of twenty-three. Professor Donaldson, as our next slide will demonstrate to us, has prepared curves (Fig. 40) from the English

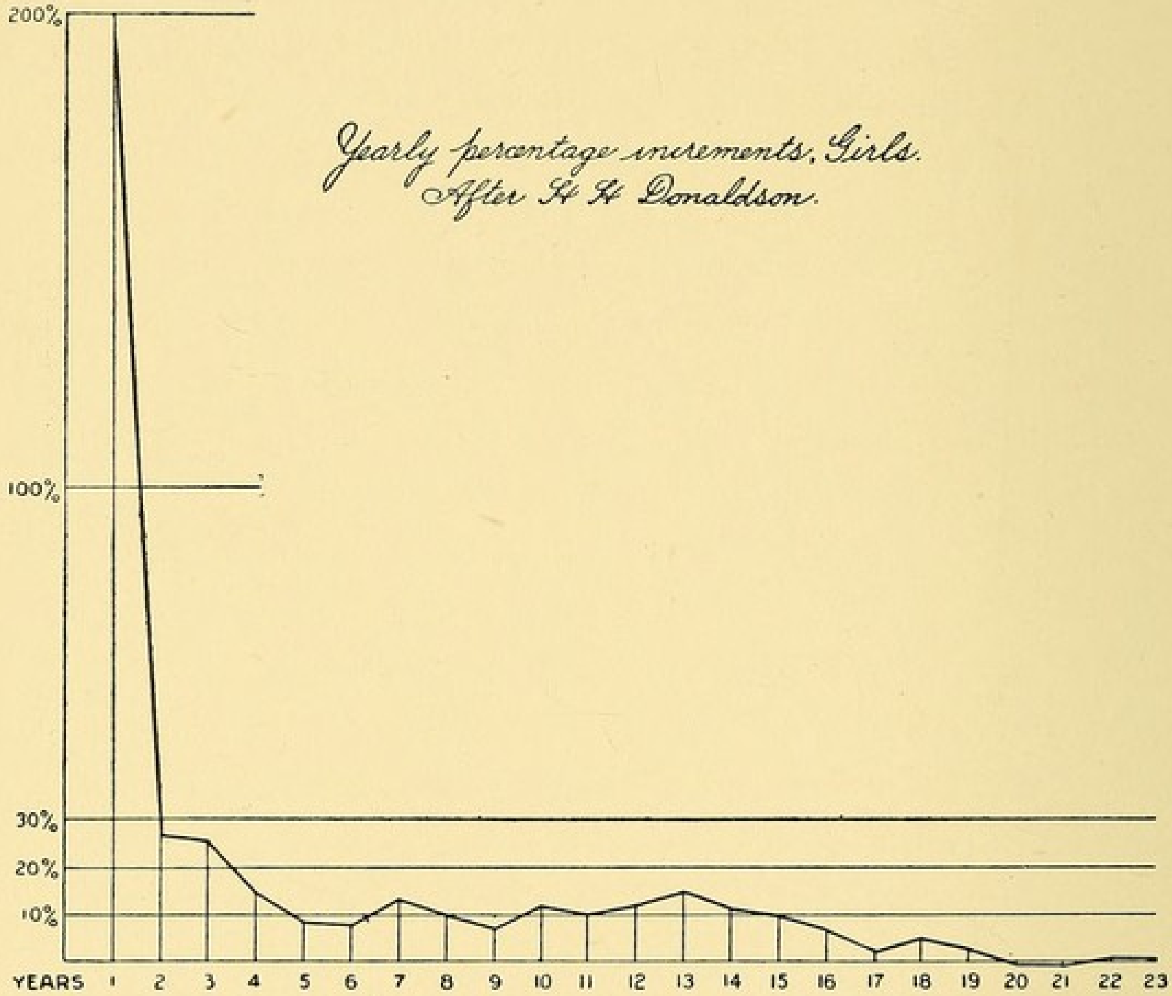

FIG. 40.

figures for girls also. They come up nearer to the 200 per cent. than in Mühlmann's table, but drop well below 30 per cent. in the second year, and down to 20 per cent. in the fourth. Then occurs the slight increase of growth in the period of twelve, thirteen, fourteen years, and next the final stage of decline. In the four cases the human rate curve is similar. The great fall takes place at the beginning, the slow fall towards the end. Professor Thoma[1] has thought he could get somewhat more accurate results by putting boys and girls together, and he has made a calculation, as shown now upon the screen, of a curve in which the two sexes are combined. His figures again differ somewhat from those we have considered, but you meet in this curve (Fig. 41) also the same general phenomena. There is an enormous percentage of growth during the first year; an enormous drop during the second; then the slow decline; the moderate fluctuation upward; and then the last slow disappearance of growth. In every instance, therefore, we have an absolute demonstration, it seems to me, of the strange phenomenon. Paradoxical it will sound, whenever it is first stated to any one, that the period of youth is the period of most rapid decline; that the period of old age is that in which decline is slowest.

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[1] R. Thoma, *Untersuchungen ueber die Grösse und das Gewicht der anatomischen Bestandtheile des menschlichen Körpers*, Leipzig, 8vo, 1882, Tabelle XXVIII., p. 149.

Professor Thoma gives only the usual data, the averages and first differences. From them I have calculated the percentage increments, in accordance with which the curve, Fig. 40, has been constructed. Thoma's table is based on Quetelet's measurements.

We shall learn in the next lecture that this double phenomenon furnishes us a clue to further investigations, and leads to certain new inquiries, which enable us to gain some further insight into the essential nature of the phenomena of age.

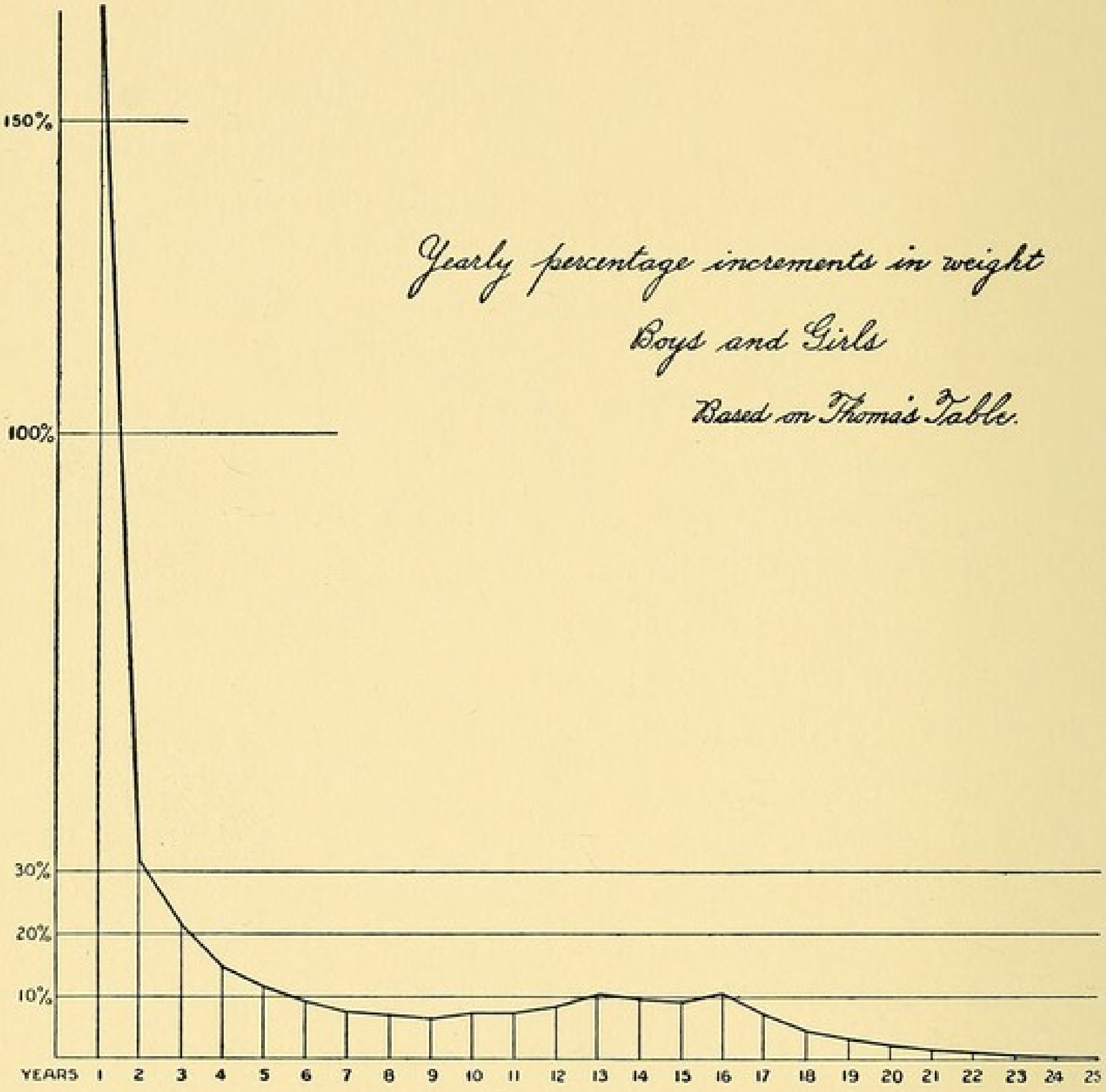

Fig. 41.

It can also be demonstrated that the decline in the growth power is proceeding during the first year of life. Taking the observations recorded by Bouchaud,[1] the following table has been calculated by Mühlmann (*l. c.*, p. 112). It is only necessary to look at the diminishing values in the third column to recognise the swift decline in the rate of growth.

TABLE IV

| Age in Months. | Weight in Grammes. | Monthly Percentage Increment. |
|---|---|---|
| 0 | 3250 | |
| 1 | 4000 | 23.0 |
| 2 | 4700 | 17.5 |
| 3 | 5350 | 14.0 |
| 4 | 5950 | 11.0 |
| 5 | 6500 | 9.2 |
| 6 | 7000 | 7.7 |
| 7 | 7450 | 6.4 |
| 8 | 7850 | 5.3 |
| 9 | 8200 | 4.4 |
| 10 | 8500 | 3.6 |
| 11 | 8750 | 3.0 |
| 12 | 9000 | 2.8 |

This completes the series of curves which I had prepared to present to you to show the rate of growth in animals from their birth only, but of course there has been also a growth of the animals which preceded their birth, and that now must briefly be considered.

The mere inspection of developing embryos of known ages gives us some idea of the rate of growth. With the aid of the lantern I will ask you to look with me at some pictures of the developing chick and developing rabbit. Let us begin with the chick (Fig. 42).[2]

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[1] Bouchaud, *De la mort par inanition et étude experimentale sur la nutrition chez le nouveau-né*, 1864.

[2] During the lectures a series of lantern slides were projected upon the screen, made from photographs of mounted specimens of chicken embryos,

We have first an embryo of twenty hours of incubation, No. 1; following it one of one day, No. 2. You can observe just a little line of structure indicated and showing where the longitudinal axis is to be situated. By the second day, No. 3, the chick has distinctly a head and a little heart, and those who are expert can differentiate with a microscope the axis of the body, the beginning of the formation of the intestine and of the muscles. At the end of the first day there was little more than a mere gathering of cells, but during the twenty-four hours of the second day the gathering has changed from a mere streak upon the surface of the yolk to a well-formed individual, with

which showed very clearly the progress of development in the chick during the very early stages. The first figure illustrated a chick of eighteen hours' incubation. The embryo had been skimmed off from the surface of the egg, hardened, coloured artificially, and mounted in the manner of the ordinary microscopical preparation in Canada balsam. At this age the naked eye can just distinguish a line, which indicates the position of the axis of the embryo. The unaided eye can recognise nothing more. In the second picture the head and neck of the embryo were easily distinguishable, and a few of the earliest primitive segments. The third slide showed a stage of a day and a half. The spinal cord and brain were distinctly differentiated, and numerous so-called "blood islands" scattered about. The final slide of the series showed a chick of three and one half days. It has not seemed necessary to reproduce these figures with the present text, as they merely duplicate, on a larger scale and with more detail, the pictures which have been included.

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Explanation of Fig. 42.

Ten Stages of the Developing Chick, after Franz Keibel's *Normentafeln*. All the figures are magnified four diameters. In No. 1 only the parts indicated in the vertical axis of the figure correspond to embryonic structures proper.

| | | | | | |
|---|---|---|---|---|---|
| No. 1. | Incubated | 20 hrs. | No. 6. | Incubated | 3 days, 16 hrs. |
| No. 2. | " | 24 hrs. | No. 7. | " | 4 days, 8 hrs. |
| No. 3. | " | 2 days. | No. 8. | " | 5 days, 1 hr. |
| No. 4. | " | 2 days, 19 hrs. | No. 9. | " | 7 days, 4 hrs. |
| No. 5. | " | 2 days, 22 hrs. | No. 10. | " | 8 days, 1 hr. |

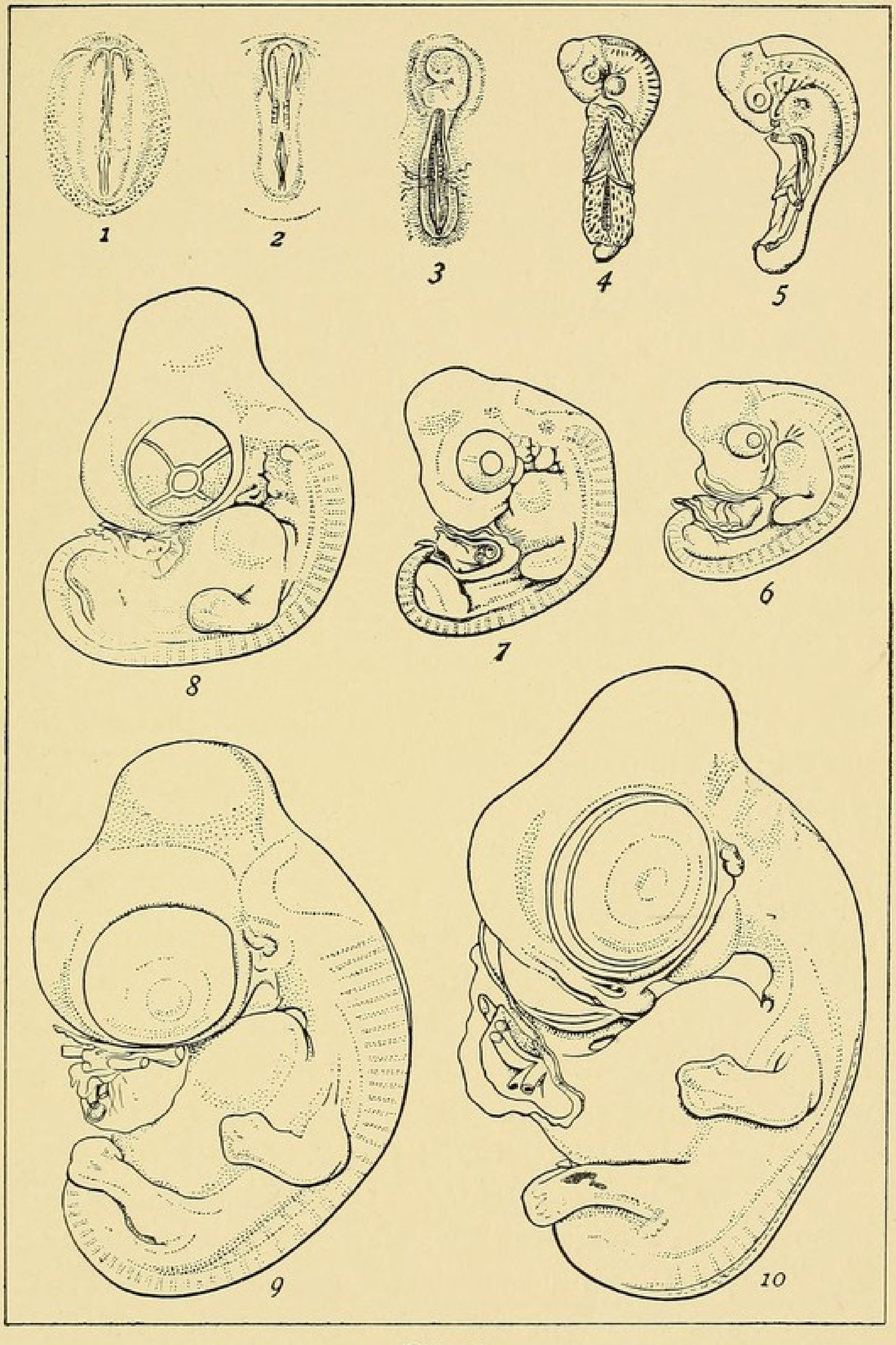

Fig. 42.

recognisable parts and several times the volume it had when one day old. The next figures, Nos. 4 and 5, illustrate the alteration which occurs during, approximately, the third day. It is obvious that the embryo has again made an enormous increase in volume. The eye has developed, the heart has become large, the tail is projecting, the dorsal curve of the future neck is distinguishable. We pass next to the fourth day, No. 6. Is it not a strange looking beast, with its wing here and leg there, a little tail at this point; an enormous eye, almost monstrous in proportion; and, finally, here a great bulge caused by the middle division of the brain. After five days, Nos. 7 and 8, we have a chick the brain of which is swelling, causing the head to be of so queer a shape that, with the eye which seems out of all proportion to the rest of the body, it imparts an uncanny look to the embryo. The wing is shaping itself somewhat, and the ends of the leg, we can see, will, by expansion, form a foot. Finally, the chick after seven, No. 9, and after eight days, No. 10, is figured. In the short interval of only six days the chick grows from the size represented by No. 2 to that shown in the last figure upon the plate. It is an enormous increase. Suppose a chick after it was born were to grow at such a rate as that! The eight-day embryo is perhaps thirty or forty times as big as it was six days before. It would seem marvellous to us if a chick after it was hatched should become in six days thirty times as large and heavy as when it first came out from the egg. It is perhaps advisable to let you follow the growth of the chick a little farther, and accordingly I present another picture (Fig. 43), which shows an embryo of about ten days. The little marks upon the surface of these embryos

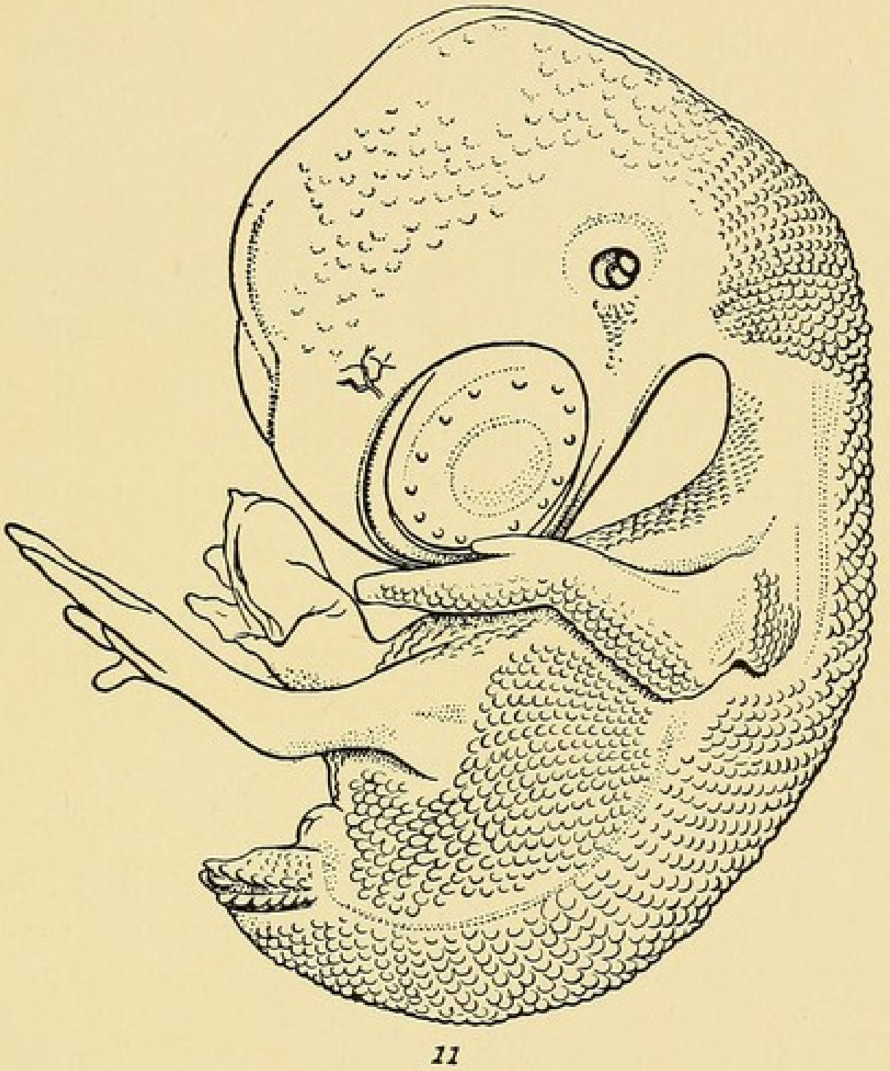

Fig. 43. A Chick Removed from an Egg which had been Incubated 10 Days and 2 Hours. Magnified four diameters. After Keibel.

indicate the commencing formation of the feathers. A comparison of the series of figures proves that the development is taking place with marvellous speed. We need only to look at these stages, comparing them with one another, to realise that the progress of the embryo in size and development proceeds with a rapidity which is never to be found in later stages.

The history of embryonic rabbits declares with equal emphasis that the earliest development is extremely rapid. I wish now to show you a series of pictures to illustrate in the same manner the progressive development of the rabbit. Numbers one to five of the figures upon the screen represent what is known as the germinal area, in the centre of which the actual embryo is gradually formed. In No. 1 merely the axis is indicated, in front of and alongside of which the parts of the embryo are to arise, as is suggested by Nos. 2, 3, 4, 5. These stages cover the seventh and eighth days. Nos. 6 to 14 figure actual embryos, No. 6 of nine and a half, No. 14 of fifteen days. No. 6 is singularly twisted into a spiral form, the reason for which is still undiscovered. No. 9 shows the condition at eleven days—notice the limbs, a leg in front and a leg behind, each only a small mound as yet upon the surface of the body; the dis-

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Explanation of Fig. 44.

Fourteen Stages of the Developing Rabbit, after Minot's and Taylor's "Normal Plates." All the figures are magnified four diameters. Nos. 2 to 5 are irregular as to age, but show successive stages of development. The early development is extremely variable and the observations do not yet suffice to determine the average typical condition for each day under nine.

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| No. 1. | Embryo of | 7½ | days. | No. 8. | Embryo of | 10½ | days. |
| No. 2. | " | 8¼ | " | No. 9. | " | 11 | " |
| No. 3. | " | 8¼ | " | No. 10. | " | 11½ | " |
| No. 4. | " | 8 | " | No. 11. | " | 12½ | " |
| No. 5. | " | 8½ | " | No. 12. | " | 13 | " |
| No. 6. | " | 9½ | " | No. 13. | " | 14 | " |
| No. 7. | " | 10 | " | No. 14. | " | 15 | " |

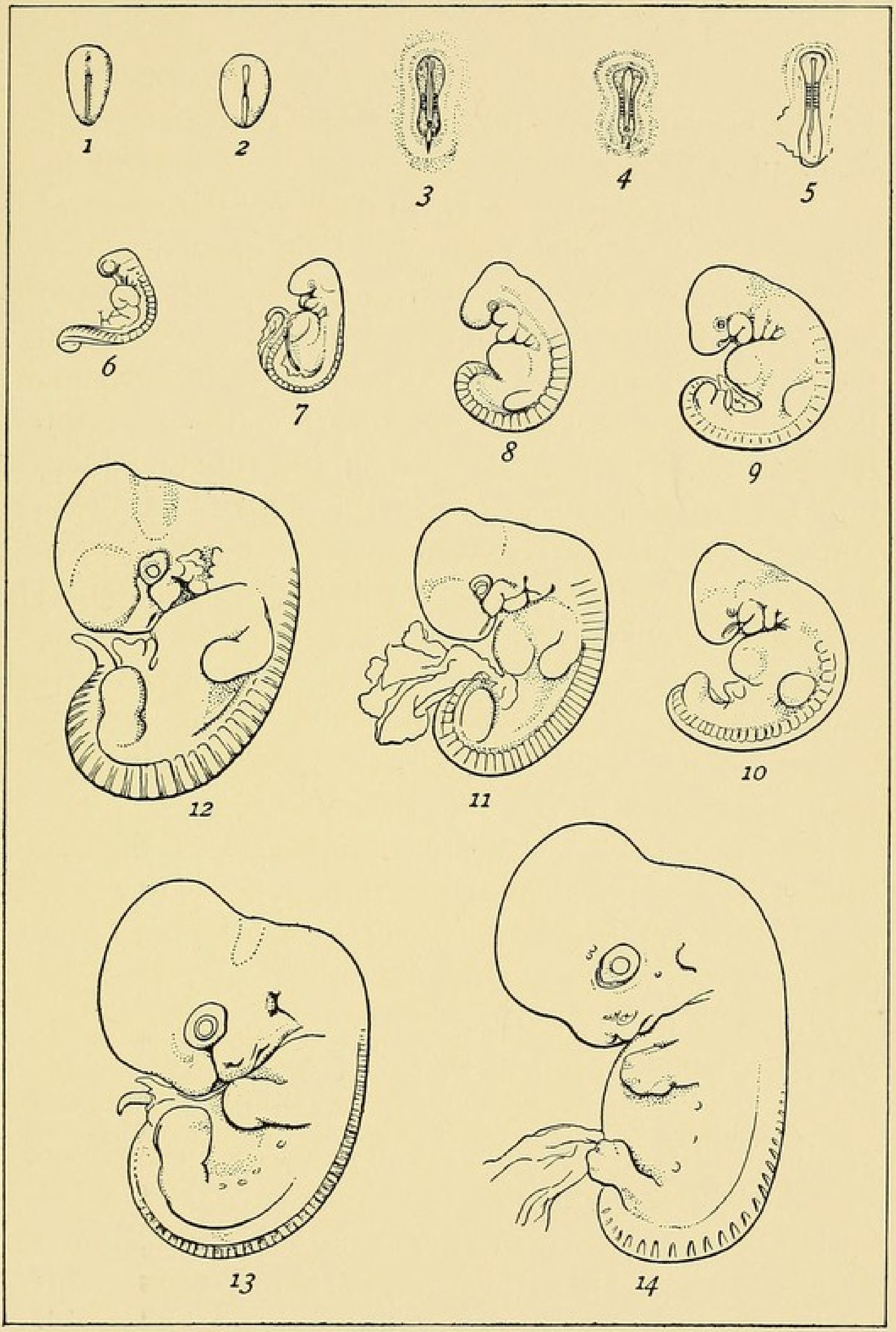

Fig. 44.

tinct eye, the protuberance caused by the heart. Nos. 11 and 12 show the embryonic shape at twelve and a half and at thirteen days—there has been a great increase of size with accompanying modifications of form. The next pair, Nos. 13 and 14, present us embryos of fourteen and fifteen days, respectively, and you see that the growth is very marked indeed, and the change of form obvious ; the creature is now passing from the embryonic type into something resembling a rabbit. Other pictures could readily be added, but, though two weeks must still elapse before the animal will be ready to enter the world, it is not necessary for my present purpose to include this period in our survey. We need only contemplate, it seems to me, the series of drawings in Fig. 44 to realise that the early embryonic growth of the rabbit, like the embryonic growth of the chick, proceeds with a speed which is never paralleled by the growth during later stages.

Now I had a considerable number of rabbit embryos preserved in alcohol, and though it was not very accurate to weigh them as alcoholic specimens, in order to determine their true weight, yet I resolved to do so as it was the best means at my disposal at the time. The result of that weighing was very interesting to me, becaused it showed that in the period of nine to fifteen days the rabbits had, on an average, added 704 per cent. to their weight daily ; but in the period of from fifteen to twenty days, the addition is very much less than this, only 212 per cent. But these rabbits at ten days have already had a considerable period of development behind them, and as we have discovered that the younger the animal the more rapid its growth, we are safe, it seems to me—since we have learned that from the tenth to the fifteenth day there is a daily increase of over 700 per cent.—in assuming that in yet younger rabbits an increase of 1000 per cent. per day actually occurs. That is not so extraordinary an assumption, for bacteria are known to divide every half-hour, and if the little bacterium divides and grows up to full size in half an hour, and then divides again, it means that within a half-hour one bacterium has become two, and has increased, obviously, 100 per cent.; and if those two again divide as before, we should have four bacteria at the end of an hour—an increase of 400 per cent., and at the end of another half-hour, of 800 per cent., and so on ever in geometrical progression. We learn, then, that bacteria may in a few hours add 1000 per cent. to their original weight, and it is not by any means an exorbitant demand upon our credulity to accept the conclusion that, in their early stages, rabbits and other mammals and birds are capable of growing at least 1000 per cent. a day. If this be true, and it doubtless is true, we can adopt it as a convenient basis for comparison. As we learned from the rate curves, which were projected upon the screen earlier during the hour, the male rabbit gains in one day shortly after birth nearly eighteen per cent.—seventeen and four tenths per cent.—and the female rabbit gains nearly seventeen per cent. Now we can estimate the loss very simply by deducting this rate, which is the capacity of the animal to grow persisting at birth, from its original capacity, which we assume to have been 1000 per cent. per day. And if we do that the result is obvious. Over 98 per cent. of the original growth power of the rabbit or of the chick has been lost at the time of birth or hatching, respectively, and the same thing is equally true of man. We start out at birth certainly with less than two per cent. of the original growth power with which we were endowed. Over 98 per cent. of the loss is accomplished before birth—less than two per cent. after birth. That, I think, is a rather unexpected conclusion, certainly not one which, until I began to study the subject more carefully, I in the least expected; and even now when I have become more familiar with it, it still fills me with astonishment, it is so different from the conception of the process of development as we commonly hold it, so different from our conclusions based on our acquaintance with the growth and progress of the individuals about us. We overlook the fact that the progress which each individual makes is the result of accumulation. It is as if money were put into the savings-bank; it grows and becomes larger, but the rate of interest does not alter. So too with us; we see there is an accumulation of this wealth of organisation which gives us our mature power. But as that accumulation goes on, our body seems to become, as it were, tired. We may compare it to a man building a wall. He begins at first with great energy, full of vigour ; the wall goes up rapidly ; and as the labour continues fatigue comes into play. Moreover, the wall grows higher, and it takes more effort and time to carry the material up to its top, and to continue to raise its height, and so, as the wall grows higher and higher, it grows more slowly and ever more slowly, because the obstacles to be overcome have increased with the very height of the wall itself. So it seems with the increase of the organism ; with the increase of our development, the obstacles to our growth increase. How that is I shall hope to explain to you a little more clearly in the next lecture.

We have one more slide, which I would like to show you. It indicates the rate of growth in

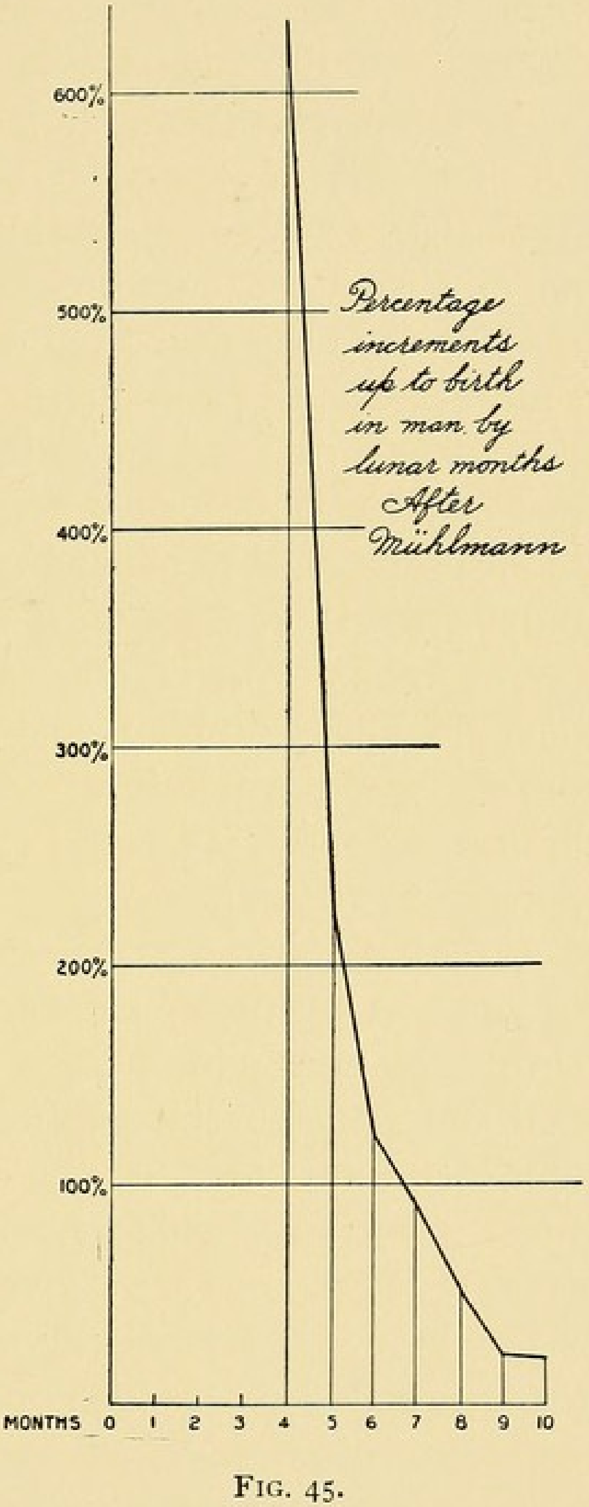

FIG. 45.

man before birth as far as it can be determined without better knowledge than I have at command. The time intervals in the diagram correspond to the so-called lunar months—the ten lunar months of prenatal life. Of our early development we know very little so far as statistics are concerned, but from the third month onward we have some records. It is found that from the third to the fourth month the increase is 600 per cent. Just contrast that with 200 per cent. added in one year after birth ; 600 per cent. in one month against 200 per cent. in one year. From the fourth to the fifth month it is scarcely over 200 per cent. It then becomes only a little more than 100. In the seventh month, less than 100 ; and finally in the ninth and tenth months, it becomes very small indeed, less than 20, so that during the prenatal life of man, as we have seen in the prenatal life of the rabbit and of the chick the decline in the power of growth is going on steadily all the time.

I shall use the few remaining moments to report to you yet another bit of evidence of the originally enormous power of growth. It has been estimated that the germ of the mammal, with which the development commences, has a weight of 0.6 milligram ; another estimate which I have found is of 0.3 milligram.[1] Perhaps I can give you some idea of what this value means by telling you that if the weight of the original germ of a mammal is assumed to be 0.6

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[1] These estimates refer to the placental mammals only. My authorities are M. Mühlmann, *Ueber die Ursache des Todes*, 1900, p. 45, and Donaldson, *Growth of the Brain*, 1895, p. 60.

milligram, we could, according to the laws of the United States, send 50,000 such germs by letter postage for two cents. It would take 50,000 germs to make the weight of one letter. That perhaps will give you some impression of the extreme minuteness of the primitive germ. In the human species at the end of even a single month it is no longer merely a germ, but a young human being, very immature, of course, in its development, but already very much larger. I doubt—even after all that I have said this evening about the startling figures of growth for the earlier stages—I doubt if you are prepared for the fact that the growth of the germ up to the time of birth represents an increase of over five million per cent. How much over five million per cent. we cannot calculate accurately, because we do not know accurately the weight of the original germ, but an increase of five million per cent. is not above the true value.[1] Contrast that with anything which occurs in the later periods. What a vast change has happened! What an immense loss has taken place! The rate of this loss is evidently diminishing. The loss occurs with great rapidity in the young—less rapidly the older we become.

Professor Richard Hertwig of Munich[2] has reached a similar result by a different method of calculation. He estimates the volume of the human fertilised

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[1] Assuming the germ to weigh 0.0006 gramme, and the child at birth 3200 grammes, the percentage increment would be 5,400,000.

[2] R. Hertwig, "Ueber die Ursache des Todes," reprinted from *Allgemeine Zeitung*, Dec. 12, 13, 1906 (*Beilage*).

ovum at 0.004 cubic millimetre and of the child at birth at 3 to 4,000,000 cubic millimetres, a billion times increase. Assuming the weight of a man of twenty years at 130 pounds, the increase after birth would be as 1:16. He thereupon emphasises the enormous diminution of cell production which must be assumed. It is a pleasure to have my own views confirmed by so distinguished a colleague.

I attempted to convince you in the first and second lectures that that which we called the condition of old age, is merely the culmination of changes which have been going on from the first stage of the germ up to the adult, the old man or woman. All through life these changes continue. The result is senility. But if, as the phenomena of growth indicate to us so clearly, it be true that the decline is most rapid at first, then we must expect from the study of the very young stages to find a more favourable occasion for analysis of the factors which bring about the loss in the power of growth and of change as the final result of which we encounter the senile organism. Not from the study of the old, therefore, but from the study of the very young, of the young embryo, and of the germ, are we to expect insight into the complicated questions which we have begun to consider together. I shall hope in the next lecture to prove to you that the supposition which has guided my own observations is correct, and to be able to show you that we do actually, from the study of the developing embryo, glean some revelations of the cause of old age.

# IV

## DIFFERENTIATION AND REJUVENATION

*LADIES AND GENTLEMEN:* In order to present the subject of this evening, I will take a few brief moments at the beginning to review the results reached in the previous lecture. I spoke then of the phenomena of growth and endeavoured to make clear to you what I consider the fundamental conception of this study—that the decline in the growth power is extremely rapid at first and slow afterwards. This change in the rate of growth is of course due to things in the animal body itself. It is a logical conclusion for us to draw that if we are to study out the cause of the loss of growth power, we should do it rather at that period of development when the change in the rate of growth is most rapid, for then we should expect those modifications to exhibit themselves most clearly because the magnitude of cause is likely to be proportionate to the magnitude of result, or, in other words, when the decline is most rapid, then we must expect to find the alterations which cause that decline in the organism to show themselves most conspicuously. You will remember, further, that we spoke of growing old as being a much more complicated question than one of growth alone, and that there occur, as the years advance, changes in the structure of the body. It is convenient to use one collective term for all these phenomena of becoming old, and that term, established by long usage, is *senescence*, the becoming old. What, therefore, we have to search for at present is a cause, a proximate cause at least, of senescence. In order to make the view I am to bring forward this evening quite clear to you, I must first of all take advantage of your kindness and recapitulate briefly what I said in regard to cells, for you will remember that the cell is the foundation and unit of organic structure. With your permission I should like to recall more exactly to your minds what I said of the cells by having thrown upon the screen the slide which we saw before and which we used as an illustration of the cell. Here is the picture. Above we see the typical cell (No. 1) from the oral epithelium of the salamander, and you remember in the centre this more conspicuous body with a granular and reticulated structure which we called the nucleus, and surrounding it is this mass which we called the body of the cell, or the protoplasm. Here (No. 2) is another condition of a cell of the skin of the salamander in which the nucleus presents a slightly different appearance. Here also we have quite a body of protoplasm about the nucleus. Every cell consists of these two essential and fundamental parts, the nucleus and the protoplasm. Now the conclusion to which I shall gradually bring you by the facts to be laid before you

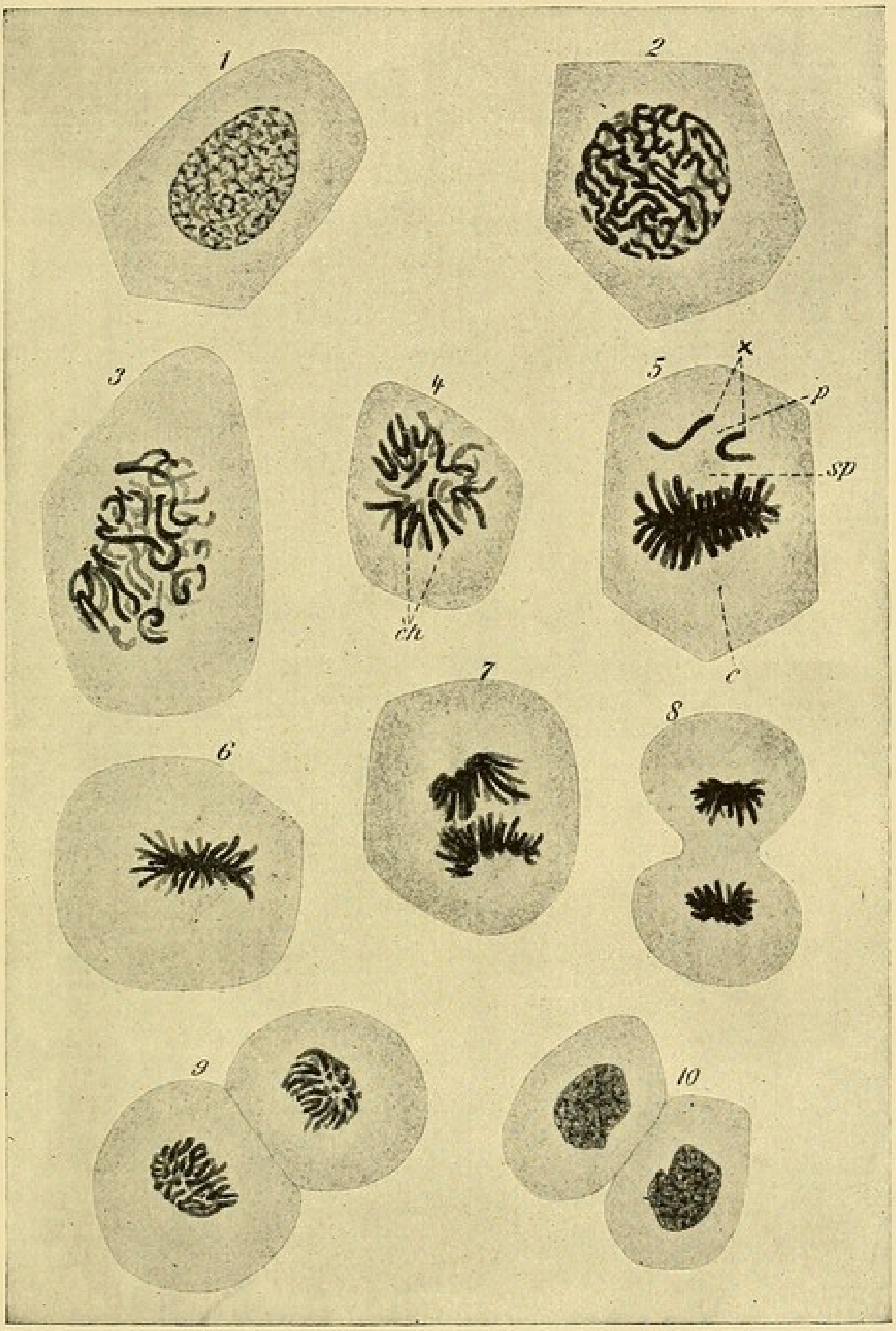

FIG. 46. CELLS FROM THE MOUTH (ORAL EPITHELIUM) OF THE SALAMANDER.—After Sobotta. 1, recticulate stage ; 2, skein stage ; 3, 4, formation of the chromosomes ; 5, 6, formation of the equatorial plate ; 7, 8, division and migration of the chromosomes ; 9, reconstitution of the two daughter nuclei ; 10, completed division into two cells.

this evening is that the increase of the protoplasm, together with its differentiation, is to be regarded as the explanation (or should we say cause) of senescence. Though protoplasm is the physical basis of life, though it is the actual living substance of the body, its undue increase beyond the growth of the nucleus changes the proportions of the two, and that change of proportion causes an alteration in the conditions of the living cell itself, and that alteration I interpret, as I shall explain more accurately later, as the cause of senescence, as the fundamental cause of old age. This slide (Fig. 46) also shows to us the early development of the cells through those phases which result in the multiplication of them. The nucleus changes in appearance and becomes a very different looking structure. These changes I need not now go through again. Suffice it to say that after the complicated alterations have completed their cycle, we get in the place of a single cell, two, and each has its own nucleus, and each its own protoplasm. Notice here that the two cells (No. 10) which finally result are smaller than the original cells from which they sprang. These are by no means imaginary pictures, but accurate microscopic drawings from real cells of the salamander. The two cells which are thus produced from one parent cell are characterised by their smaller size, and this smaller size applies not only to the cell as a whole, but likewise to its nucleus. After having been thus reduced in size, the nuclei and the cells will both expand, and soon the daughter cells will return to the mother dimension and be as large as the parent cell from the division of which they arose. There is thus, we learn, the constant fluctuation in the size of cells, a fluctuation in their dimensions accompanying the process of cell division. Presently we shall have more to say in regard to this matter of the change in the cell in size. The next picture (Fig. 47) which I want to recall to you is one which we also had in an earlier lecture. It represents three slices through a very young rabbit before any of the organs of the animal have begun to develop. We can see here clearly the nuclei, as I pointed out to you before, nearly uniform in structure, and you notice that the protoplasm around each nucleus is quite small in amount. If you will recall the previous picture (Fig. 46) of the skin of the salamander, upon the screen a moment ago, you will realise immediately, in comparing the two, that in these young cells the proportion of the protoplasm to the nucleus is very small. That is again one of the fundamental facts to which we shall recur in a moment. I wanted to show you this picture in order to revive in your minds the conception which I endeavoured to give you before of the undifferentiated tissue, where the cells have nuclei pretty uniform in appearance and in size, each with its little mass of protoplasm about it, and this protoplasm appearing in all the cells under microscopic examination very much the same. We cannot in this stage of development say of a given cell that it displays structure by which, if we saw the cell isolated under the microscope, we could determine from what part of the young embryonic body it was derived. When we see a cell

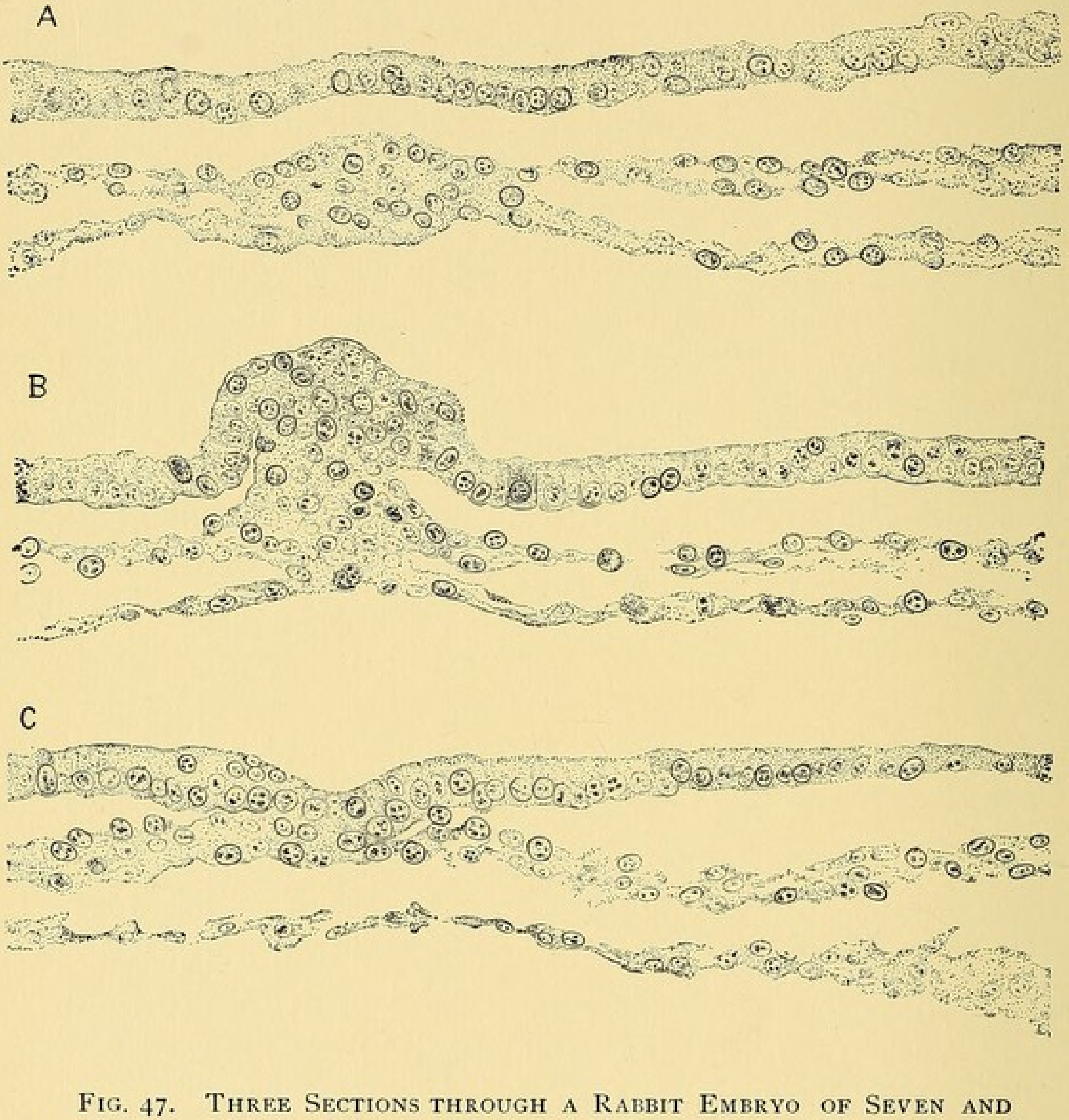

FIG. 47. THREE SECTIONS THROUGH A RABBIT EMBRYO OF SEVEN AND ONE HALF DAYS. For explanation, see Fig. 9, of which this is a repetition.

from the adult we can determine its origin in most cases with certainty by its microscopic appearance

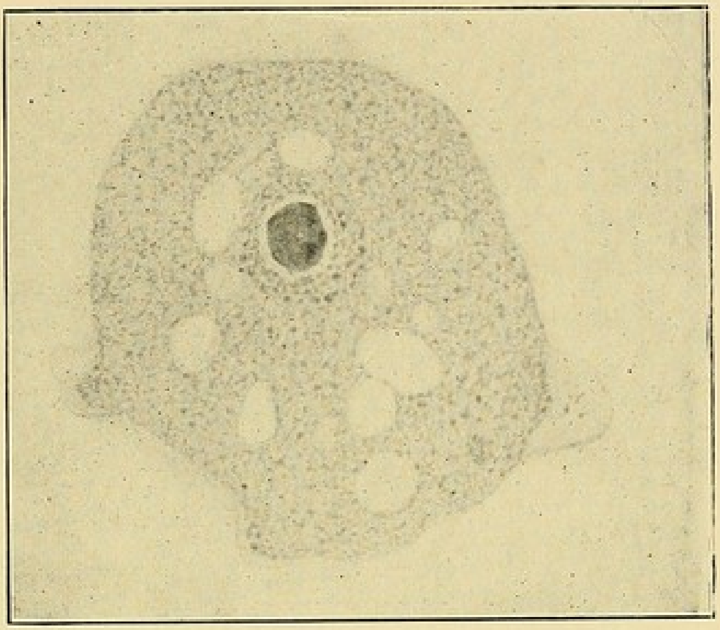

FIG. 48 *A.* *Entamœba histolytica*, HIGHLY MAGNIFIED. Living specimen drawn from a cover-glass preparation from a twenty-four-hour culture, by E. S. Kilgore.

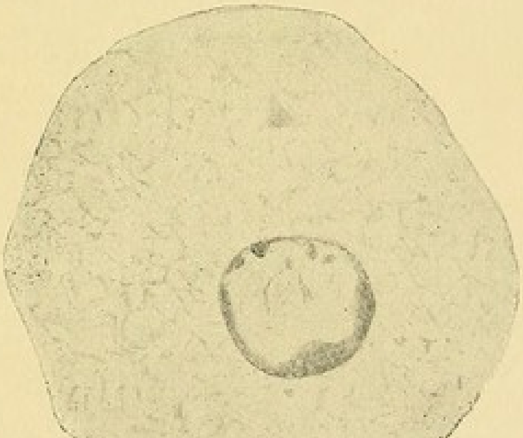

FIG. 48. *B.* PRESERVED SPECIMEN OF *Entamœba histolytica*, artificially coloured to demonstrate the large round nucleus. Same magnification as Fig. 48 *A.*—From a preparation loaned by Dr. Councilman.

alone. As development progresses, the simple condition of the cells is gradually obliterated, but we find another condition arising which we call the differentiated one. Differentiation is a process which goes on in the body as a whole, but of course it is also a function of each individual cell.

We can see something of the process of differentiation if we study the unicellular organisms, those creatures, each of which is complete in itself, although it consists of but a single cell, not of countless millions of cells as we do. The picture, Fig. 48, which I have chosen to throw upon the screen, is one which I think may have an additional interest to you, for it is a photograph from the living cell known as the parasite producing dysentery. Its name is *Entamœba histolytica.* Fig. 48 *A* is drawn from a living specimen, which had thrown out three short protuberances (*pseudopodia*) and had swallowed some foreign body, which shows as a rounded dark mass. As the nucleus did not show in this specimen, Fig. 48 *B* has been added, a drawing from an individual which had been preserved and artificially stained, by which double treatment, as you see, the nucleus has been rendered conspicuous.[1] Of course in the living specimen the nucleus was equally present although hidden by overlying granules. Our *Amœba* is a unicellular parasitic

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[1] It gives me pleasure to thank Dr. W. T. Councilman for the loan of this specimen, obtained from the intestine of a fatal case of amœbic dysentery. It is on Dr. Councilman's brilliant investigations that our knowledge of this disease is based,

organism with scarcely any differentiation of its structure. The next of the slides shows us again another of these parasitic simple organisms, namely *Plasmodium vivax*, the cause of tertian malarial fever. The tiny creature inhabits the blood corpuscles of man; when it enters the corpuscle it is very minute, scarce an eighth of the diameter of the corpuscle; it grows very rapidly, feeding on and destroying the corpuscle and yet meanwhile by its own growth causing the corpuscle to enlarge. Our picture, Fig. 49, shows three human red blood corpuscles, two in their normal condition, the third (on the right) distended by the overgrown parasite, which is heavily charged with pigmented granules, and almost completely fills the corpuscle. The nucleus at this stage of the

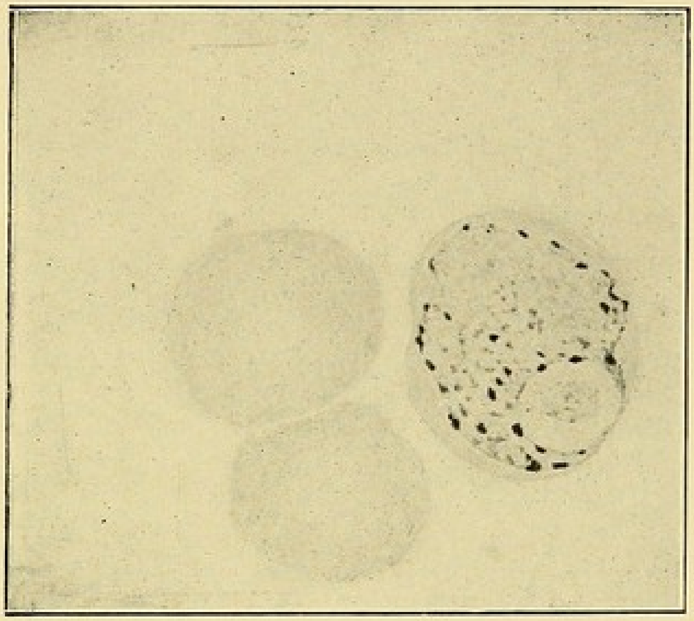

FIG. 49. TERTIAN MALARIAL PARASITE. Two human blood corpuscles alongside and drawn on the same scale, by E. S. Kilgore.

parasite's development is distributed as a series of small scattered granules, which cannot be demonstrated satisfactorily until they have been artificially coloured. The parasite itself is a small mass of undifferentiated protoplasm. In another stage of its life cycle the *Plasmodium vivax* has a distinct nucleus with only a very little protoplasm, and while in that stage it multiplies with that enormous rapidity which renders it such a dangerous parasite to the human race. I will now show you another picture of parasites—one form of which, in a related species, occurs in man. This particular form is one which occurs in the rat and is called the *Trypanosoma.* You can see that the body, instead of being a small and simple structure, has elongated, acquired a peculiar form, and

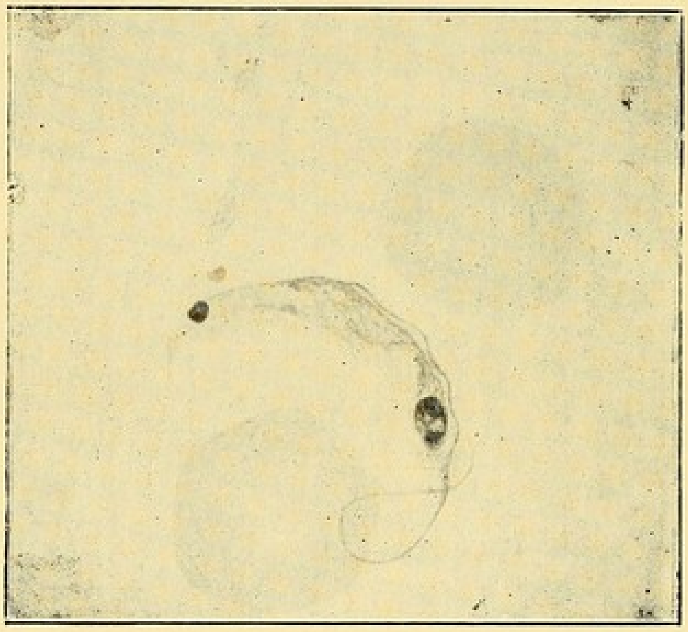

FIG. 50. *Trypanosoma Lewisi*, from the rat's blood, with two blood corpuscles alongside drawn on the same scale, by E. S. Kilgore.

here in the interior are lighter and darker spots. These do not show very clearly in the picture, because it is from a photograph of a living specimen under the microscope. The lighter and darker spots correspond to the details in the structure of the organism.

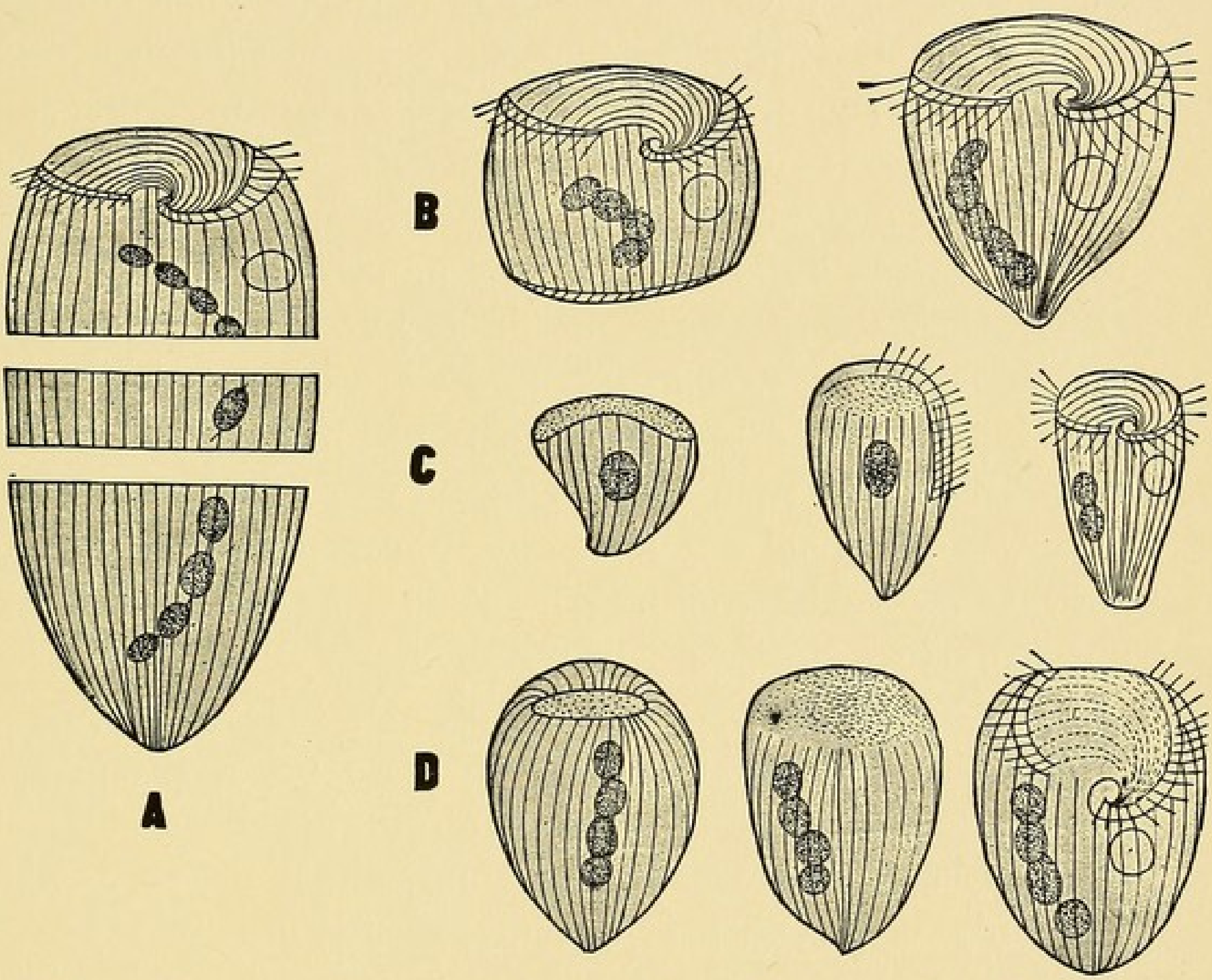

FIG. 51. *Stentor cœruleus; A*, cut into three pieces; *B*, regeneration of the first piece; *C*, of the middle piece; *D*, of the posterior piece. After Gruber.

Here is the tail of the organism, twisted, as you see, and in life capable of being bent. The movement of the animals in the natural fluid in which they are suspended is quite active. Alongside are some blood corpuscles; the figure is magnified about the same as the one of the malarial parasite which I showed you a few moments ago. The next slide, Fig. 51, exhibits an organism which swims free in the water, and is pretty well shown in this figure. It is called the *Stentor*, Fig. 51, *A*. Here the chain of beads represents the nucleus. The peculiar shape of the nucleus is a constant characteristic of this animal. Upon the surface of the body there are fine lines indicating superficial structure. At the top there occurs what we call the mouth. Over the rest of this minute organism there is a thin cuticle, but at the mouth the cuticle is absent, and the protoplasm is naked or uncovered so that food can be taken in. There are bands of hairs showing coarse and stiff in the figure but capable of movement, and with the aid of its vibratile hairs, or cilia, the organism can swim about in water. There is another internal structure, the vacuole, shown in the upper part of *A* as a circle. Obviously in an animal like this we no longer have simple protoplasm alone, but protoplasm in part changed into other things. Here then within the territory of a single cell we have differentiation. If now in these unicellular organisms we study both the protoplasm and the nucleus, we learn that most of these modifications which are so conspicuous upon microscopic observation are due to changes in the protoplasm. It is the protoplasm which acquires a new structure. In the resting nucleus, on the contrary, we find perhaps a change of form, minor details of arrangement by which one sort of nucleus, or one stage of the nucleus, can be distinguished from another, but always the nucleus consists of the same fundamental constants. There is the membrane bounding it; there is the sap or juice in the interior, and there is the network of living threads stretching across it. Here and there imbedded in and connected with the network are spots of a special substance, which we call chromatin. These four things exist in the nuclei and are apparently always present, and there is usually not to be seen in the resting nucleus anything of change comparable, in extent at least, with the change which goes on in the protoplasm — on the other hand, the protoplasm acquires items of structure which were totally absent from it before. The nucleus rearranges its parts rather than changes them. This is a very important fact, and shows us, if we confine our attention even to these little organisms only, that the differentiation of the protoplasm is *quantitatively* the more important of the two—the differentiation of the nucleus the less important.

We can now turn from a consideration of these low organisms to the higher forms, among which we ourselves of course are counted, in which the body is formed by a very considerable number of cells. Again I should like to take advantange of your kindness and show you some of the pictures we have already reviewed, in order to utilise the features which they show as illustrations of the fundamental principle that the conspicuous change is in the protoplasm. First we have nerve cells, Fig. 52. In the two upper drawings are represented two isolated nerve cells, to show their shape. They have been coloured by a special process[1] so dark that the nucleus which they contain in their interior is hidden from our view; it is of course none the less there. This dark staining enables us to trace out the shape of these cells very clearly, and you can see that instead of being round and simple in form they have their elongated processes stretching out to a very considerable distance; these processes serve to catch up from remote places nervous impulses and carry them into the body of the cell, and thus assist in the work of nervous transmission. The elongation of these threads is, as you see, adapted, like the elongation of a wire, to long-distance communication. Here are two other figures which represent nerve cells treated by a different process,[2] and again artificially coloured. But the colour in this case has attacked certain spots in the protoplasm, consequently we see that the protoplasm around the nucleus in both of these figures is no longer simple and uniform, but contains these deposits of dark-coloured material.[3] Below are three other nerve cells; the one in the centre shows you the accumulation, *p*, of pigmented matter in the protoplasm; again an index of change because the previous uniformity has been replaced by diversity in the composition of the various parts of the single cell.

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[1] Carmine.

[2] Nissl's methylene blue method.

[3] The "tigroid markings"—compare p. 54.

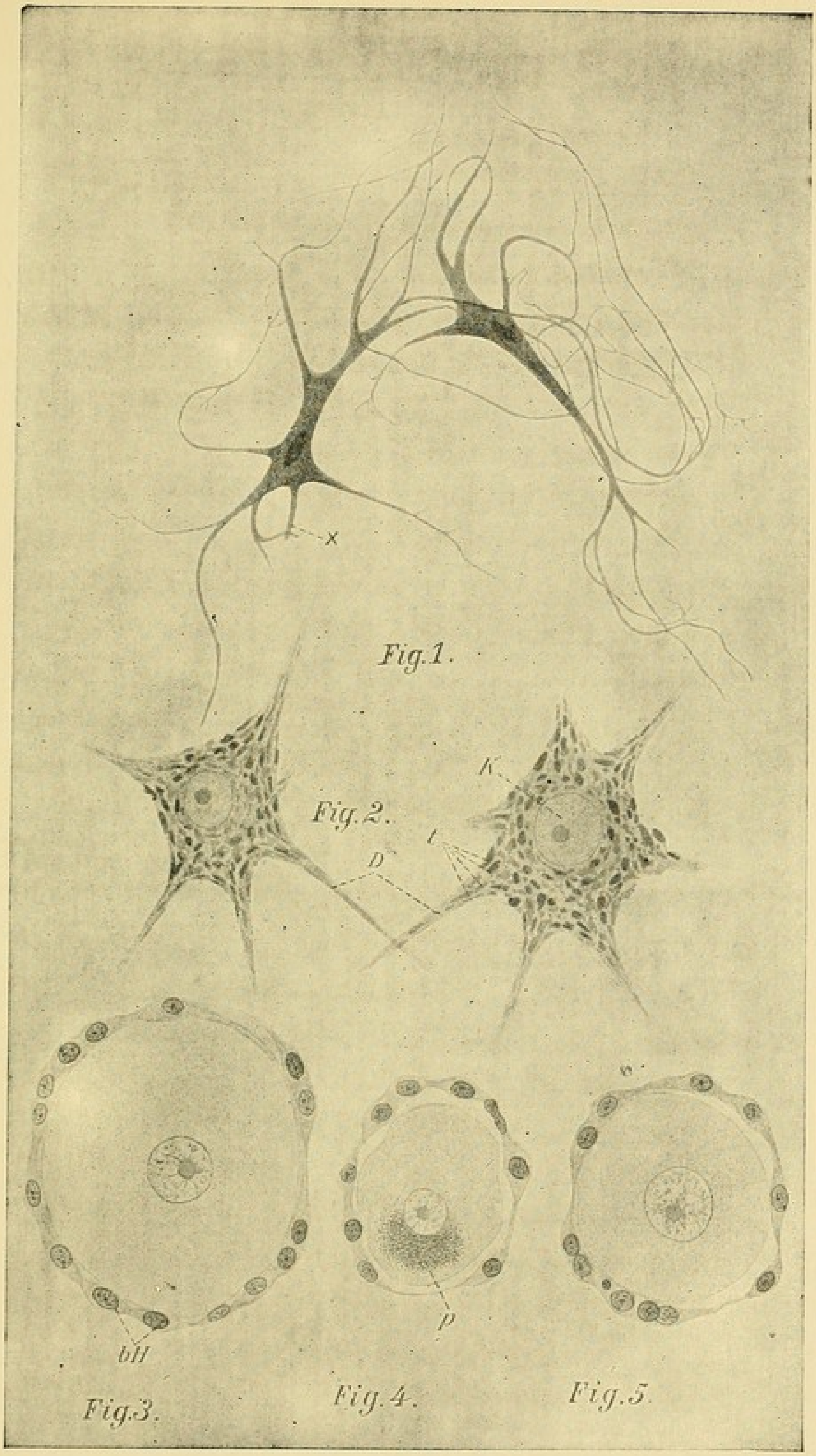

FIG. 52. VARIOUS KINDS OF HUMAN NERVE CELLS.—After Sobotta. 1. Two isolated multipolar ganglion cells from the human spinal cord. × 160 diams. 2. Two multipolar ganglion cells from the lumbar enlargement of the spinal cord of a child. × 480 diams. 3. Three cells from a human spinal ganglion, stained with hæmatoxyline and eosine. × 420 diams.

Figure 11, p. 50, shows us more clearly the principle of structure of a nerve cell, for there we have the central body of the cell composed of protoplasm with its nucleus in the middle and a small spot in the centre of the nucleus, and the long branching processes running out in all directions which can take up nerve impulses from other similar or dissimilar cells, as the case may be, and carry them to the central body. To carry the message out there is typically but one process, which is different in appearance from the other processes which carry the impulses in. The latter are branching and are therefore called the tree-like or dendritic processes. Here is a single process (Fig. 11, *Ax*) like a long thread to carry the impulses away, and which is called the axon of the nerve cell. In this case the modification of the shape of the cell has adapted it to the better performance of its functions. Notice also in these cells the enormous increase in the amount of protoplasm as compared with the nucleus. In the young cell of the rabbit germ, of which I showed you several illustrations a few moments ago, we had very little protoplasm for each nucleus, but here the protoplasm has many, many times the volume of the nucleus, and this is a relatively old cell.[1]

Next let us look again at the figure of the striated

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[1] The nerve fibres of vertebrates are usually each surrounded by a protective covering of cells, making a sheath. Kölliker pointed out in 1886 that the sheath cells are very small in young embryonic stages and that their size increases with age, owing not to the growth of the nuclei, but to the growth of the cell body, including the myelin, the special substance which characterises the differentiation of these cells. See "Histologische Studien an Batrachier Larven," *Zeitschr. für wiss. Zoölogie*, xliii., p. 1.

muscle fibre, Fig. 53, which you may recall from the second lecture, so that it will suffice if your attention is again directed to the oval nuclei, and to the lines stretching crosswise on the muscle giving it a "striated" appearance. You remember, doubtless, that such fibres are the ones which enable us to make voluntary motions. Originally each fibre was a set of cells, and the cells had some protoplasm, but, gradually, as development progressed, there appeared in them longitudinal fibrils different from the protoplasm, and the fibrils also created ultimately the appearance of cross lines on the fibre. It is the fibrils which perform the muscular contractions. It is not the original unmodified protoplasm, but the modified or differentiated muscular cell which is capable of voluntary contraction.

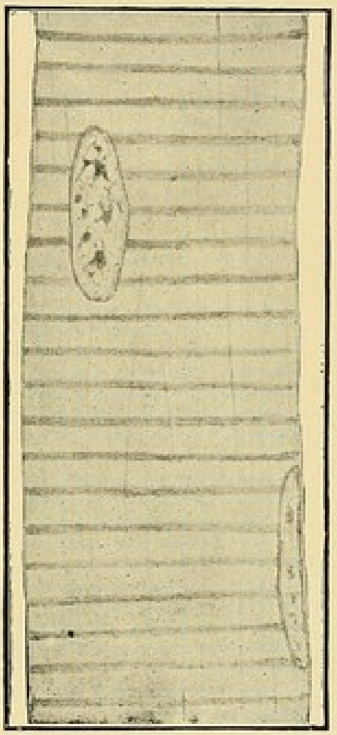
FIG. 53. PART OF A HUMAN MUSCLE FIBRE.

The next picture, Fig. 54, shows us clearly and strikingly how much the differentiation may vary. We have here another type of differentiation. These are gland cells; we can see here, as I pointed out to you before, the material in the form of granules, which is to produce the secretion from these gland cells. This is an orbital gland, and here are the cells, which are very much smaller because they have discharged their secretion and are very conspicuous on account of their dark colour. Three typical cells are represented separately (Fig. 55). The first shows us a cell full of the material which is to be discharged and is to form a part of the salivary secretion. The second is a cell which has partly lost its accumulated material, and the third is one which has discharged it almost completely, so that it has become very much reduced in size. We learn from these observations and others similar that the size of cells may vary also according to their functional condition. Let me refer back to an earlier picture (Fig. 16) representing a section of the so-called salivary gland of the intestine, better termed the pancreas. Here we can see for each of these cells a nucleus and a body divided into two parts, a darker portion around the nucleus and a lighter part with little granules in it, which represents the accumulation of material which is to form the secretion. When the cells have discharged their secretion, they, like the

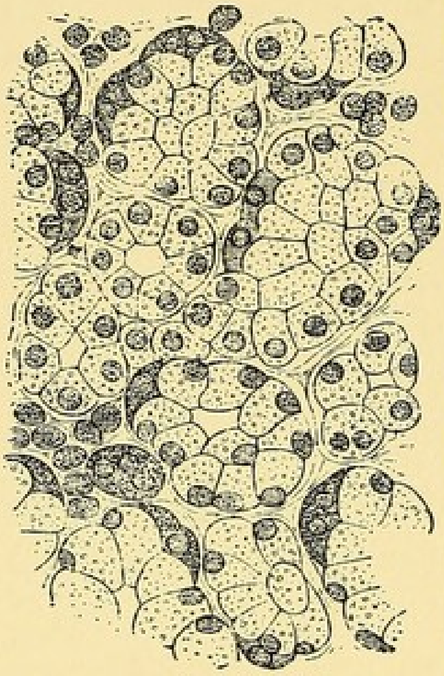

FIG. 54. SECTION FROM AN ORBITAL GLAND OF A DOG—After Lavdowsky.

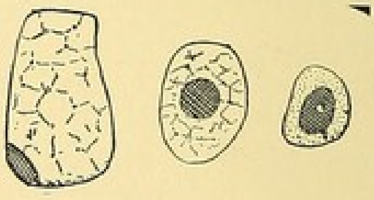

FIG. 55. DIAGRAM OF THREE CELLS OF A SALIVARY GLAND, TO ILLUSTRATE THE CHANGE RESULTING FROM THE DISCHARGE OF THE SECRETION.

cells in the salivary gland, are found to have diminished in size and become very much smaller indeed than they were in their earlier state when charged with the zymogen destined to be given out. In this case also we have an illustration of a functional variation in the size of the cells. This ends the series of pictures which I wanted especially to show to you as illustrating the changes of the cells as their differentiation progresses. We can see in the bodies of the cells the changes which have occurred.

Here is a picture (Fig. 56) which teaches us one thing more about these cells. Notice the scattered nuclei, each surrounded by protoplasm, completing the cell. The protoplasm of each of these cells is connected across with the protoplasm coming from another, so that the whole set of cells forms an irregular protoplasmic network. Now in the spaces between these cells are fine lines. These represent delicate structures which we call connective tissue fibrils, which have a mechanical function. By their tensile strength, their power to resist a pull, they give a certain supporting power to the tissues. Our picture represents one of the tissues which support and connect other portions of the body. Now the fibrils apparently lie entirely disconnected from the cells, but a more careful study of the history of the connective tissue has revealed the very interesting and instructive fact that the fibrils, now separate from the cells, arose by a metamorphosis of the protoplasm of the cells—that they are first formed out of some of the protoplasm of these cells, then split off from them, and come to lie in the intercellular regions, so that here we have another type of cell differentiation brought to our notice, one in which the product is separated from the parent body to which it owes its origin. Now you will perceive immediately, if you recall the series of pictures which have just passed before us, very great differences in the types of differentiation which occur in the body, and had we time we might find a very much larger range easily to be represented before us.

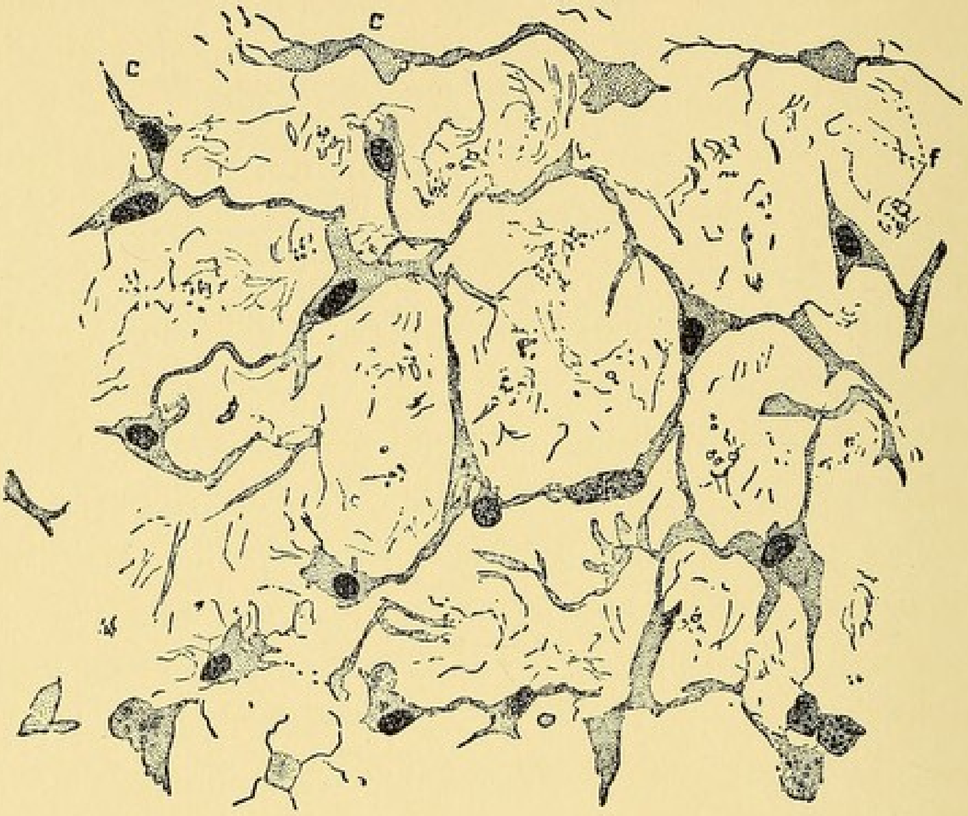

Fig. 56. Embryonic Syncytium from the Umbilical Cord of Man; *c*, *c*, cells; *F*, fibrils.

In the second lecture a picture was projected upon the screen (Fig. 22) which showed motor nerve cells of various animals. You will recall that I directed your attention to the fact that the largest animal, the elephant, has the largest cells, and the smallest animals, the rat, the mouse, and the little bat, have the smallest ones. But let me point out to you that the question of the size of cells is exceeding complex, and that in studying it we have to exercise a great deal of caution. We know that, with the exception of the nerve cells and to a minor degree with the exception of the muscle fibres, the cells in each animal are more or less uniform constants in size. The cells of different organs differ somewhat from one another. A single organ may have in its different parts typical sizes of cells, but each of these kinds of cells has its definite dimensions. When one animal is larger than another, it has more cells. Now it is a very important fact for us that animals have a more or less constant size of their cells. They do not differ from one another by a difference in the size of their cells; the bigness of an animal does not depend upon the size, but upon the number, of its cells. We can, therefore, in studying the changes of size, to which I shall next direct your attention, omit altogether these details, and speak of the cells in a general way safely as having a certain uniform or standard size. This will save us a great deal of time, for we learn, as we study cells, that their size increases with the age of the animal. Since the animal, when it is young, has cells with a small amount of protoplasm, the increase of protoplasm with age is an absolutely necessary corollary of the discovery that differentiation is mainly a function of the protoplasm. If there is to be a large degree of differentiation it is necessary that the quantity of protoplasm in the single cells should be increased, so that there may be the raw material on hand out of which the differentiated product can be manufactured. If there is not such a preliminary increase of the protoplasm, then the differentiation cannot occur. In order that the perfection of the adult structure should be attained, it is necessary that the mere undifferentiated cells, each with a small body of protoplasm, should acquire first an increased amount of protoplasm, and that then from the increased protoplasm should be taken the material to result in differentiation, in specialisation.

An undifferentiated cell performs all the fundamental functions of life. An amœba, or any unicellular organism such as I have presented to you upon the screen, does everything which is indispensable to life. It takes food; it forms secretions and excretions; its activity depends upon chemical alterations going on in the food in the interior of its body; it is capable of sensation and of locomotion. It is probable that every living cell has all of these fundamental properties of protoplasm. When a cell becomes differentiated, however, though it does not necessarily give up any of its vital properties, it becomes different from other cells because one of its properties is made conspicuous, and in order to acquire that conspicuousness, that excess of development of one function of the cell, a modification in the structure is necessary. The apparatus in the interior of a cell to produce the exaggeration of the function must be developed, so that to effect the complex physiological machinery of the adult body, this differentiation, of which I have so often spoken, is indispensable. A nerve cell carries on all the vital functions, but it has in addition a special

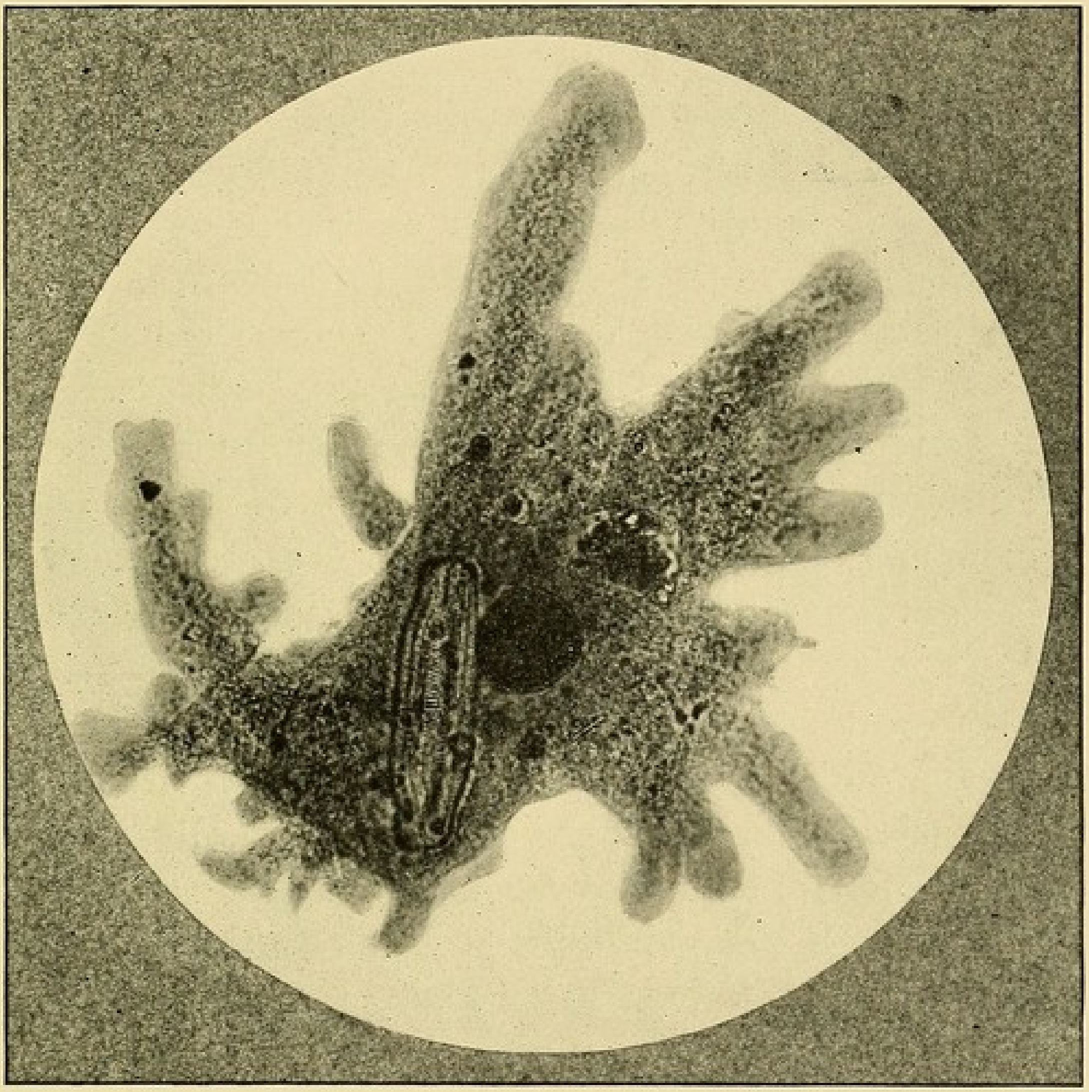

FIG. 57. AMŒBA PROTEUS, photograph of a specimen prepared by Prof. G. N. Calkins.

series of modifications of its protoplasm which enable it to accomplish the transmission of the nervous impulses with greater efficiency than ordinary protoplasm can do, probably at a higher speed and with a more perfect adjustment of communication between the various parts of the body than is possible with any machinery of pure protoplasm. So, too, the glands have cells which are especially capable of elaborating chemical substances which, when they are poured out, accomplish the work of digestion, for instance. But these cells are likewise alive in all their parts. They have all the fundamental vital properties, but there is a tremendous exaggeration of one faculty, and that involves an alteration so great in the protoplasm that we can see it with the microscope; the microscope affords us a perfect visible demonstration of differentiation, which we can correlate with the function.

The primary object, therefore, of all differentiation is physiological. The higher organism, with its complex physiological relations, is something really higher in structure than the lower organism. The term "higher" in biology implies a much more complex interrelation of the parts, a much more complex relation of the organism to the outside world; and above all it implies in the highest animals a complex intelligence of which only a rudimentary prophecy exists in the lowest forms of life, possibly scarcely more than a mere sensation. We owe then to differentiation our faculties, which we prize. It is the result of differentiation that I am able to address you and present before you the thoughts which have been accumulated as the result of the studies of many years. It is a result of differentiation that you have such parts that you not only hear the actual sound of my voice, but interpret—at least I hope so—the meaning of my words and can understand the ideas which I am endeavouring to present to you. If you carry away something from these lectures, and recall it at some future time, that also will be a result of the differentiation of structure; for every one of you started as a minute germ, consisting of protoplasm with a nucleus, and entirely without any differentiation; and by a process so intricate that the mystery of it escapes entirely all our powers of analysis, those parts which you have have been slowly and secretly fashioned. We have approached one of the fundamental problems of existence. When we talk of dfferentiation, we talk of the endowments which bring us into relation with the external world—into relations with our kind, and which make our internal life so complex, a complexity which in itself is a great problem. We touch here the fundamental mysteries of existence; we are hovering upon the outskirts of our human conceptions. We are not yet able to press beyond. But perhaps the time may come when the limit to which I can now bring you will be moved farther back, and some of the things which are at the present time utterly mysterious and incomprehensible to us will be comprehended and be explicable to you.

The increase of the protoplasm is then, as we have clearly seen from the pictures, the mark both of advancing organisation and of advancing age. It is certainly somewhat paradoxical to assert that the increase of the protoplasm is a sign of old age, a sign of senescence, since protoplasm is the physical basis of life. It undoubtedly is such, and we should hardly anticipate that its increase would have a deleterious effect. But such is, it seems to me, clearly the case. But it is not merely, of course, a question of the increase of protoplasm which we must bear in mind in estimating the cause and effect, but also the question of differentiation, in consequence of which protoplasm becomes something else and different from what it was before. This alteration, then, together with the increase of the protoplasm, is the change which in all parts of the body marks the passage from youth to old age.

It seems to me not going at all too far to say that the increase of protoplasm is a fundamental phenomenon. I wish to give you a more precise notion of this increase; and I am glad to be able to do so in consequence of a research carried on by Professor Eycleshymer in my laboratory and completed by him afterwards in his own laboratory at the University of St. Louis.[1] He studied the development of the muscle fibres in the great salamander, known scientifically by the name of *Necturus*. These muscle fibres are somewhat cylindrical in shape. Their ends can be accurately

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[1] A. C. Eycleshymer, "The Cytoplasmic and Nuclear Changes in the Striated Muscle Cell of *Necturus*," *American Journal of Anatomy*, iii., 285-310. This paper is of exceptional importance as a contribution to our knowledge of the life-history of cells.

determined so that the precise length of a fibre can be measured, and its diameter also. Hence the total volume of a fibre may be calculated. It is possible also to measure the nuclei and to count the number of nuclei in a fibre. Thus by measuring the diameter and length of the fibre, and then estimating the number and the diameters of the nuclei, the author was able to calculate the relative proportions of the nuclei and the protoplasm. As a matter of fact, the nuclei remain nearly constant in volume, not really quite so, but sufficiently constant to serve as a basis of measurement. Dr. Eycleshymer found that when a *Necturus* had a length of eight millimetres, it possessed, for each nucleus in its muscle fibre, 2737 units of protoplasm, but when it was seventeen millimetres, it possessed for each nucleus, 4318 units per nucleus; at twenty-six millimetres, 8473 units; and in the adult, which measures approximately 230 millimetres, it has 22,379 units per nucleus. In other words, as a salamander passes from the eight-millimetre condition, when the development of its muscle fibers is just fairly begun, up to the adult state, when the differentiation of the muscle fibres has been completed, it increases the proportion of protoplasmic substance and protoplasmic derivatives from 2700 to 22,300 per nucleus. I give round numbers. The increase is approximately eightfold. There is in the adult in the muscle fibre eight times as much protoplasmic substance in proportion to the nucleus as there was at the start of development when the muscle fiber could first be clearly recognised as such.

This is an accurate measure and gives us a good idea of the general law of protoplasmic increase. It is the only instance, I yet know of, in which we have an accurate measure and can give quantitative values, though we do know that there is a more or less similar increase occurring in perhaps every tissue of the body.

While the increase of the protoplasm is going on, we find that there is an advance in the structure, in the differentiation. Now you may recall what I have mentioned, earlier in this lecture, the further fundamental fact that the loss in the rate of growth is greatest in the young, least in the old, and that as we go back from old age towards youth, and then into the embryonic period, we find an ever-increasing power of growth, but that it is during the embryonic period that the loss of the power of growth is greatest. It is to the embryonic period, therefore, that I have turned in order to ascertain whether the rate of differentiation shows a similar relation in the development of the organism.

We have a large series of microscopic preparations of rabbit embryos in the embryological laboratory of the Harvard Medical School. Utilising these, I found that at seven or eight days of development there is scarcely a trace of differentiation. The cells are in the condition of those which I showed to you earlier in the lecture upon the screen (Fig 47). At sixteen and a half days, a stage of development of which I have some good preparations, I found that a great deal had been accomplished. At seven days there was no brain, there was no spinal cord, nothing that could possibly be called skin or muscle, or intestine or heart. None of those things were yet produced. But at sixteen and one half days—in other words, after a very brief period indeed—only nine days of the whole life of the animal—there have arisen from this inchoate beginning all the principal organs of the body. The brain is there, divided up into its principal fundamental parts; the spinal cord has its nerves in connection with the various parts of the body; there is a trace of the skeletal element; the stomach, the liver, the pancreas, the intestines, are all present and well defined; the heart is a large and beating organ, amply supplied with blood, connected with vessels, which carry out and bring back the blood and are all far along in their development. Equally instructive is the microscopic examination, for we can see that the cells themselves have been changed. Not only have the great organs been mapped out in this brief period, but the cells which belong to them have for each organ acquired a characteristic quality. In the brain there are nerve cells with their long processes to carry the impulse in; the single process (axon) to carry it out. The glands in the stomach have the cells which are to build them already there. The muscles which are to move the stomach are beginning to appear as cells of a special form. Nerve fibres extend down into the gastric region and to the various distant organs of the body. Muscle fibres can be recognised along the back and in the limbs, and so in every part of the body we can detect cells already far advanced in their development. It is not certainly too much to say that in the brief period of these nine days fully as much differentiation has been accomplished as is accomplished during the entire remainder of the life of the animal. We do not, at present at least, possess any method of measuring differentiation which enables us to state it numerically, but no one who is familiar with these matters and observes the structure, as I have myself observed it, would hesitate for a moment, it seems to me, to decide that my assertion is perfectly within the bounds of truth, that within a period of nine days, half of the entire differentiation which is to occur in the whole life of the rabbit has been completed. We must from this conclude that the rate of differentiation is very rapid at first and afterwards declines, and as we compare the different stages of development we can see readily that this is the case. The progress in the additional development in the rabbit from sixteen and one half days up to the time of its birth is far greater than the progress which occurs after birth. We find, moreover, in the study of these embryonic conditions, some instructive things, for in certain parts of the body the process of differentiation hurries along, and as the cells are differentiated their power of growth, to a large extent, is stopped. On the other hand, there are various provisions in the developing animal for keeping back certain cells, allowing them to remain in the young state. Such cells may afterward differentiate.

From all that has been said it seems to me legitimate to conclude that there is an intimate correlation between the rate of differentiation and the rate of growth. I am inclined to go the one step farther, and bring them into the relation of cause and effect; and I present to you as the main general conclusion of this first part of our series of lectures, the conception that *the growth and differentiation of the protoplasm are the cause of the loss of the power of growth.*[1]

Now if cells become old as their protoplasm increases and becomes differentiated, we should expect to find that there would be a provision for the production of young cells. It is rather mortifying to reflect that the simple conception which I have now to express to you, although it lay close at hand, failed to combine itself in my mind for many years with the conception of the process of senescence as I have just described it to you. It is somewhat, it seems to me, like two acquaintances of mine who lived long side by side, seeing one another frequently until they were fairly past the period of youth, when their attachment became very close and by a sacrament they were permanently joined together. So in the minds of men often two ideas lie side by side which ought to be married to one another, and there is no one ready so dull is the owner of the mind, to pronounce the sacramental words which shall join them, and the rite

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[1] The hypothesis that the increase of protoplasm is the cause of old age was originally put forward in 1890 (C. S. Minot, "On Certain Phenomena of Growing Old," *Proc. American Assoc. Adv. Science*, xxix., Address of the Vice-President, Section **F**).

long remains unperformed, and when at last such neighbour ideas, which naturally should be united in close companionship, are brought together and made, as it were, into one, we are astonished that the inevitableness of the union had not obtained our notice before, it is so very obvious. And so in regard to the conception of what constitutes the restoration of the young state, I have only this excuse to offer, which I have indicated to you, that even the natural thought fails to occur to us. We are very dull even if we are scientific.

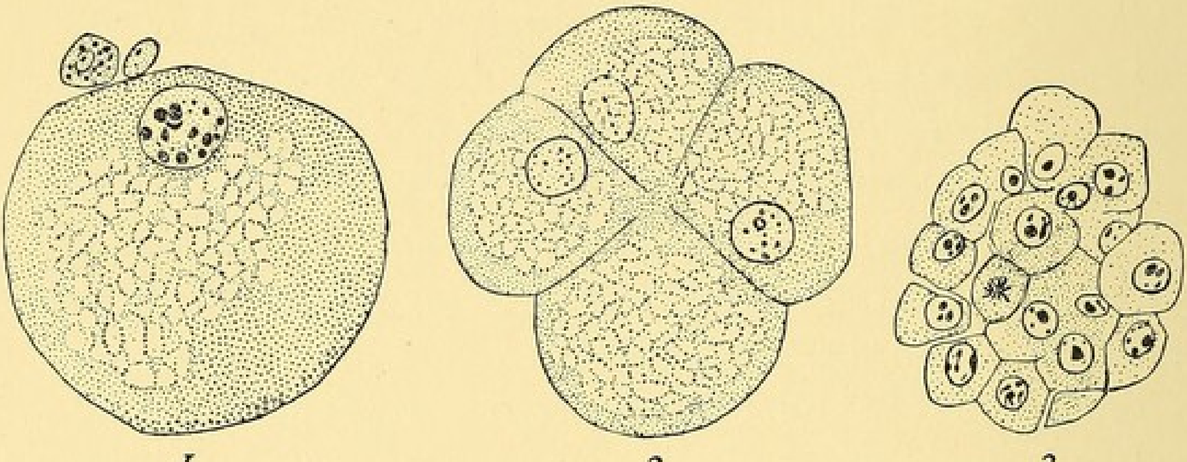

FIG. 58. *Tarsius spectabile.* SECTIONS OF THREE OVA IN VERY EARLY STAGES. 1, before cleavage; 2, cleavage into four cells; 3, multicellular stage.

The pictures now before you represent certain early stages in the progress of development of a mammal by the name of Tarsius, a creature related to the lemurs. The various figures illustrate the multiplication of the cells. That which I wish to call your attention to can be well demonstrated by the comparison of the first figure, in which there is a single nucleus, with the figure on the right having a number of nuclei. Both figures represent the very earliest stages of development and show the full size of the whole germ, which is about the same in the two stages. The total amount of living material has not changed essentially, but evidently there has occurred a marked increase of the nuclear substance. The nuclei have in the right-hand figure multiplied in number and their combined volume is much greater than the total volume of the single nucleus in the left-hand figure.

The increase in the amount of nuclear material during the segmentation of the ovum occurs in all classes of animals and has been recorded by hundreds of observers. It has hitherto attracted very little attention and despite the constancy and universality of the phenomenon no special significance has been attributed to it. I emphasised the constancy of the phenomenon in 1890 in an address delivered before the American Association for the Advancement of Science.[1] Since then Richard Hertwig has been the only author to lay special stress on the fact, but he fails to make the interpretation, which I shall offer you in a few moments.

We can get a further notion of the nuclear increase by studying the very early development of a salamander (Fig. 59). Here upon the screen is the egg of a salamander, No. 1. It represents really but a single cell. It then divides into two cells: each of those cells has a nucleus which we cannot see because these

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[1] *Proc. A. A. A. S.*, xxxix.

pictures are taken from the living egg, and the living egg is not transparent. Here (No. 4), it is dividing into four, here (No. 5), the upper portion of the four cells has been split off, and we have seven cells showing

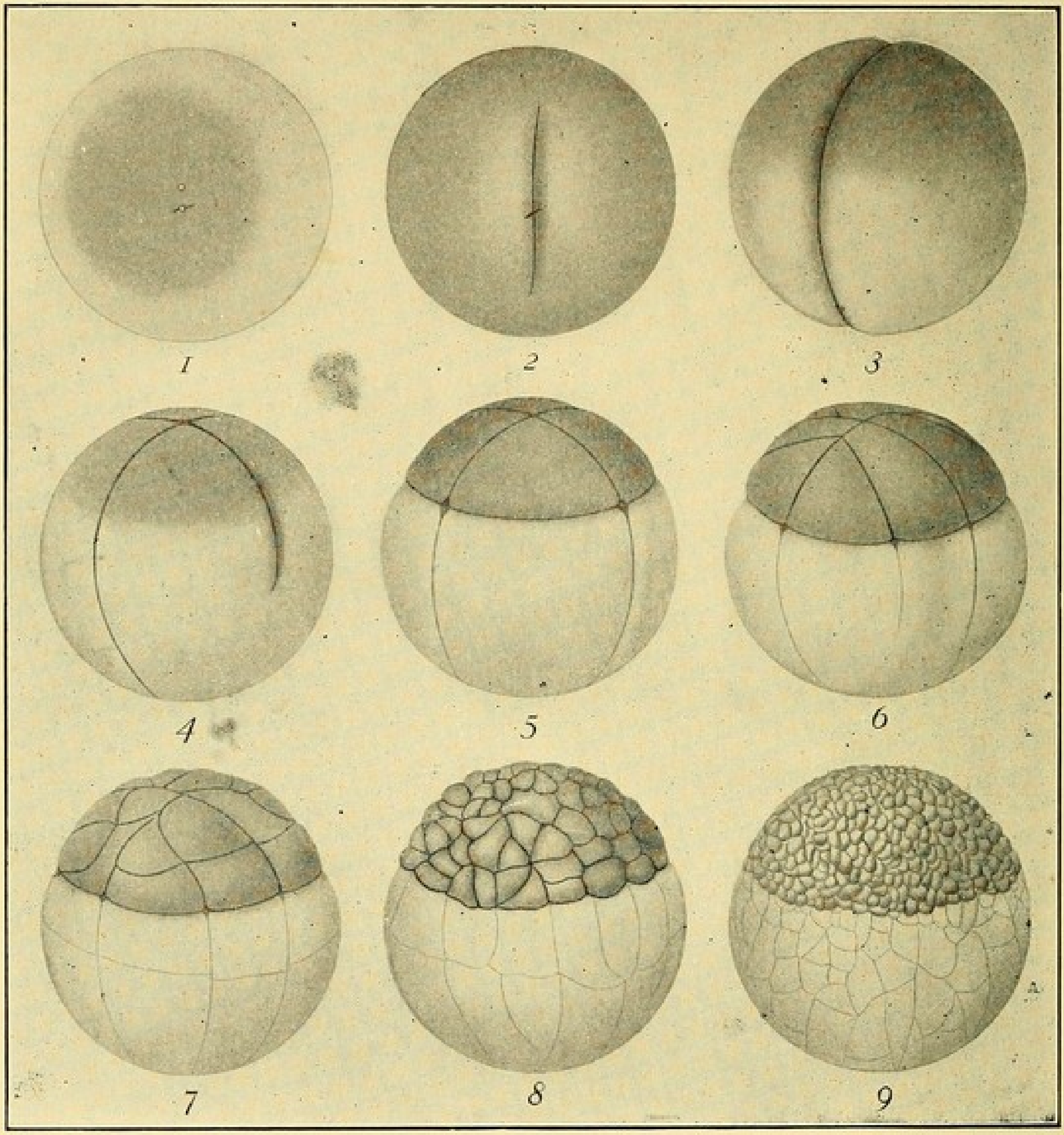

FIG. 59. *Amblystomum punctatum.* PROGRESSIVE SEGMENTATION OF THE OVUM. 1, unsegmented ovum; 9, advanced segmentation.—After A. C. Eycleshymer.

in the figure, and an eighth on the back. Here (No. 9) the number of cells has increased very much. As you view these figures you will notice that they look very much indeed like oranges divided into segments. It seems, in fact, as if this egg, which was spherical in form, were being divided up into a certain number of segments. The process was first observed in the eggs of some of the amphibia (frogs, toads and salamanders), and it was therefore called segmentation, because it was not known at that time what the process really meant. We have then before us an ovum and a series of stages of the segmentation of the ovum, and the result of that segmentation is to produce an ever-increasing number of cells which, in the last of the figures upon the screen, have become so numerous that we are no longer able to count them readily. Every one of these cells has its own nucleus. When the process of segmentation is complete and reaches its final limit, we then see, if we examine that stage of development, cells of the young type, such as I have described to you, in which there is a nucleus with a small amount of protoplasm about each nucleus. It seems to me, therefore,—and this is a new interpretation which I present to you,—that the process of segmentation of the ovum, with which the development of all the animals of the higher type invariably begins, is really the process of producing young cells. It is the process of rejuvenation. There is not any considerable growth of the living protoplasmic material of these eggs, and at the final stage the total volume of the egg is scarcely bigger than before; and such increased volume as has occurred has been due to the absorption of some of the surrounding water. In many animals not even this increase by the absorption of water takes place. During the segmentation of the ovum the condition of things has been reversed so far as the proportions of nucleus and protoplasm are concerned. We have nucleus produced, so to speak, to excess. The nuclear substance is increased during this first phase of development. Hence our conclusion: *Rejuvenation is accomplished chiefly by the segmentation of the ovum.*

Naturally, as we embryologists looked upon these things in earlier days and thought of the progress of development, we conceived of the earlier stage as younger, and of the ovum as being the youngest stage of all, a conception which in terms of time is obviously correct, but as regards the nature of the development, it seems to me clearly, is not correct. The ovum is a cell derived from the parent body, fertilised by the male element, and presenting the old state to us, the state in which there is an excessive amount of protoplasm in proportion to the nucleus; and in order to get anything which is young, a process of rejuvenation is necessary, and that rejuvenation is the first thing to be done in development. The nuclei multiply; they multiply at the expense of the protoplasm. They take food from the material which is stored up in the ovum, nourish themselves by it, grow and multiply until they become the dominant part in the structure.

To be exact, it must be added that the relative increase of the nuclei may be prolonged beyond the period of segmentation as commonly defined. Then begins the other change; the protoplasm slowly proceeds to grow, and as it grows, differentiation follows, and so the cycle is completed. Whether other naturalists will be inclined to accept this conception that the process of the segmentation of the ovum is that which we must call rejuvenation or not, I cannot say, for the matter has as yet been very little discussed, but you must admit that the conception hangs as a theory well together with the main facts of senescence as now known to us. We have first an explanation of the process of the production of the young material, and next out of that young material the fashioning of the embryo. The cycle of life has two phases, an early brief one, during which the young material is produced, then the later and prolonged one, in which the process of differentiation goes on, and that which was young, through a prolonged senescence, becomes old. I believe these are the alternating phases of life, and that as we define senescence as an increase and differentiation of the protoplasm, so we must define rejuvenation as an increase of the nuclear material. The alternation of phases is due to the alternation in the proportions of nucleus and protoplasm.

In the next lecture I shall be able to convince you, I hope, that this conception of the relation of the power of growth to the proportion of nucleus and protoplasm enables us to understand various problems of development, certain possibilities of regeneration and reconstruction of lost parts, and that it also leads us naturally forward to the consideration of the problem of death as it is now viewed by biologists, so that our next lecture will be upon the subject of regeneration and death, the natural topics to follow after to-night's discussion.

## V

## REGENERATION AND DEATH

*LADIES AND GENTLEMEN:* In the last lecture I treated the conception I had formed of the processes of regeneration and told you that I looked upon the change which occurred first in the developing germ as one of rejuvenation. The process has for its technical name the segmentation of the ovum. The appearance of the segmentation process was illustrated to you by the pictures thrown upon the screen. Cytomorphosis is a term which we have frequently used in the course of these lectures, and I have led you, I hope, to the appreciation of the idea that in cytomorphosis we have at least a part of the explanation of old age. We have learned that the young cells, which are produced by the segmentation of the ovum, are in large part changed into old cells, and also that old cells cannot go back in their development and again become young[1]; so that

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[1] Pathologists are familiar with a phenomenon which at first thought might be held to invalidate this assertion. I refer to the growth power of connective tissue cells under certain abnormal conditions. I think this must be interpreted as a case of cellular regeneration effected by undifferentiated protoplasm, left over in each cell after a part of the protoplasm has been changed into fibrils, matrix, etc. In brief, the process involved is similar to that in the regeneration of striated muscles, described later in this lecture.

one might easily be led to the suspicion that there could be no possible new young, a conclusion obviously absurd, for there is a constant renewal of the generations. Some device, therefore, must exist by which that which is young is perpetuated, for that which is old cannot again become young, and of that device I should like to say something this evening.

Formerly the notion was prevalent that under suitable conditions old cells could resume the young state and undergo redifferentiation. Hans Dreisch, E. Korschelt,[1] and a few other contemporary German and American writers still regard the occurrence of retrogressive development ("*Entdifferenzirung*") as credible. I have recently been over the few cases of alleged evidence in favour of the notion in question, so far as they are known to me, but in no case has it been proved that a differentiated cell has changed into an undifferentiated one. Provisionally, at least, we can maintain that there is no exception to the law that an old cell cannot go back in its development. A most singular theory involving the assumption of the redifferentiation of cells has recently been enunciated by a German author, Kronthal,[2] who says that nerve cells arise each by the fusion of several white blood corpuscles (*leucocytes*) into a single mass. In answer to him it may be said: *firstly*, that the origin of nerve

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[1] E. Korschelt, *Regeneration and Transplantation*, Jena, 1907, Gustav Fischer. See especially pp. 76 and 99. Compare also T. H. Morgan, "The Physiology of Regeneration," *Journal of Experimental Zoölogy*, iii., p. 493 (1906).

[2] Kronthal, *Von der Nervenzelle un der Zelle im Allgemeinen*, 8vo, pp. 274, (1902, G. Fischer, Jena). Compare also *Anatomischer Anzeiger*, xxii., 448.

cells from the embryonic cells of the nervous system has been amply proved; *secondly*, that at the time the nerve cells arise no outside cells enter the nervous system; and, *thirdly*, that the nerve cells are produced in mammals before there are any leucocytes present in the embryo. You need hardly take Kronthal's theory seriously.

As a preliminary to the discussion of this interesting phenomenon, it is necessary to say a few more words in regard to the nuclei. We have learned that the units out of which the body is constructed, the cells, consist each of a little mass of protoplasm with a central body called the nucleus: and we have also learned that the increase of the protoplasm and the subsequent differentiation of the cell is to be looked upon as the cause of old age, and the increase of the nucleus as the cause of youth, of rejuvenation. In addition to what has been said concerning the size of the nucleus, some further explanation is necessary, and that can best be given with the aid of illustrations upon the screen. The first of the pictures, Fig. 59 (see p. 164), may serve to recall to your minds what I said in regard to the process of the segmentation of the ovum. Here is an ovum, No. 1, a single cell, but relatively of enormous size; it is the ovum or germ of a newt, and the plate illustrates to us the gradual process of division of the original single cell into a number of distinct cells, each of which we call a *segment*, and the formation of them we call *segmentation*, a name which we keep from the olden time when the process was first observed by some French investigators,[1] because it is so descriptive of the appearance presented to the eye by the changes which are going on. Were we to name the process now we should certainly call it a process of cell production.

The next of our pictures (Fig. 60) shows us the eggs of a common animal, the *Planorbis*, a little fresh-water snail, the coils of which lie flat in one plane—hence its name.[2] No. 1 shows the original germ, which has an actual diameter of 0.132 5*mm.;* No. 2 shows it about to divide into two. No. 3 is a side view and No. 4 a top view of the ovum with two segments; No. 5 is cleft into four segments; No. 6 into eight. Nos. 7 and 8 illustrate the further progress of the cell multiplication; No. 9 represents the under side of the same egg, of which the top is figured as No. 8. The number of cells (segments) is thus constantly increasing, and already it is evident that they have become somewhat unlike in character. The pictures were made from the living egg, and therefore do not give satisfactory views of the nuclei, but nevertheless there is during segmentation a change going on in them, which, however, I can better demonstrate to you by means of Fig. 58. Taken from sections through the early developing germ

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[1] Especially Prévost and Dumas, "Developpement des œufs des batraciens," *Annales des sciences naturelles*, 1842, Tome II., pp. 100 and 129, and earlier papers.

[2] The figures are copied from Carl Rabl's classic memoir, a fine monument of capable and thorough research; see "Ueber die Entwickelung der Tellerschnecke," *Morphologisches Jahrbuch*, v., 561–655, Taf. XXXII.–XXXVIII.

of a mammal named *Tarsius spectabile.* It is a creature nearly related to the lemurs, having a special interest to naturalists, owing to the fact that in its early development it offers features of resemblance to man which are very striking and instructive. The plate is from a series of drawings made under the

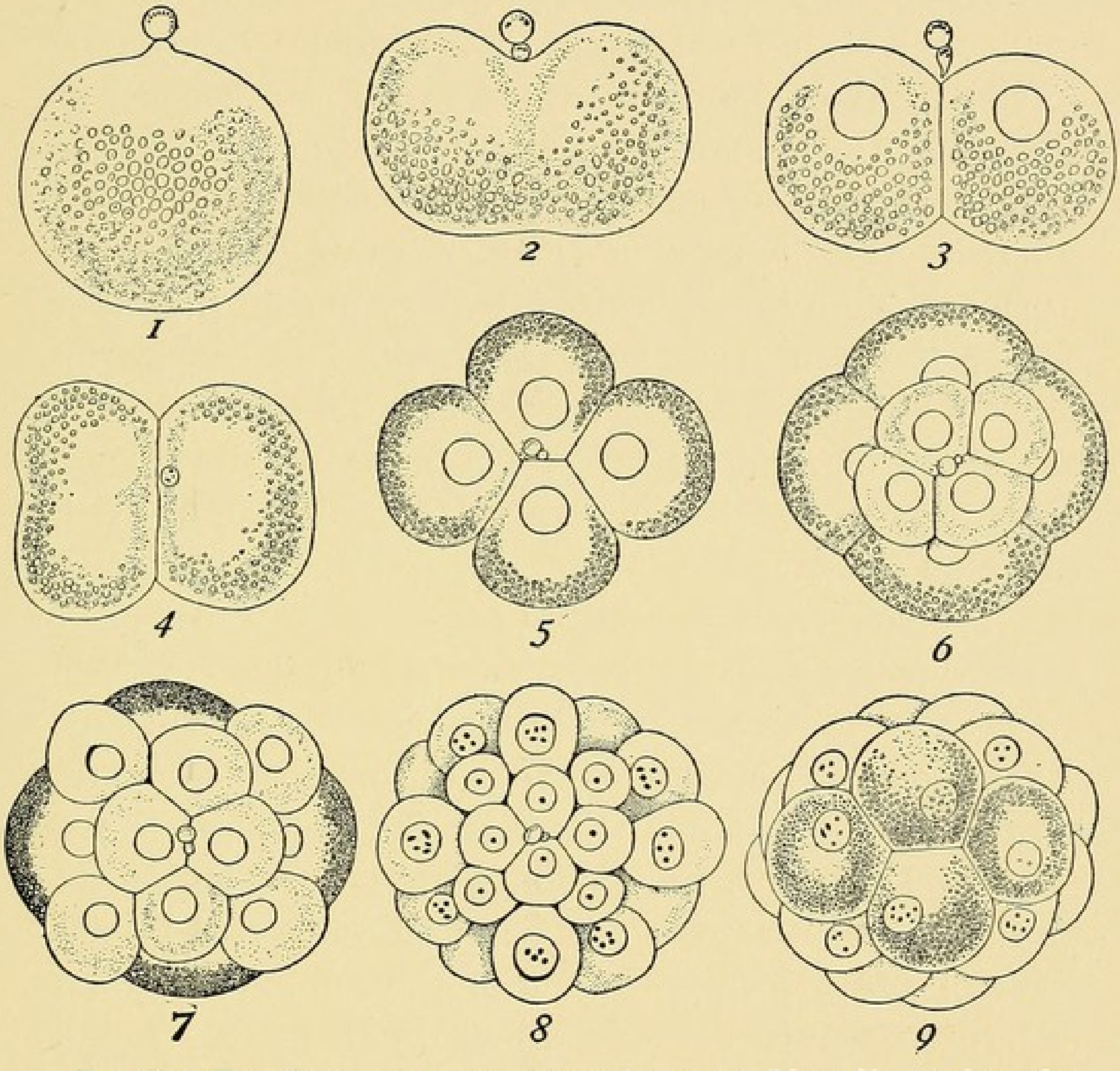

Fig. 60. The Segmentation of the Ovum of *Planorbis*, to show the earliest phases of development of the egg of a pond snail; magnified about 320 diameters.—After Carl Rabl.

direction of Professor Hubrecht, the principal student of the development of this type of animal. Here, No. 1, we can see an early stage in which the germ consists of but a single cell, and at this point is the nucleus. Note its size and then compare it with the nuclei in No. 2, in which several of these cells, as they appear in a section, are represented. The cells themselves are now smaller because they have multiplied by the division of the original germ, but the nuclei in them are likewise smaller; and in the older stage, No. 3, where the number of cells has begun still further to increase, we see that there is another and more marked reduction in the size of the nuclei. Contrast the single nucleus of the early stage with the small nuclei of the later one, and notice how very striking is the change in the size. Thus, during the early development of *Tarsius*, we find that there is an actual rapid reduction in the size of the nucleus. That the nuclei become smaller during the segmentation of the ovum may be asserted safely to be a general law. I have examined a large number of publications in which the segmentation of representatives of the principal classes of the animal kingdom is figured. Without exception the *drawings* of all the authors show the fact, but very rarely have I found even an allusion in the text to the progressive alteration in the diameters of the nuclei. The only author known to me who has explicitly recognised the invariable occurrence of the change, and who has clearly emphasised its importance, is Professor Richard

Hertwig of Munich. As we have learned that the proportion of the nucleus and the protoplasm is so important, we must attribute to this alteration in the dimensions of the nucleus during segmentation great significance.

We have next a series of figures which have interested me very much and which I only recently secured as the result of studies I have been making in my own laboratory at the Harvard Medical School. These pictures are now shown publicly for the first time, and record a fact which, so far as I know, has never yet been clearly noted and recognised as important by any investigator. The four drawings at the top, Fig. 61, represent four single nuclei taken from different parts of a rabbit seven and one half days after the commencement of its development. The second set of drawings, 5, 6, 7, 8, show nuclei from different characteristic parts of a rabbit embryo of ten days. Note, please, the size of these nuclei, the curious network of threads in their interior, and the existence, generally more or less in a central position, of a mass of material which stands out conspicuously and represents a condensation of the nuclear stuff at that particular point. Such a central body is highly characteristic of these early stages. Next we come in the series of drawings from 9 to 20, stretching across the screen in two lines, to a rabbit embryo of twelve and one half days. Instead of having nuclei of large size we have now nuclei which are obviously small. Instead of having nuclei which are more or less alike in appearance, we

FIG. 61. NUCLEI FROM RABBIT EMBRYOS. 1–4, age, seven and one half days; 5–8, age, ten days. 9–20, age, twelve and one half days. 21–33, age, sixteen and one half days.

1, ectoderm ; 2, mesoderm ; 3, entoderm ; 4, Hensen's knot; 5, entoderm; 6, mesenchyma; 7, entoderm; 8, medullary groove; 9, ectoderm; 10, large motor neurone; 11, spinal ganglion; 12, mesenchyma; 13, cartilage; 14, Wolffian body; 15, kidney; 16, striated muscle; 17, heart muscle; 18, esophageal entoderm; 19, tracheal entoderm; 20, liver; 21, ectoderm; 22, motor neurone; 23, spinal ganglion; 24, dermis; 25, hypodermis; 26, cartilage; 27, 28, Wolffian tubules; 29, pelvis of kidney; 30, heart muscle; 31, esophageal entoderm; 32, tracheal entoderm; 33, liver.

have now nuclei of great diversity. Every one of these nuclei, as you will readily see if you run your eye along from one end of the lines to the other, has a distinctive character of its own. In this period, then, of two and one half days, there has been a revolution in the character of the nuclei of the developing embryo. Where before the nuclei were alike, now they have become unlike. Two of these I should like especially to call your attention to, because they are the nuclei of the nerve cells—this one, No. 11, from the spinal cord, and the right-hand one, No. 10, from the cluster of nerve cells upon the root of a spinal nerve. Finally we have the series of drawings from a rabbit of sixteen and one half days represented in the two lower rows, 21 to 33. In these, if you will leave aside from consideration for the moment 22 and 23, which are obviously of a different size, all are now smaller than they were at twelve and one half days. Every one of the nuclei here represented is characteristic. We have here, for instance, 27, 28, nuclei of the excretory organ, a nucleus of the connective tissue, 24; we have nuclei from the lining of the wind-pipe, 32; and the lining of the gullet, 31. Every one of them differs from every one of the others pictured. But if we had drawings of a number of nuclei from the same part of the body and same kind of tissue, we should see that they would be essentially similar. We learn then that there is acquired a great diversity in the structure of the nuclei as well as in that of the protoplasm, of which we have seen so many examples in the previous lectures. You will recall that as regards the size of cells, the nerve cells present a noteworthy exception in that they differ according to the size of the animal; and their nuclei differ also, for as the cells become big the nuclei grow likewise. Here are nerve-cell nuclei, 10 and 11, in the rabbit of twelve and one half days, not differing in their dimensions essentially from the nuclei of other types, but in the two lower figures, 22 and 23, we see nuclei of corresponding cells of the rabbit at sixteen and one half days. These cells have begun to enlarge, to assume the greater dimensions of the nerve cells which are characteristic of the rabbit when adult; and accompanying the enlargement of the cells there has been an expansion of the nuclei also. But this does not affect, as you will readily see by the pictures upon the screen, the nuclei of any other sort of tissue, the nuclei of any other organ of the body.

The differentiation of nuclei has been little studied. We have the valuable observations of Eycleshymer on the nuclei of muscles, which I have already cited. I know of no other exact work except in regard to the nuclei of nerve cells, the genetic changes in which have been recently studied with care by Bombici, Olmer, Hatai, Marinesco, Lache, and Remy Collin.[1] The paper

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[1] Bombici, "Sui caratteri morfologici della cellula nervosa durante le sviluppo. Osservazioni eseguite sull' embrione di pollo," *Archivio Sci. Mediche*, xxiii., 101–125 (1899).

D. Olmer, "Quelques points concernant l'histogénèse de la cellule nerveuse," *C. R. Soc. Biologie*, Paris, 1899, pp. 908–911.

Shinkishi Hatai, "A Note on the Significance of the Form and Contents of by the last-mentioned author deserves special mention. The investigation of nuclear genesis will lead, I believe, to results of great general biological importance.

We must therefore add to our conceptions in regard to the relations of the nucleus and protoplasm, as quantitatively expressed, this further notion—that there is during the early period of development an actual reduction in the size of the nucleus. When this reduction has taken place it is of course evident to any one at all acquainted with the principles of cytology that the cells are in a very different state from theirs before. They are no longer such cells as they were when the nucleus was large, and the nuclei in the different parts of the body alike in character. Here the relations are fundamentally changed. We do not find that these nuclei ever get back from the complex variety of organisation, which they present to us in later stages, to the earlier condition when they were all alike; yet only with cells of this uniform sort does development begin. We should, therefore, if we reasoned only from the data which I have thus far presented to you, come to the conclusion that

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the Nucleus in the Spinal Ganglion Cells of the Fœtal Cat," *Journ. Comp Neurol.*, xiv., 26–48 (1904).

G. Marinesco, "Recherches sur le noyau de la cellule nerveuse à l'état normale et pathologique," *Journ. für Psychol. und Neurol.*, v., 151–172 1905).

Jon G. Lache, "Sur le nucleole de la cellule nerveuse," *Journ. de Neurologie*, 1905, 501–511.

R. Collin, "Recherches cytologiques sur le developpement de la cellule nerveuse," *Le Névraxe*, viii., 181–309, pls. iv.–vi (1906).

reproduction would be impossible; that the cells of the body, having been so changed, as we have seen, are no longer capable of returning backwards along the path they have journeyed; they can only remain where they are, or go yet farther onward in the career of cytomorphosis. Nature, however, has met this difficulty by a way which we have only recently discovered. We are not yet sure that the way we have discovered is the only way, that it is the universal method in the case of all animals for accomplishing the purpose. The discovery of this method of providing for the perpetuation of youthfulness from one generation to another is due to the investigations of Professor Nussbaum, of Bonn.[1] The theory which he put forward has been verified by subsequent examinations and investigation, and confirmed, I am glad to say, in part by some very interesting and careful observations which have been made here in Boston by Dr. F. A. Woods,[2] at that time a member of my laboratory staff. Perhaps the very best confirmation of all is the recent extension of our knowledge in regard to this theory which comes from the investigations[3] of Dr. B. M. Allen, made at Madison, on the perpetuation of germ cells in the developing

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[1] M. Nussbaum, "Ueber die Veränderungen der Geschlechtsprodukte bis zur Eifurchung; ein Beitrag zur Lehre der Vererbung," *Archiv. für Mikrosk Anat.*, xxiii., 155; *cf.* also xli., 119.

[2] F. A. Woods, "Origin and Migration of the Germ-cells in *Acanthias*," *American Journ. of Anat.*, vol. i, p. 307.

[3] Bennet M. Allen, *Science*, vol. xxi., p. 850 (1905); *Amer. Journ. of Anatomy*, vol. v., pp. 79–94; *Anatomischer Anzeiger*, xxix., 217, and xxx., 391; and on the frog, see *Anatomischer Anzeiger*, xxxi., 339–347 (1907).

turtle and frog.[1] It is really essentially a very simple thing. Nature seems to take some of the cells which are in the primitive condition, with the protoplasm still undifferentiated and the nucleus of the embryonic or simple organisation, and hold them apart from the rest of the body; not separating them so that they come off and leave the body, but so that they have a different history, so that they escape the change which the other cells of the body must pass through. These cells of a simpler character, which have been named *germ cells* or *sex cells*, are gathered together, kept asunder for a while from all the other cells of the body, and never allowed to share in the development of the other cells which form the body proper. For instance, Dr. Woods discovered that in the development of the dog-fish, very early, before any organs exist, the germ cells are formed into a cluster (Fig. 62). They lie by themselves, are easily recognised under the microscope, and they have obviously the primitive character which I have endeavoured to explain to you, and which they long retain. Meanwhile, as development progresses, all the remaining cells—all those not part of these clusters—pursue their proper careers, become differentiated; but the cells

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[1] In birds, although closely related to reptiles, the relations are less clear than in turtles. Germ cells in an early stage (chick of two days' incubation with 26–30 primitive segments) occur in the rudiment of the wall of the intestine (splanchnopleure), as they do secondarily in the turtle, and from there migrate during later stages as in the turtle into the sexual glands. Unfortunately their *earlier* history has not been traced. See W. Rubaschkin, *Ueber das erste Auftreten und Migration der Keimzellen bei Vogel-embryonen*, Anat. Hefte. Erste Abth., xxxv., pp. 241–262, Taf. 1–3 (1907).

in the clusters do not change for a long period. Later, as the organs become differentiated, we can recognise in the direct descendants of these cells,

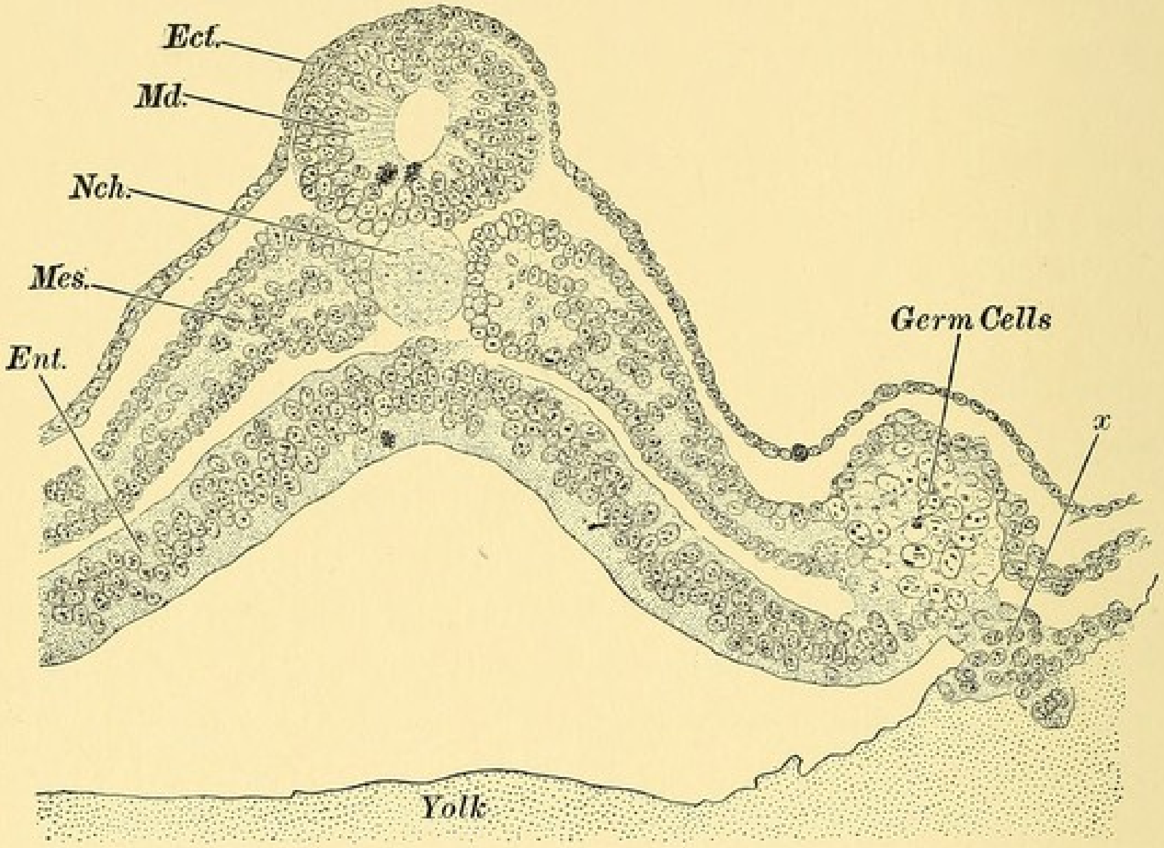

FIG. 62. SECTION ACROSS THE POSTERIOR PART OF AN EMBRYO DOG-FISH (*Acanthias*) of 3.5 *mm.*, to show the compact cluster of germ cells on one side. The germ cells in later stages migrate from this primitive position, moving singly or in small groups. *Ect*, ectoderm; *Md*, medullary canal or primitive spinal cord; *Nch*, notochord; *Mes*, mesoderm; *Ent*, entoderm; *X*, cellular strand connecting the germ-cell cluster with the yolk. (From the Harvard Embryological Collection, Series 463, Section 147. Already figured by Dr. F. A. Woods, but with a lower magnification.)

which have been traced from stage to stage so that their history is known with certainty, those cells which in the adult we call the germ cells, and which are to serve for the reproduction of the species. These cells are set apart at all periods. They represent germinal matter which is withheld from the metamorphosis which the rest of the body undergoes. They have a continuous history. Hence we bestow upon this method, under the conception that it is applied to secure propagation of the species, the term—theory of germinal continuity. It is the theory of hereditary transmission, which I think is now universally held by all competent biologists. Our study of nuclei and of their relations to protoplasm serves to clear up in our minds, it seems to me, to some degree at least, the necessity which really exists for this device of germinal continuity, of the setting apart of certain cells of the rejuvenating sort, of the young sort, of the embryonic type (the term you apply to them matters little), which cells are those used to produce the new offspring of the next generation. All this, of course, fits perfectly with the doctrine which I have been telling you of again and again in this course of lectures, that the progress of differentiation is always in one direction and ends in the production of structure which, if it is pursued to its legitimate terminus, results in the degeneration and death of the cell. Obviously cytomorphosis cannot produce the sort of a cell which is necessary for reproduction.

I wish there were time to enter more fully into the question of the size of nuclei, for there is much which might be said concerning it. This much more, however, ought to be said to you—that the problem of the size of nuclei is by no means a simple one. It has been found, for instance, in the experiments made upon some of the simple algæ, the so-called *Spirogyra*, which every elementary student of botany probably has looked at in the laboratory, that by certain artificial conditions, as made in the experiments of Professor Gerassimow,[1] the size of the nucleus can be changed in the cells, and when the size of the nucleus is changed, the size of the cell alters also. Professor Richard Hertwig has made some very interesting experiments,[2] proving that in the case of certain protozoa, the size of the nucleus varies with the temperature; he says of *Dilepta*, the form experimented on, "Kühle Temperatur veranlasst grosse, warme Temperatur kleine Kerne" (p. 10). We considered a few moments ago the reduction in the size of nuclei during the early stages of the embryonic development. Later, however, there is again an increase of size in the nuclei, occurring during the later embryonic development and during youth. Recently K. A. Heiberg[3] has given some data, from which I have

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[1] J. J. Gerassimow, "Ueber den Einfluss des Kerns auf das Wachsthum der Zelle," *Bulletin Soc. Impér. Naturalistes, Moscou*, 1900, pp. 185–220.

"Die Abhängigkeit der Grösse der Zelle von der Menge ihrer Kernmasse," *Zeitschrift f. allgem. Physiologie*, i., 220–258.

"Über die Grösse des Zellkernes," *Beihefte z. Botan. Centralblatt*, xviii., 45–118.

"Zur Physiologie der Zelle," *Bulletin Soc. Impér. Naturalistes, Moscou*, 1904, pp. 1–134.

[2] Richard Hertwig, "Ueber das Wechselverhältniss von Kern und Protoplasma" (see pages 10 ff.), *Sitzungsber. Gesell. Morphol.*, München, 1902–3.

[3] K. A. Heiberg, "Ueber eine erhöhte Grösse der Zelle und deren Theile bei dem ausgewachsenen Organismus, verglichen mit dem nicht ausgewachsenen,"

calculated the sizes of nuclei. His observations were on the liver and pancreas of white mice. The figures in the table give the average diameters, based in each case on the measurement of fifty nuclei. Professor Hertwig, in the article just referred to, has demonstrated that for each kind of cell there is a characteristic proportion between the nucleus and the protoplasm, so that large cells have large nuclei, and small cells have small nuclei. This conception is certainly most valuable, and if we make the necessary allowance for the change in proportion during cytomorphosis, it seems to be fully justified by the facts. And again, we know that the nucleus provides certain chemical supplies for the life and functioning of the cells. This is very strikingly the case, for instance, in regard to the cells which secrete. These, when they give off the material which they have accumulated in their protoplasm as a preparation for the act of secretion, are found not only to reduce the bulk of their protoplasmic bodies, but the bulk of the nuclei as well. And we know again that the size of nuclei may be changed by somatic conditions, by food supply, so that in every generalisation reached by the study of the size of

|  | New born | Half grown | Full grown |
|---|---|---|---|
| Liver | 5.9 $\mu$ | 6.2 $\mu$ | 8.2 $\mu$ |
| Pancreas | 5.06 $\mu$ |  | 5.75 $\mu$ |

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*Anatomische Anzeiger*, xxxi., 306–311 (1907). It is singular that the author has not reduced his measurements so as to give the absolute dimensions of the nuclei. By supplying this omission I have obtained the values given in the main text.

nuclei, we must be very circumspect, and not fancy too easily that we have reached a safe conclusion unless we have taken into consideration all the possible factors by which the size may have been varied.

In what I have said to you hitherto in regard to the power of growth, I have directed your attention chiefly to the power of growth as it exists in a cell in consequence of that cell's condition. When the cell is in the young state, it can grow rapidly; it can multiply freely; when it is in the old state it loses those capacities, and its growth and multiplication are correspondingly impeded, and if the organisation is carried to an extreme, the growth and the multiplication of the cell cease altogether.

We find, however, that it is not merely a question of the capacity of the cells, but also of the exercise of that capacity, which we must deal with. Here enters a factor of which we learn from the study of regeneration. The phenomena of regeneration are important and very instructive. We shall come to them presently. It will make our study of regeneration clearer, more significant, I think, if we pause for a moment to consider certain fluctuations in the natural development of the organism. We see, for instance, in the brain that early the cells begin to assume the character of nerve cells and that thereafter their multiplication ceases. But, curiously, there will be a spot in the spinal cord, for example, where the change of the cells into nerve cells has not taken place, and from that growth will go on. Cells will migrate from that spot and reach their ultimate destination. When the child is born it is incapable of movement. There is scarcely more than the power of twitching about in a disorderly fashion. Its muscles can contract, to be sure, but any sort of motion that implies a harmonious working together of various muscles, the baby at birth is quite incapable of.

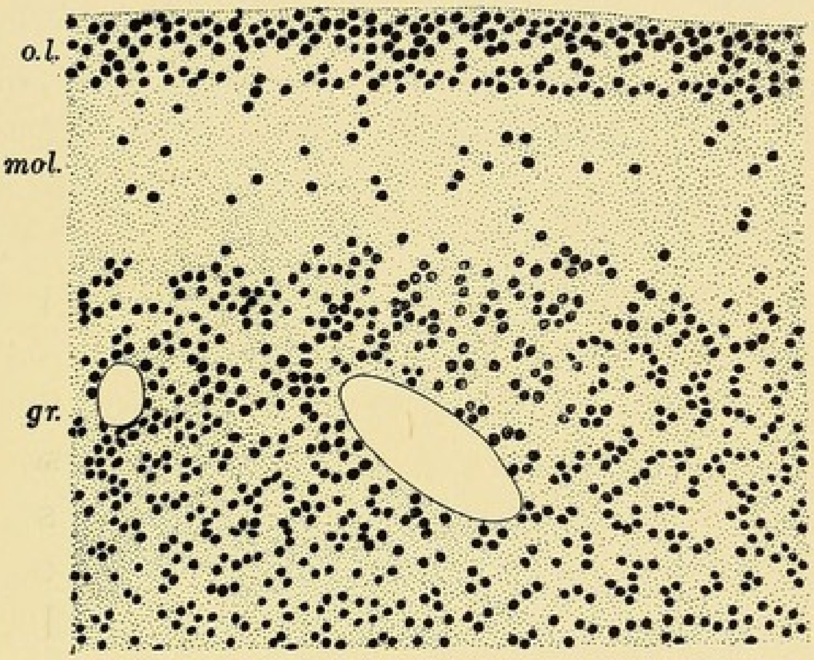

FIG. 63. SECTION OF THE CEREBELLUM OF A CHILD OF THIRTEEN DAYS. Only the nuclei, which are represented as black dots, are drawn. *o. l.*, outer layer, which disappears during childhood; *mol*, molecular layer; *gr*, granular layer. × 120 diams.

This phenomenon is doubtless due to the fact that the cerebellum, the small brain, is as yet imperfectly developed. If we examine the brain of the child at birth, we find at the edge of the cerebellum a line along which the production of new cells is going on. These new cells migrate over the surface of the cerebellum without changing at all into nerve cells. They form a distinct layer, Fig. 63, which is well known to every investigator of brain structure. Soon after birth these cells accomplish a second migration, but in a different direction. Instead of moving in a constant current over the surface of the brain, each one takes a vertical pathway from the surface down towards the interior of the cerebellum ; and arrived there, it changes and becomes a nerve cell, or at least a part of them do ; and with that the machinery of the cerebellum is complete. Thus, structurally, the cerebellum at birth is an uncompleted organ. Now, the cerebellum is that portion of the brain which regulates the combination of muscular movements, which secures what the physiologists term co-ordination of movements, and it is not until the cerebellum has been perfected that it can perform this function. Were there not some provision of this special sort for allowing cells to be produced and added to the brain, the full complexity of the brain could not be attained, because after the cells have begun to change into nerve cells they lose their power of multiplication, and this is a device very exquisite in its working to supply to the brain the number of cells needed to give it its full measure of complexity.

Another instance of the reservation of cells of a simple type is afforded us by the skin, about which I shall have something more to say in a few moments when we speak of the process of regeneration. It is not only in the period of childhood, and not only in the cerebellum, that we find cells exist such as I have just described to you, but it is in other parts of the body also and at other periods of life that we find the like phenomena; and in part I have already referred to these. You remember I told you in a previous lecture that there is always in the body, even at the extreme of life, a store of cells of the young type, which is garnered in the marrow of the bones. The cells in question can multiply, and their descendants in part undergo a change in consequence of which they are converted into blood corpuscles. The undifferentiated or young cells are preserved in the marrow precisely for the purpose of making up the necessary number of blood corpuscles to replace those which are lost either by accident or in consequence of normal physiological processes.

We can speak in more general terms. In the very early stages of the embryo the growth is diffuse, or—as it is sometimes termed technically—interstitial. Of course growth depends upon cell multiplication, and when we say growth is diffuse, we mean that cell division takes place throughout the organ or tissue. For example, in the three germ layers, in a stage preceding the differentiation of organs, we find the mitotic figures (which prove active cell division) to be scattered about. They may occur in any part of each layer. As development progresses the growth becomes in many parts focal, that is to say, there are established centres of growth, at each of which the multiplication of cells proceeds, while in the immediately surround-

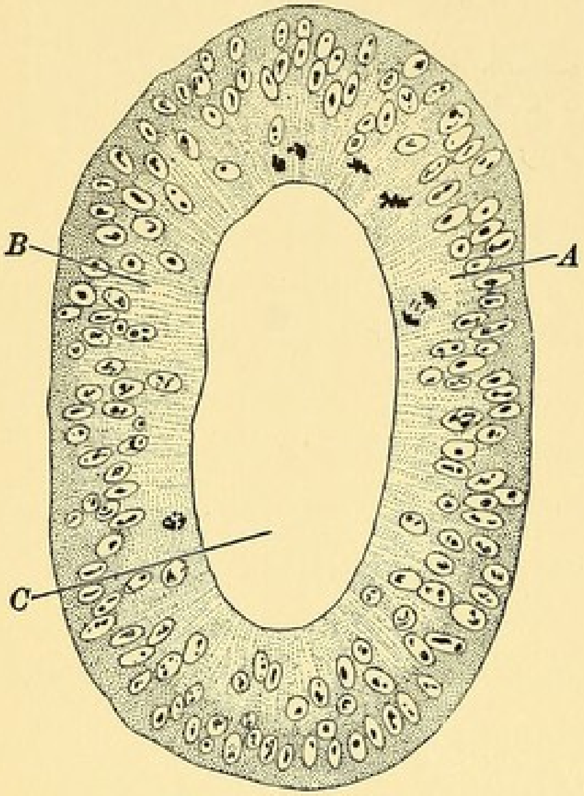

FIG. 64 A. SECTION OF A LENS OF THE EYE OF A CHICK OF 68 HOURS' INCUBATION. *A*, outer or anterior wall; *B*, inner or posterior wall. The dark irregular spots show the distribution of the mitotic figures. *C*, central cavity. 350 diameters.

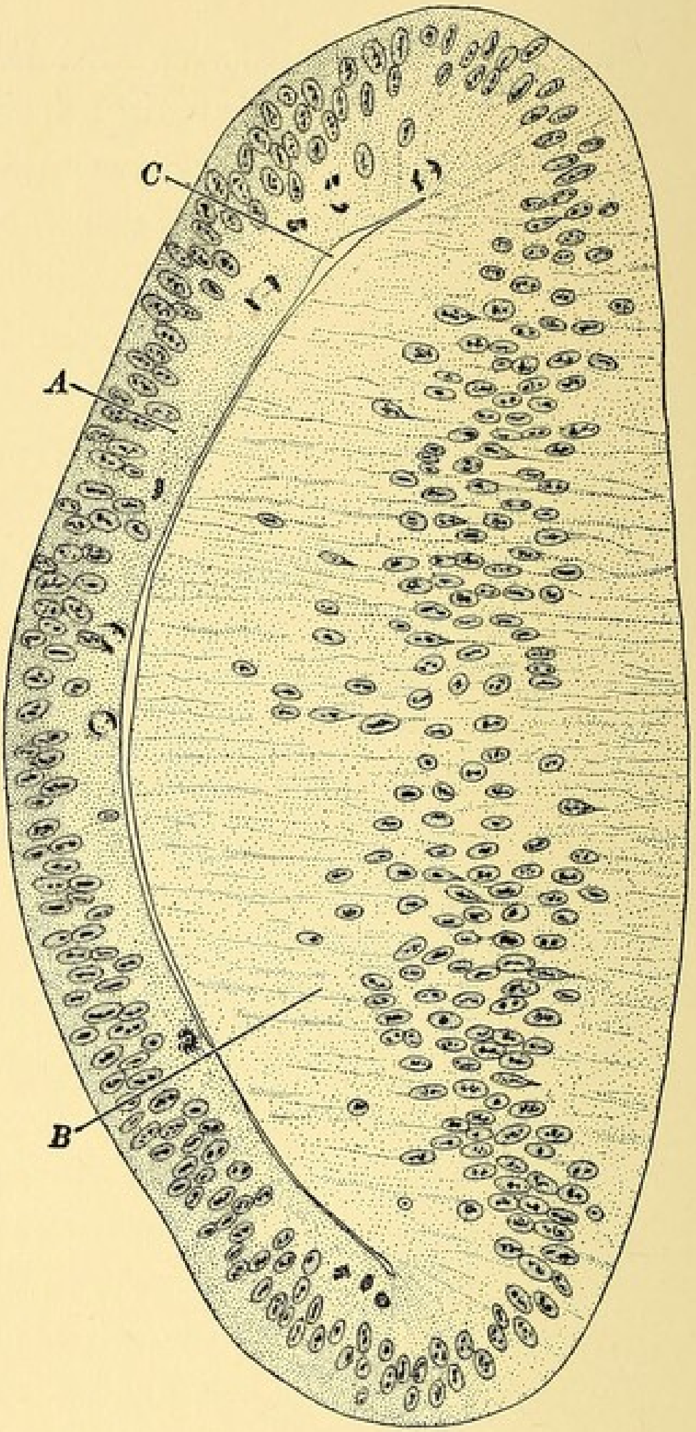

FIG. 64 B. SECTION OF A LENS OF THE EYE OF A CHICK OF 96 HOURS' INCUBATION. *A*, outer wall; *B*, inner wall; *C*, central cavity. The dark irregular spots show the distribution of the mitotic figures. 350 diameters.

ing parts it ceases. In all the cases known to me the cells in the foci of growth are small and embryonic in character, while the surrounding cells, which do not multiply, are larger and more or less differentiated. Fig. 64 illustrates the matter. The drawing on the left, A, represents the beginning (*Anlage*) of the lens of a chicken embryo, as seen in section. The mitotic figures, produced by the dividing cells, are scattered and may occur anywhere. The drawing on the right, B, represents a section of a differentiated but still growing lens. The inner layer, *B*, has completely changed owing to the differentiation of its cells, which have been transformed into lens fibres and no longer multiply. The outer layer, *A*, on the contrary is still undifferentiated and that its cells are still capable of muliplication is evidenced by the mitotic figures scattered through it. The mitotic figures, owing to their deep staining, are conspicuous. The main volume of the structure is formed by lens fibres, each of which is a differentiated cell and has never been found in process of cell division. Only at its edge can the inner layer of the lens acquire new elements; the cells there produced are added to it and give rise to additional lens fibres. In *A*, we observe the lens growing interstitially; in *B*, by apposition. Appositional growth plays many important rôles in the ontogeny of vertebrates.[1] It occurs in the retina, in the enamel organ

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[1] Schaper und Cohen, "Beiträge zur Analyse des thierischen Wachsthume," II. *Theil, Arch. für Entwickelungs-mechanik*, xix., 348–445 (1905). This article gives a clear exposition of the distinction between diffuse, or interstitial, and focal,

of teeth, in the spinal cord, and in many other cases. In all of these instances the focus of cell production might be described aptly as a growth-zone. In many other instances the growth centres are very small. For example, at the root of every hair there is such a centre. The hair grows exclusively at its base; the steady addition of new cells forces the older ones up, lengthening the hair. Every little gland in the stomach and intestines has its own growth centre. Each of the glands in question is a minute tube from one to two millimetres in length, with its orifice (Fig 65), at the inner surface of the digestive tract; the opposite end, or base, ends blindly. We have now before us a picture of a gland from the large intestine of a cat. It is seen in vertical section. The irregularly shaped dark spots, *mi*, represent dividing nuclei, and they are all located near the bottom of the gland.[1] As the new cells are produced the older ones are shoved up towards the orifice and undergo differentiation. After getting to

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or appositional growth. This investigation was one which I suggested to Dr. Schaper, while he was a member of my staff at the Harvard Medical School, and I pointed out to him the difference involved between the two types of growth and the bearing of it on the general notions which I had already formed and in part published at that time. I also called his attention to a number of the specific illustrations which he and Cohen studied. I regret that Dr. Schaper has failed in this paper to mention the actual source of the general conceptions which he has put forward as original with himself. The research by Schaper and Cohen is an excellent piece of work and contains much that is new.

[1] The manner in which intestinal and gastric glands grow was discovered by Bizzozero, "Sulle ghiandoli tubulari del tubo gastro-enterico, etc., Nota prima," *Atti Accad. Sci. Torino*, xxiv., 110–137, Tav. III. (1888). He has also written several subsequent articles,—see especially *Archiv. für mikrosk. Anat.*, xlii., 82–152, Taf. VII.–IX. His observations have been abundantly confirmed by later investigators.

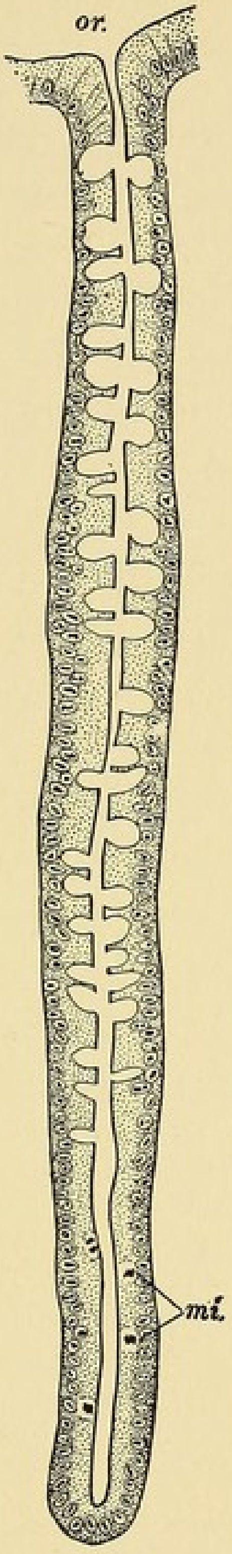

**Fig. 65.** Section of a Gland of the Large Intestine of an Adult Cat. *or*, orifice of the gland, *mi*, dividing nuclei (mitotic figures). 130 diameters..

the top, the cells are cast off. I have already spoken of the enormous loss of cells from the lining of the digestive canal which occurs throughout life.

I could multiply these instances almost indefinitely, but perhaps it will be better to call your attention to an illustration of quite a different sort. We know that in order to have a very complex organisation, the number of cells in the body must be very large indeed. Obviously a small insect, a mosquito or a little beetle, whatever it may be, is not big enough to have a great many cells; and, unless it has a great many, it cannot attain the differentiation of complicated organs such as we possess. Now, the lower animals are born, so to speak, early, and as soon as they hatch out, they have to support themselves. We see that, for instance, in caterpillars. They are born very little creatures, but each tiny caterpillar must take care of itself, obtain its own food, move about to that food, must, when the food is swallowed, digest it, and must carry on the correlated functions of secretion and excretion; it must breathe. In order to do all this the larva, or young caterpillar, to follow our special instance, must have some differentiation already established; but, as we have learned, differentiation impedes growth. In other words, in such a larva the multiplication of cells is held back by the very demands of the condition of its existence. If it is to have organs which are to function, it must have differentiated parts, and, if it is differentiated, its growth power must be sacrificed.

How has nature proceeded in order to produce a higher type of animal, one in which the number of cells is much greater? Very ingeniously. She provides the developing organism with a food supply which it carries itself. If, for instance, you recall the egg of the salamander, which I showed you upon the screen, you will remember that that is a structure of considerable size, and its size is due to the accumulation of food material, material which we designate by the term *yolk granules*, which lie in the living protoplasm of that germ. This supply of food is so great that it will last the organism a considerable period. While it is growing it has nothing to do but to digest that food supply which it already possesses. It does not have to exert itself to obtain it, and no further digestive process is necessary than that inherent in all living protoplasm. So the young salamanders develop under most advantageous conditions, and can actually produce a much greater number of cells because it is possible, with this internal food supply, for the growth to go on only with the cells of the embryonic or youthful type for a considerable period, and then, when their number has considerably increased, steps in the process of differentiation.

In the higher animals the accumulation of food for the nourishment of the germ is carried yet further. As you know, the egg of the bird is much bigger than that of the salamander. Again, in the highest animals, in the placental mammals, there are other special contrivances which nature has introduced to secure ample and adequate nourishment of the developing germ. By means of the placenta the uterine period has been lengthened, and the embryo is nourished at the expense of the mother with little physiological exertion on its own part. Moreover, in all mammals lactation and maternal care serve to further prolong the developmental period. By these means the protective processes have been wonderfully perfected and the result is that in mammals there is a long period during which the production of cells goes on; the cells at first all remain relatively simple, and by the time they begin to change the number of cells is so great that the possibilities of an almost infinite variety of peculiarities in them are given. There are cells enough to allow this variety to be worked out. This type of development we call the embryonic. We know, therefore, that nature has recognised a restriction which she herself has put upon development, the restriction which obliges development, if it is to be ample, to prolong the accumulation of the undifferentiated cells. In response to this condition, she has instituted for higher types of animals that development which we call embryonic, leaving for the lower types that development which we call larval.[1] Thus we meet in the growth and formation of the higher animals, and in the history of the comparative develop-

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[1] The comparison between the larval and embryonic types of development was first made by me in 1895, "Ueber die Vererbung und Verjüngung," *Biologisches Centralblatt.*, xv., 571–587; translation in *American Naturalist*, xxx., 1–9, 89–101.

ment of the animal kingdom, fresh illustrations of the great importance of the young type of cells.

We can learn the same thing from the study of regeneration. The regenerative process depends to a large extent upon partial differentiation, or even upon its total absence. Regeneration is a most interesting and wonderful process. I took pains only this afternoon to look at that famous classic by Trembley[1] on hydroids, or polyps as he called them. *The Fresh-Water Polyps*, a book published in 1744, was well printed, and on such good paper that it looks to-day almost like a new book. He performed the curious experiment of cutting one of these minute fresh-water polyps—they are perhaps an eighth of an inch long—in two, and made the startling discovery that each half of the polyp would make up what the other half had deprived it of; each half, in other words, would become a new polyp. That which was lost was regenerated. After him came a series of yet more remarkable experiments by the famous Italian naturalist, Spallanzani, one of the masters of experimental research, and he discovered that regeneration was a property which was not peculiar by any means to polyps, but existed in the

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[1] *Mémoire pour servir à l' histoire d' un genre de polypes d' eau douce à bras en forme des carnes*, par A. Trembley, de la Société Roiale, à Leide, MDCCXLIV., 4to, pp. xvi., 324; 13 plates. A German translation by J. A. E. Goeze was published at Quedlinburg in 1775.

Abraham Trembley was born at Geneva, Switzerland, in 1700 and died there in 1784. His famous experiments were made in Holland while he was engaged as a tutor in the family of Count Bentinck.

earthworm, and even among vertebrates ; for he it was that proved that if the head of an earthworm be cut off, the worm will form a new head, with a new brain and a new mouth.[1] He first discovered that if you cut off the tail or the leg of a salamander, a new tail, or a new leg, as the case may be, would grow out. He also made similar experiments on the regeneration of the tail in tadpoles. He it was, moreover, who discovered that this power of replacing the lost part is greater in the young—greater in the earlier stage than in the later. These examples may

FIG. 66. VIGNETTE FROM TREMBLEY'S CLASSIC MEMOIR, representing Trembley making his experiments on regeneration in fresh-water polyps.

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[1] Lazaro Spallanzani, *Prodromo di un opera da imprimersi sopra le reproduzione animali*, 8vo, Modena, pp. 102, 1768. (French translation by de la Sabionne, Geneva, 1768. English translation, *An Essay on Animal Reproductions*, 8vo, London, 1769, pp. 86. The "Prodromo" has been republished in volume four of Spallanzani's *Opere Scelte*.)

suffice to indicate to you the nature and process of regeneration.

We have many kinds of regeneration; we may have that of the single cell or that of the whole organism. Let us consider first unicellular regeneration, and accordingly we pass to the examination of the next of our slides, which represents a creature of the kind called *Stentor*, Fig. 67. It is a single cell. The nucleus of the cell has a singular form, for it consists of nine bead-like enlargements, with the parts between constricted to mere delicate connecting

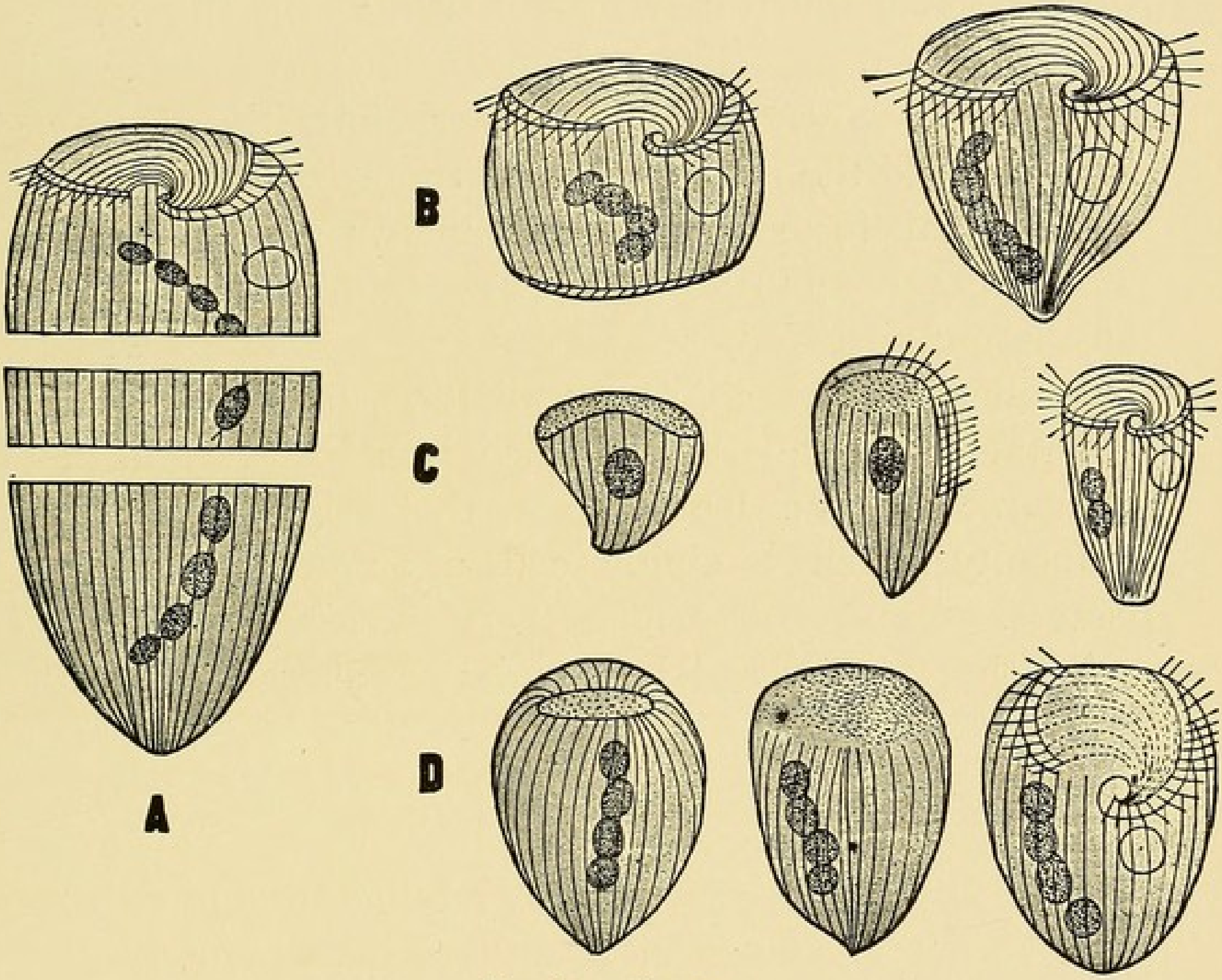

FIG. 67. *Stentor*.

threads; its protoplasmic body is large, and something of its structure I have told you in a previous lecture. A German investigator, Professor Gruber, has succeeded in dividing one of these Stentors, a unicellular creature, animalcule, common in fresh water, into three parts, in such a method of cutting as is illustrated by the figure on the left. Each of the three parts restored itself and became a complete *Stentor*. In such experiments the protoplasm around the nucleus begins to grow; gradually the original form is again assumed; the creature grows larger and larger, until each piece acquires the parent size, and, so far as we can see with the ordinary microscopic examination, identically the parental structure. That which was lost has been regenerated. We learn, then, that regeneration is a faculty which a single cell, a single unit, may possess.

Another example of unicellular regeneration is offered us by nerve fibres. A nerve fibre is a thread-like prolongation of a nerve cell (neurone) and is of course a part of the cell, as much so as the protoplasmic body immediately surrounding the nucleus. When a nerve is cut across, as happens, for instance, necessarily in every surgical operation, the nerve fibres are severed. The part which is separated from the central cell dies by a degenerative process, the part which is connected with the cell, on the contrary, may grow and elongate itself. In other words, the cell regenerates the part which it lost, just as a salamander may regenerate its lost tail. By the growth of nerve fibres a whole nerve may be regenerated, a fact which is often of the utmost practical medical and surgical importance. Many researches upon the regeneration of nerves have been made, and some questions about it are still subject to dispute, but I have confined myself to such statements as seem to me beyond controversy.

Our next picture demonstrates a similar phenomenon. It represents muscle fibres which have been injured. Every muscle fibre contains in its interior its contractile substance, the fibrils, in regard to which I have already spoken to you ; but it also contains a certain amount of substance which is still undifferentiated protoplasm. Now when a muscle fibre of this sort is injured, we find that the muscular structure, properly so-called, will in many cases quite disappear, but then the protoplasmic material, which is the undifferentiated substance, will begin to grow and the nuclei will begin to multiply, *a*, *b*. This may happen at the end of a muscle fibre—*e*, *f*—producing there a considerable mass of protoplasm, with nuclei multiplying in it ; or we may find a chain of nuclei, each with its separate protoplasmic body, *b ;* such nuclei will multiply. When the increase of the undifferentiated protoplasm has gone on far enough, the injured muscle will produce again the muscular substance proper—the contractile fibrils. Muscular fibre, in other words, can be regenerated by itself, but only by the growth of its undifferentiated portion ; the fibrillated or differentiated portion of a muscular fibre has no regenerative power.[1]

Let us re-examine another figure, Fig. 69. Here is represented the lining layer of the œsophagus with the cells composing it, the upper ones being horny, the lower ones those which are capable of active growth. We are rather dull. We do not often stop to think about things. We buy a new horse which

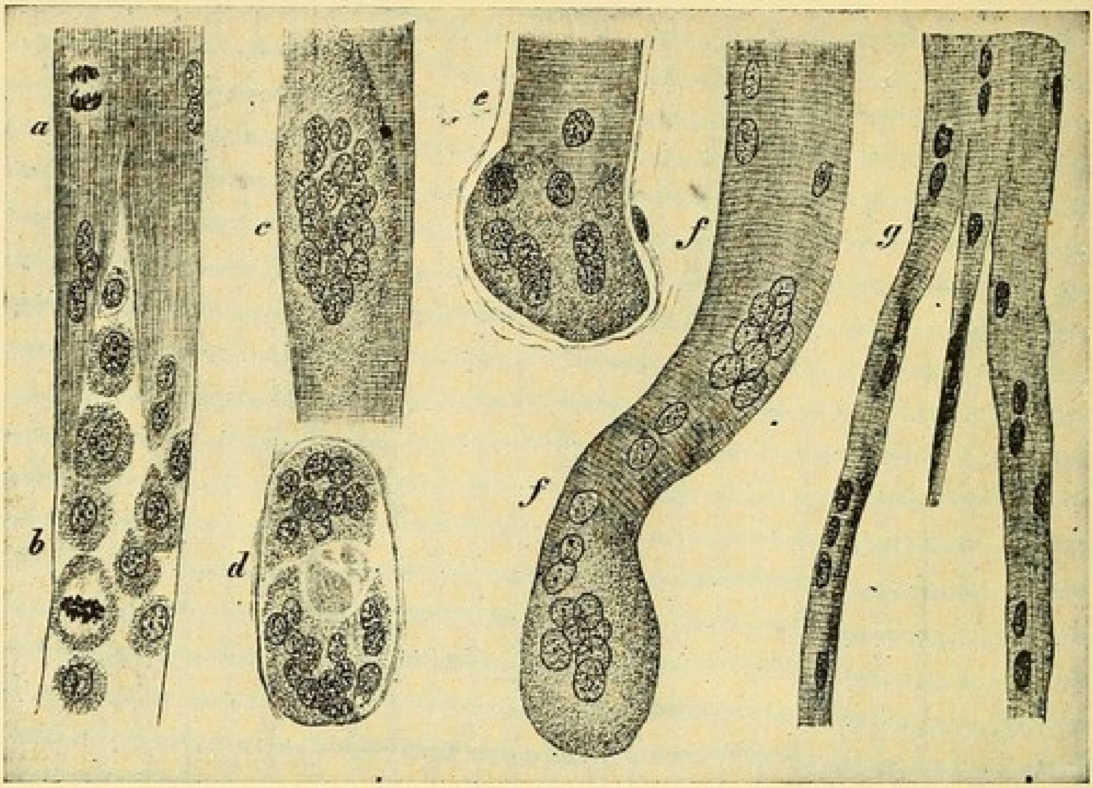

FIG. 68. STRIATED MUSCLE FIBRES IN PROCESS OF REGENERATION. *a*, *b*, three days after rupture of the muscle; *c*, eight days after rupture; *d*, 26 days; *e*, 10 days; *f*, 21 days; *g*, 43 days.—After Ernst Ziegler. × 350 diameters.

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[1] The regeneration of muscle fibres has been studied hitherto mainly by pathologists, for in the higher animals muscular regeneration occurs chiefly as the sequel of injury to the muscle fibres, injury either mechanical or from pathological causes, as, for example, in abdominal typhus. The literature of the

comes from the country and has never seen a train; drive him to the station, and are frightened, perhaps, because the horse himself is so much alarmed—possibly have a narrow escape because of the excitement which his first sight of a train causes him. But the same horse, after a few months' discipline, will scarcely

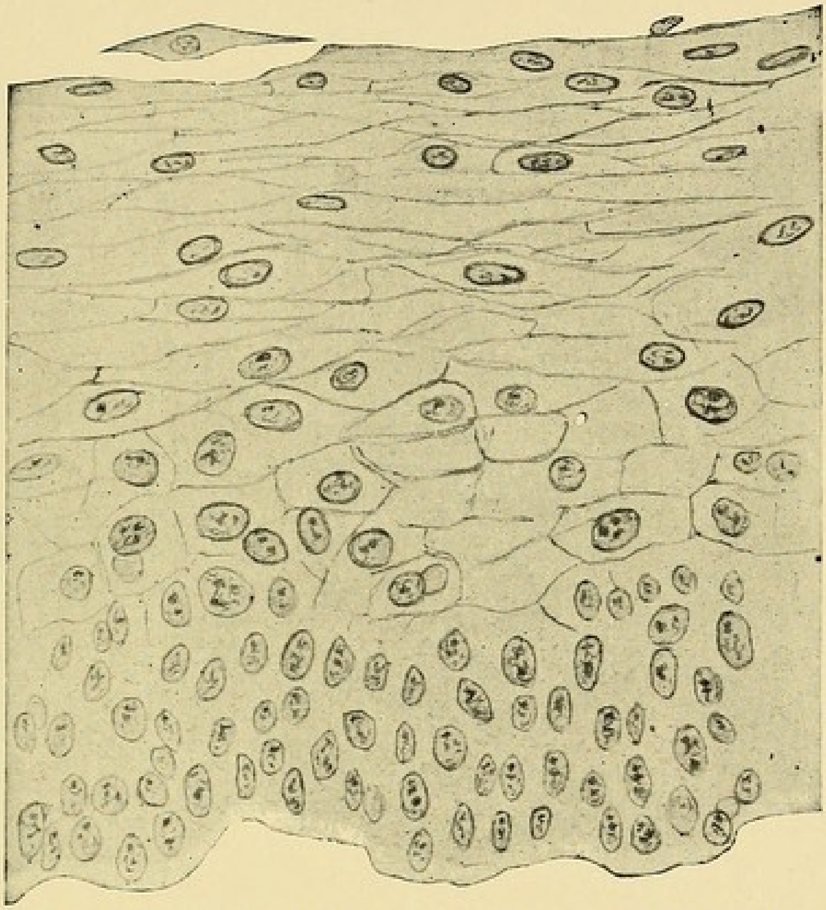

FIG. 69. SECTION OF THE EPITHELIAL LINING OF THE HUMAN ŒSOPHAGUS.

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subject is quite extensive; nearly sixty articles are known to me. I select the following, by consulting which access to the remaining literature may be had:

W. Waldeyer, "Ueber die Veränderung der quergestreiften Muskelfasern bei der Entzündung und beim Typhusprocess, sowie ueber die Regeneration derselben bei Substanzdefekten," *Virchow's Archiv f. Pathol.*, xxxiv, 473, 1865.

turn his ear, much less his head, to inspect the train which a short time before so frightened him and held his attention that nothing else could get into his mind save the fright the train gave him. So we, too, act a good deal like the horse. We see a thing the first time and it surprises us; the next time it seems like an old acquaintance, a thing familiar and therefore unregarded. I say this apropos of the skin. How many of you have thought what the lesson of the skin is in regard to the power of growth? Spring is coming; we shall soon be taking to our boats, rowing or canoeing, and the first day we do so doubtless we shall have blisters upon our hands, and the outer part of the skin, raised by the blister, will probably fall off and be lost altogether. The softer underlying skin will be exposed, will be sensitive and uncomfortable for a while, but soon the cells behind the surface will assume a horny character, the cells underneath will grow and multiply, and presently the wound will be healed over. Did you ever stop to think that that means that there is a reserve power of growth in

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P. Fraisse, *Die Regeneration von Geweben und Organen bei den Wirbelthieren*, Berlin, 1885.

Nauwerck, *Ueber Muskelregeneration nach Verletzungen*, *Jena, 1890.*

R. Volkmann, "Ueber die Regeneration des quergestreiften Muskelgewebes beim Menschen und Säugethier," *Ziegler's Beiträge Pathol.*, xii., 233, 1893.

E. Ziegler, "Ueber die Reparation verletzter Gewebe," *Deutsche med. Wochenschrift*, 1900, p. 783.

Alex. Schmincke, "Die Regeneration der quergestreiften Muskelfasern bei den Wirbelthieren. Eine vergleichend pathologische Studie. I. Ichthyopsiden," *Verhandl. Phys.-med. Gesellschaft Würzburg, N. F.*, xxxix., 15–130, Tafel I., II. (Gives an exhaustive review of previous investigations.)

the skin all the time? always ready to act, to come forward, waiting only for the chance, and that there is besides something which keeps it in, which holds it back, which stops it? We call this stopping physiological function—inhibition; we say that the growth of the skin is inhibited; though in the deep part of the skin all the time there are the cells ready to grow as soon as that power of inhibition is taken away, while it is active they will not grow. The simple blister tells us all that. There is, then, a power of regulation which expresses itself in this inhibitory effect. When a salamander has its tail cut off by the experimenter and the new tail grows, just enough is produced. The new tail is like the old. The tissues grow out until the volume of that which is lost is replaced, and then they stop. But if the tail should be cut off again, regeneration would occur again. The experiments may be repeated many times over. It indicates to us that always the growing power is there, but it is held in check. What that check may be is one of the great discoveries we are now longing for. The discovery, when made, is likely to prove of great practical importance. The phenomenon of things escaping from inhibitory control and overgrowing is familiar. Such escapes we encounter in tumors, cancers, sarcoma, and various other abnormal forms of growth that occur in the body.[1] They are due to the inherent growth

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[1] A semi-popular exposition of this view regarding malignant tumors has been published by V. Dungern and R. Werner, *Das Wesen der bösartigen Geschwülste. Eine biologische Studie*, 8vo. pp. 159, Leipzig, 1907.

power of cells kept more or less in the young type, which for some reason have got beyond the control of the inhibitory force, the regulatory power which ordinarily keeps them in. No picture of the growth or development of the living animal would be complete if it confined its attention only to the power of growth in relation to cytomorphosis. It must also include the contemplation and study of the regulatory power of the organs. Experiments are being made in many places, minds are at work in many laboratories upon this problem of the regulation of structure and growth. Much is to be hoped from such researches; not merely insight into the normal development, but insight also into the abnormal. Nothing, perhaps, is more to be desired at the present time than that we should solve the mystery of the regulatory power which presides over growth. It would be of immense medical importance. Could we understand it, and could we from our understanding derive some practical application of our scientific discoveries in this field,--in other words, could we learn to regulate the formation and growth of tumors,—we should say of it justly that it was as noteworthy a contribution to medical knowledge as the discovery of the germs of disease, and would doubtless prove equally beneficial to mankind. Although, then, the study which I have been laying before you must necessarily seem in many respects abstruse and far away from practical applications, we learn that it is not really so, and that it leads by no very remote path to the consideration of problems the useful applications of which are immediately obvious to every one.

We find in the process of regeneration of organs or parts of the body that it is always the young cell which plays the principal part. This is beautifully illustrated in the picture upon the screen, Fig. 70. There is a little creature, which many of you have seen in the garden, consisting of joints, which rolls itself up into a little ball, and therefore is often called the "pill-bug." It is not, however, an insect or a bug, properly so-called, but belongs to a family of crustaceans. It has on its head a little feeler which we call the antenna. The particular kind of arthropod, the antenna of which has been studied and drawings of it made to furnish us this plate, is known by the name of *Oniscus*. In his researches the experimenter, Dr. Ost,[1] cut off the antenna in the middle of a joint and found that it rapidly healed over. Here are pictured the stages of the progressive restoration. Part of the antenna has been cut off in this case; the wound was healed over here, No. 1, *a*, the new tissue has begun to grow, No. 2, *b*, and the cells at this point are very simple in character. They spread out and grow, and then, within the interior of the hard shell of the feeler, a retraction of the substance occurs, and the new growing cells within this space gradually begin to shape themselves out, No. 3, *b*, and we see presently an accumulation of cells which is assuming

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[1] Ost, J., "Zur Kenntniss der Regeneration der Extremitäten bei den Arthropoden," *Archiv f. Entwickelungsmechanik*, xxii., 289–324, pls. x–xii.

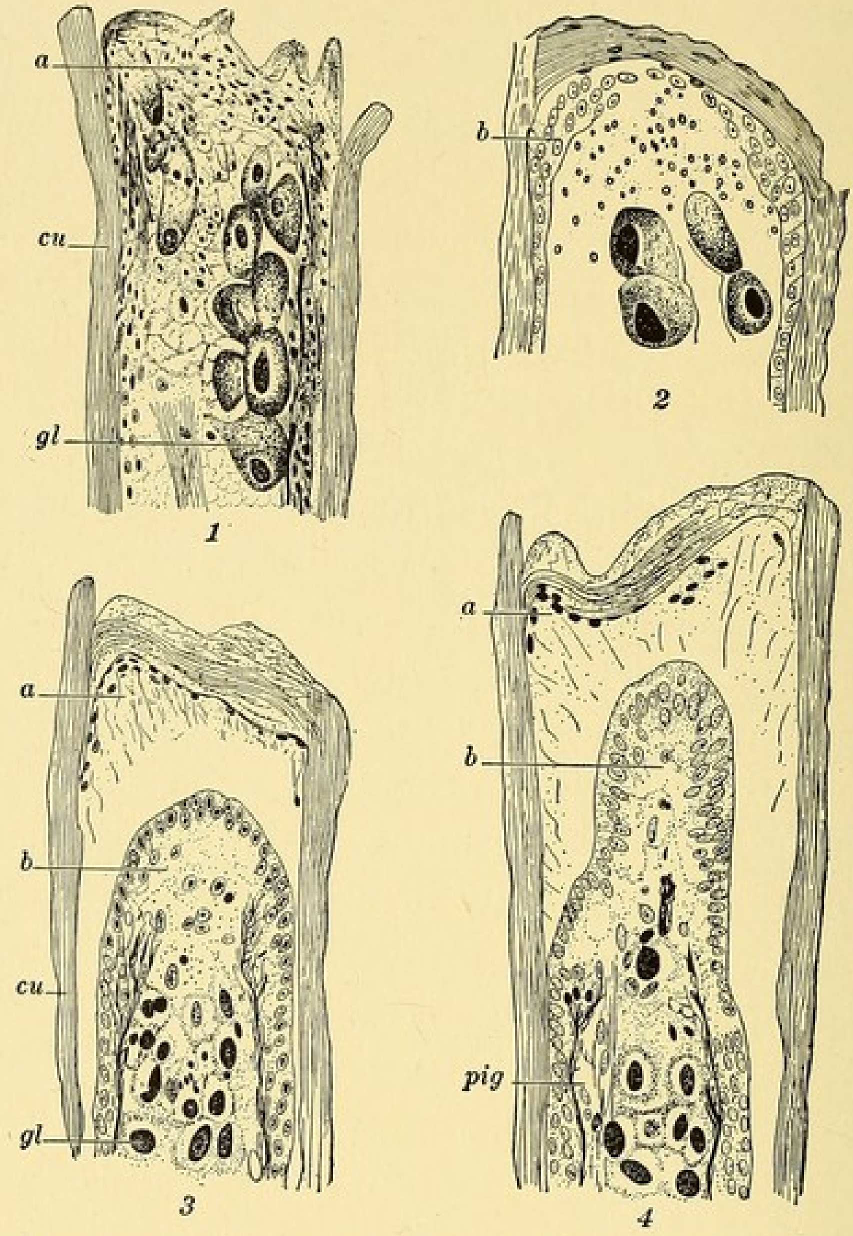

Fig. 70. Longitudinal Sections through the Antenna of *Oniscus* in Various Stages of Regeneration after Amputation.—After Ost.

*a*, cicatricial tissue; *b*, regenerated tissue; *cu*, cuticula, or outer shell; *gl*, glands; *pig*, pigment. Magnified.

a definite form, No. 4, *b*, that in the next figure has clearly become the promise or beginning of a new terminal joint, Fig. 71, which will become free when at the next moult the old shell or cuticle is cast off. The minute study of this process has shown that the regeneration depends practically exclusively upon the cells of the young type, and that after they have grown out and accumulated here in this manner, No. 3, *b*, some of them undergo differentiation, becoming muscle cells; others change in the manner indicated here, No. 4, where we see a commencing alteration of the nuclei, which is further accented in Fig. 71, and leads to such a grouping of the cells that the glands, which were originally present there, are also reproduced. The regenerative process, then, clearly illustrates to us, from another point of view, the great importance of the young type of cells.

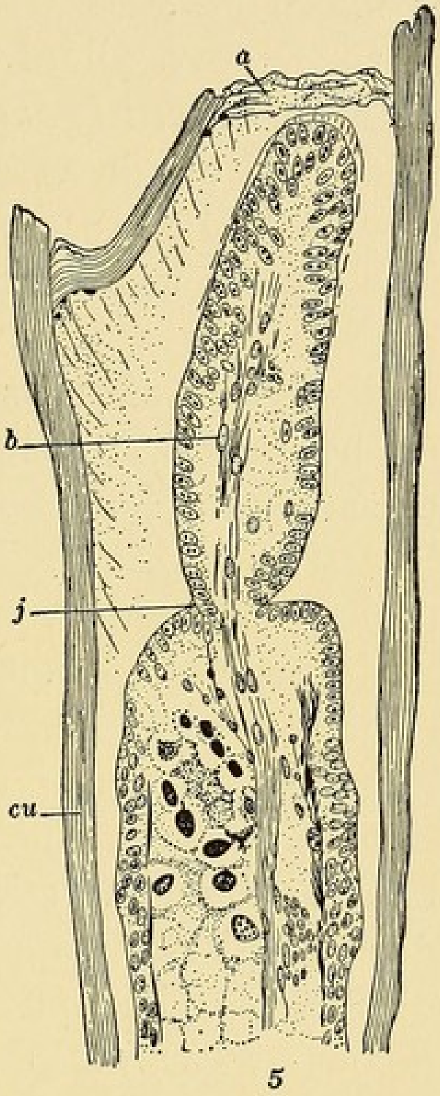

FIG. 71. SECTION THROUGH A REGENERATING ANTENNA OF *Oniscus*.—After Ost. Advanced stage, in which the young new joint is already shaped within the old shell. *a*, cicatricial tissue; *b*, regenerated tissue; *j*, new joint; *cu*, cuticula (old shell). Magnified.

The eyes of crabs and related animals (*Decapoda*) are born on stalks. If these stalks are cut partly off so as to remove all of the eye, but leave part of the nervous centre (*ganglion*) in the base of the stalk, it is found that in a considerable percentage of cases a new eye will be formed. Miss M. I. Steele[1] has made a study of this regeneration. She states that the healing over of the wound and the growth of the undifferentiated cells of the outer layer (ectoderm or hypodermis) occurs much as just described for the antenna of *Oniscus*. Later the hypodermal cells lose their primitive and simple character and by passing through various but co-ordinated differentiations evolve new complete *ommatidia*, as the structural units are termed which constitute the eye in crabs and other crustacea. It may interest you to know that if the whole or nearly the whole eye-stalk be cut off, regeneration may still take place, but if it does a feeler-like appendage or antenna results, without any special optic apparatus. This singular phenomenon was first observed by Professor Herbst.[2]

One of the interesting illustrations of the importance of undifferentiated cells is afforded, according to recent observations, by certain worms of lowly organisation, known as planarians. The space between the organs of one of these animals is occupied by a low form of connective tissue,—a syncytium termed the

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[1] Mary Isabelle Steele, "Regeneration in Compound Eyes of Crustacea," *Jour. Exp. Zool.*, v., 163–244, 16 pls. (1907).

[2] C. Herbst, *Arch. f. Entwickelungsmechanik*, ii., 455–516 (1896). See also Bd. ix., 215–293 (1900).

mesenchyma,—scattered about in which are free simple cells,[1] which are referred to by recent authors as "parenchymal" or "formative" cells. Now if the head or tail of a planarian be cut off, the part lost is regenerated. The regeneration is effected not by the growth of the old tissues, each producing of its own kind, but chiefly (perhaps wholly) by the multiplication and differentiation of the "formative" cells which, after migrating to where they are needed, produce outer skin (epidermis), intestine, muscle, etc. They constitute a store of undifferentiated cells, ready to enter upon various active differentiations when occasion arises.

There is a marine animal called *Ciona:* it belongs to the class of the Ascidians. Professor Jacques Loeb[2] discovered in 1892 that if the portion of the animal containing the nerve ganglion, or rudimentary brain, be cut out, it will be regenerated, and a new brain formed. This discovery was confirmed by Pio Mingazzini,[3] a gifted Italian zoölogist whose early death we lament. Recently, L. S. Schultze[4] has shown

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[1] So far as known to me these cells were first described by H. N. Moseley ("On the Anatomy and Histology of the Landplanarians of Ceylon." *Philos. Transactions*, 1874, p. 105). J. Keller in 1894 (*Jena'ische Zeitschr. f. Naturwiss.*, xxvii., 371–407) demonstrated their rôle in regeneration. Keller's interpretation has been confirmed by W. C. Curtis (*Proc. Boston Soc. Nat. History*, xxx., pp. 515–559) and Miss N. M. Stevens (*Arch. f. Entwickelungsmechanik*, xxiv., 350–373, 1907). The cells are of the embryonic type, that is to say, without any specialisation or differentiation.

[2] J. Loeb, *Untersuchungen zur Physiologischen Morphologie*, 1891–92.

[3] P. Mingazzini, "Sulla regenerazione nei tunicati," *Boll. Soc. Naturalisti*, Napoli, v. (1891.)

[4] L. S. Schultze, "Die Regeneration des Ganglions bei Ciona intestinalis, L.,

that the regeneration is accomplished by the growth of undifferentiated cells, which subsequently undergo differentiation.

The cases of regeneration which we have reviewed are all connected with the repair of injuries. But there are also cases known of spontaneous and normal regeneration, as they might be called. For example, there are certain fresh-water jointed worms, annelids, which produce in the midst of their body from time to time a budding zone, a narrow band of tissue intervening between two segments. The anterior part of the zone forms a new tail for the anterior part of the worm, the posterior part of the zone forms a new head for the posterior part of the worm ; division follows, and thus out of one worm two are produced. The external features of this wonderful process were described very well indeed in 1771, by the celebrated naturalist O. F. Müller.[1] It was reserved for Carl Semper,[2] under whom I had the honour to study in 1875–76, to demonstrate, at that very date, that the cells of the budding zone are of the embryonic type, and that after having multiplied sufficiently they begin to differentiate into the tissues

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und über das Verhältniss der Regeneration und der Knospung zur Keimblattlehre," *Jena'ische Zeitschrift*, xxxiii., 263–344, Taf. XII., XIII. (1899). For our present purposes it is a matter of regret that on the cytological side Schultze's observations leave much to be desired.

[1] O. F. Müller, *Naturgeschichte einiger Wurmarten des süssen und salzigen Wassers*, Kopenhagen, 1771.

[2] Carl Semper, " Die Verwandschaften der gegliederten Thiere, III." *Semper's Arbeiten*, Zool. Zootom. Inst. Würzburg, iii., 115. See especially p. 161 *ff*.

necessary to complete the new tail and the new head. Through Professor Semper's kindness I had the privilege of seeing many of his preparations, and can therefore speak with confidence about his results.

This completes the evidence which my time permits me to lay before you in order to convince you that the young type of cells really is physiologically and functionally important, that it really does possess the power of growth that I have attributed to it.

We will pass now to another part of our subject, with which the lecture will close. Age represents the result of a progressive cytomorphosis. We have learned that of cytomorphosis death is the end, the culmination. It is a necessary result of the modification and change of structure which goes on in every individual of our species and of all the higher animals. We are familiar with the death of cells. It occurs constantly and, as I have endeavoured to explain to you, it plays a great part in life. It promotes the performance of various functions which are of advantage to the body as a whole, which could not be accomplished without the death of some cells. But the death which we have in mind when we speak ordinarily of death is something different from this. It is the death of the whole. But even the death of the whole has its strange complications. A great deal of our knowledge of the functioning of the body is due to the fact that the parts do not die when, as we commonly say, the body as a whole, the individual, is dead. The organ is alive and well. One of the most impressive sights which I have ever seen has been the sight of the heart of a quadruped, a dog, continuing to beat after it had been taken out from the body. The dog was dead—the rest of the body was dead—but the heart lay upon the physiologist's table, beating. The experimenter could supply it with the necessary circulation. He could give stimuli to it, and under these favourable conditions make important discoveries in regard to the functioning of the heart. So, too, I myself made experiments upon a muscle once part of a living dog, separated entirely from the parent body, supplied with its own artificial circulation, and from those experiments was able to discover some new unexpected results in regard to the nutrition of the muscle, and the changes which chemically go on in it.[1] This over-living, then, of the parts of the body, their separate life, is something which we must familiarise ourselves with, and the great importance of which we must carefully acknowledge, for much of the benefit which the medical practitioner is able to render to us and to our friends to-day is due to the knowledge which has been derived experimentally from the study of the over-living or surviving parts of a body which as a whole was dead.

Death is not a universal accompaniment of life. In many of the lower organisms death does not

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[1] Charles S. Minot, "Die Bildung der Kohlensäure innerhalb des ruhenden und erregten Muskels," *Ludwig's Arbeiten der Physiol. Anstalt*, Leipzig, xi., 1–24 (1876).

occur, so far as we at present know, as a natural and necessary result of life. Death with them is purely the result of an accident, some external cause. Our existing science leads us therefore to the conception that natural death has been acquired during the process of evolution of living organisms.[1] Why should it have been acquired? You will, I think, readily answer this question, if you hold that the views which I have been bringing before you have been well defended, by saying that it is due to differentiation,[2] that when the cells acquire the additional faculty of passing beyond the simple stage to the more complicated organisation, they lose some of their vitality, some of their power of growth, some of their possibilities of perpetuation; and as the organisation in the process of evolution becomes higher and higher, the necessity for change becomes more and more imperative. But it involves the end. Differentiation leads up, as its inevitable conclusion, to death. Death is the price we are obliged to pay for our organisation, for the differentiation which exists in us. Is it too high a price? To that organisation we are indebted for the great array of faculties with which we are endowed. To it we are indebted for the means of appreciating the sort of world, the kind of universe, in which we are placed. To it we are in-

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[1] On death among Protozoa see Appendix No. III.

[2] The theory that natural death is the incidental result of cellular differentiation was first put forward by me in 1885; compare *Proceedings American Association Adv. Science*, vol. xxxiv., p. 311.

debted for all the conveniences of existence, by which we are able to carry on our physiological processes in a far better and more comfortable manner than can the lower forms of life. To it we are indebted for the possibility of those human relations which are among the most precious parts of our experience. And we are indebted to it also for the possibility of the higher spiritual emotions. All this is what we have bought at the price of death, and it does not seem to me too much for us to pay. We would not, I think, any of us, wish to go back to the condition of the lowly organism, which might perpetuate its own kind and suffer death only as a result of accident, in order that we might live on this earth perpetually; we would not think of it for a moment. We accept the price. Death of the whole comes, as we now know, whenever some essential part of the body gives way—sometimes one, sometimes another; perhaps the brain, perhaps the heart, perhaps one of the other internal organs may be the first in which the change of cytomorphosis goes so far that it can no longer perform its share of work and, failing, brings about the failure of the whole. This is the scientific view of death. It leaves death with all its mystery, with all its sacredness; we are not in the least able at the present time to say what life is, still less, perhaps, what death is. We say of certain things—they are alive; of certain others—they are dead; but what the difference may be, what is essential to those two states, science is utterly unable to tell us at the present time. It is a phenomenon with which we are so familiar that perhaps we do not think enough about it.

In the next lecture there will be some other general aspects of our subject to present to you, and a formulation of the general conclusions toward which all the lectures have aimed.

# VI

## THE FOUR LAWS OF AGE

*LADIES AND GENTLEMEN:* I have referred in these lectures repeatedly to the cell and its two component parts, the nucleus and the protoplasm. To-night I shall have only a few references to make directly to these, and shall pass on for the latter part of the hour to another class of considerations bearing upon the problem of age. Before we turn to these new considerations, however, I wish to say a few words by way of recapitulation concerning the changes in the cells as corresponding to age. Cells, as you know from what I have told you, undergo in the body for the greater part a progressive change which we call their differentiation. We may say that there are four kinds of cells for purposes of an elementary classification to be used in a simple exposition like the present. The first kind are those cells of the young type, in which the protoplasm is simple, and shows as yet no trace of differentiation. These cells are capable of rapid multiplication, and some of them are found still persisting in various parts of the adult body, and serve to maintain the growth of the body in its mature stage. Another class of cells presents to us the curious spectacle of a partial differentiation; such are the muscle fibres by which we accomplish our voluntary movements. These fibres consisted originally only of protoplasm with the appropriate nuclei, but, as they are differentiated, part of the protoplasm changes into contractile substance. Another part remains pure protoplasm unaltered. If now the muscular or contractile portion of the fibre be destroyed, the undifferentiated part of the protoplasm then shows that it has still the power of growth. It has only been held back by the condition of organisation, and we perceive in the regeneration of these fibres evidence of the fact that so long as the protoplasm is undifferentiated it has the power of growth, which, however, does not reveal itself unless an opportunity is afforded. Third, we come to the cells which are moderately differentiated; such, for instance, are the cells of the liver, and if for any reason a portion of the liver be injured by accident or disease, we find that these partially differentiated cells reveal at once that they have a limited power of growth still left. If we pass on to the fourth class, that in which differentiation is carried to the highest extreme, we find that the cells do not have the power of multiplication. Such are the nerve cells by which the higher functions of the body are carried on. They represent the extreme of cellular differentiation, and almost never do we see these cells multiplying after the differentiation is accomplished. Presented in this form, we then recognise, it seems to me clearly, the effect of differentiation upon the growth of cells. The facts are clear as to their meaning.

We can, however, proceed a little farther than this, because we can actually ascertain, approximately at least, the rate at which cells multiply. We accomplish this by determining the *mitotic index*. The mitotic index is the number of cells to be found at any given moment in the active process of division out of a total of one thousand cells.

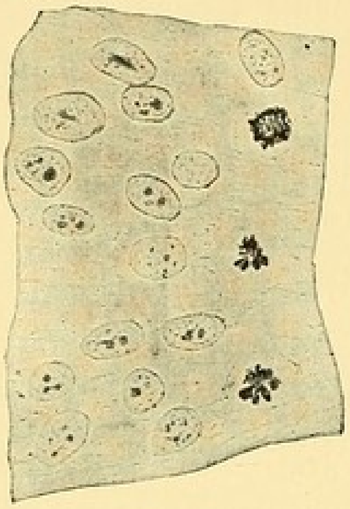

FIG. 72. PORTION OF THE OUTER WALL OF A PRIMITIVE MUSCULAR SEGMENT OF A CAT EMBRYO OF 4.6 MM. Harvard Embryological Collection, Series 398, Section 115. The resting nuclei are oval, pale, and granular. The dividing or mitotic nuclei, of which there are three, are dark, irregular in outline, and show the chromosomes. In this case the dividing nuclei all lie near the *inner* surface of the wall. The picture illustrates the ease with which mitotic figures may be recognised.

May I pause a moment to recall this picture to you and ask you to notice at this point the curious darker spot which represents a nucleus in process of division? You will see it would be easy in such a preparation as this to count the nuclei one by one until one had got up to a thousand, and to record, as one went along, how many of the nuclei are in process of division, for the nucleus in division is easily recognised. This process of division is named mitosis: the figure which the nucleus presents while it is undergoing division we call a mitotic figure. Counting the dividing nuclei, we may determine that in a thousand cells there are a given number which have nuclei in process of division, and such a number I propose to call "the mitotic index."[1] I wish now only to call to your attention this picture because it enables me to illustrate before you the method of measuring the mitotic index.

In the rabbit embryo at seven and one half days, I have found by actual count that there are in the outer layer of cells, known technically as the ectoderm, 18 of these divisions per thousand; in the middle layer, technically the mesoderm, 17, and in the inner layer, the entoderm, 18. At ten days we find the number already reduced, and the figures are, respectively, 14, 13, and 15, and for the cells of the blood only 10. There has already been a great reduction. In the next phase of development (rabbit embryo of thirteen days), we find, however, that the parts are growing irregularly, some faster, some slower. We note that wherever a trace of differentiation has occurred, the rate of growth is diminished; where that differentiation does not show itself, the rate of growth may even increase in order to acquire a certain special development of a particular part. So that instead of uniformity of values for the mitotic index, we get a great variety. But, nevertheless, the general decline can be demonstrated by the figures. In the spinal cord the

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[1] Cells are known to divide without mitotic figures appearing; the process is then termed amitosis. Amitosis occurs in certain degenerating cells of mammals and is said to occur in sundry invertebrates as a normal process. So far as I am aware there is, however, at least as yet, no evidence that amitosis occurs in the embryos of the higher vertebrates. If it did occur it might diminish the validity of the mitotic index.

index is 11, in the general connective tissue of the body 10; for the cells of the liver 11; in the outside layer of the skin 10; in the excretory organ 6; in the tissue which forms the centre of the limb also 6. There has, then, been a rapid decline in the rate of cell multiplication just in this period when differentiation is going on. This is, so far as I know, an entirely new line of research. The counting of a thousand cells is not to be done very rapidly; it must be undertaken with patience, care, and requires time. It has not, I regret to say, been possible for me yet to extend the number of these counts beyond those I have given you, but it is safe to say that in the yet more differentiated state, the number of cells in division is constantly lessened, and it is only a question of counting to determine the mitotic index accurately. That there is a further diminution beyond that which the mitotic indices I have demonstrated to you represent is perfectly certain. I only regret that I am not able to give you exact numerical values.

I wish very much that my time permitted me to branch off into certain topics intimately associated with the general theme we have been considering together on these successive evenings, but we can only allude to a few of these. The first collateral subject on which I wish to speak to you briefly is that which we call the *law of genetic restriction*,[1] which

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[1] C. S. Minot, *Laboratory Text-book of Embryology* (1903), p. 30. This law of genetic restriction had been foreshadowed by M. Nussbaum (*Arch. f. microsk. Anat.*, xxvi., pp. 522, 524). He expresses well and ingeniously the change of progressive differentiation in Metazoan cells. His idea is that each cell is a

means that after a cell has progressed and is differentiated a certain distance, its fate is by so much determined. It may from that pass on, turn in one direction or another, always progressing, going onward in its cytomorphosis; but the general direction has been prescribed, and the possibilities of that cell as it progresses in its development become more and more restricted. For instance, the cells which are set apart to form the central nervous system after they are so set apart cannot form any other kind of tissue.[1] After the nervous system is separated in the progress of development from the rest of the body, its cells may become either nerve cells proper or supporting cells (neuroglia), which latter never acquire the nervous character proper, but serve to uphold and keep in place the true nervous elements. They represent the skeleton of the central nervous system. After the

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"multiplum lebensfähiger und gestaltender Substanz." As the ovum can produce two ova, it can produce two individuals. Ectoderm cells can produce more ectoderm, but not a whole new individual.

[1] An unexpected exception to this statement has been discovered, which is, however, more apparent than real. In certain Amphibia it has been found that, if the lens of the eye is extirpated from a young larva, a new lens will be formed at the expense of the retina, which itself arises from an outgrowth of brain tissue. At the time the retinal lens is produced, however, the retinal cells are still in an undifferentiated state, and those retinal cells which have advanced to the stage of young differentiated elements cannot produce a lens. The normal lens is developed from the outer skin (epidermis) of the embryo. See A. Fischel, *Anatomische Hefte*, xiv., p. 1, (1900) and *Archiv. f. Entwickelungsmech.*, xv., p. 1; G. Wolff, *Archiv. f. Entwickelungsmech.*, i., pp. 380–390, and xii., pp. 307–351; W. H. Lewis, *American Journal of Anatomy*, iii., 505–536, 1904. It is important to note that the retinal lens differs greatly in its cell structure from the normal lens, and is smaller, though resembling it in general form.

cells of the nervous system are separated into these two fundamental classes they cannot change. A cell forming a part of the supporting framework of the brain cannot become a nerve cell; and a nerve cell cannot become a supporting cell. The destiny of them becomes more and more fixed, their future possibilities more and more limited, as their cytomorphosis goes on.

The law of genetic restriction has a very important bearing upon questions of disease. When disease occurs, the cells of the body offer to us two kinds of spectacles. Sometimes we see that the cells causing the diseased condition are more or less of the sort which naturally belong in the body; that they are present where they do not belong, or they are present where they ought to be, but in excessive quantity. There is a kind of tumor which we call a bony tumor. It consists of bone cells such as are naturally present in the body, but that which makes this growth of bone a tumor is its abnormal dimensions, or perhaps its being altogether in the wrong place. The second sort of pathological alteration, which I had in mind, is that in which the cells really change their character. Now, the young cells are those which can change most; in which the genetic restriction has least come into play; and accordingly we find that a large number of dangerous, morbid growths, tumors, arise from cells of the young type, and these cells, having an extreme power of multiplication, grow rapidly, and they may assume a special character of their own; their genetic restriction has not gone so far that all their possibilities of change in the way of differentiation have been fixed; there is a certain range of possibilities still open to them, and they may turn in one direction or the other. Hence there may be pathological growths of a character not normally present in the body. It seems to me, so far as my knowledge of this subject enables me to judge, to be true that all such pathological growths depend upon the presence of comparatively young and undifferentiated cells being turned into a new direction. The problem of normal development and of abnormal structure is one and the same. Both the embryologist and the anatomist, on the one hand, and the pathologist and the clinician on the other, deal ever with these questions of differentiation, and practically with no others. All that occurs in the body is the result of various differentiations, and whether we call the state of that body normal or pathological matters little; still the cause of it is the differentiation of the parts.

The second of the collateral topics which I should like briefly to allude to is another branch of the study of senescence. The fact was first emphasised by the late Professor Alpheus Hyatt that in many animals there exist parts formed in an early stage and thereafter never lost. The chambered nautilus is an animal of this kind. The innermost chamber represents the youngest shell of the nautilus, and as its age increases, it forms a new chamber in its shell, and so yet more and more until the coil is complete. When we examine a shell of that kind we see permanently before us the various stages, both young and old, as recorded in shell formation. And so too in the sea-urchin, and in many of the common shell-fish, we find the double record, of youth and old age, preserved permanently. This has made it possible for Professor Hyatt and for Professor Robert T. Jackson, who has adopted a similar guiding principle, to bring new light into the study of animal changes, and to attack the solution of problems which without the aid of this senescent interpretation, if I may so term it, would be utterly impossible. This is an enticing subject, and I wish I had both time and competency to dwell upon it. But it is aside, as you see, from the main inquiries with which we have been occupied, for our inquiries concern chiefly the effect of cell-change upon the properties of the body, and the correlation of cell-change with age.

A natural branch of our topic is, however, that of longevity, the duration of life.[1] Concerning this, we have very little that is scientifically satisfactory that we can present. We know, of course, as a fundamental principle, that every animal must live long enough to reproduce its kind. Did that not occur, the species would of course become extinct, and the mere fact that the species is existing proves, of course,

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[1] We are indebted to August Weissmann for raising the discussion of longevity to the level of science. His essay, *Ueber die Dauer des Lebens* (Jena, 1882), is by far the best on the subject known to me, and includes numerous data on the longevity of animals.

this simple fact—that life has lasted long enough for the parents to produce offspring. The consideration of this fact has led certain naturalists to the supposition that reproduction is the cause of the termination of life; but it is not, it seems to me, at all to be so interpreted. We know, in a general way, that large animals live longer than small ones. The elephant is longer lived than the horse, the horse than the mouse, the whale than the fish,[1] the fish than the insect, and so on through innumerable other instances. At first this seems a promising clue, but if we think a moment longer we recognise quickly the fact that a parrot, which is much smaller than a dog, may live one hundred years, whereas a dog is very old at twenty. There are insects which live for many years, like the seventeen-year locusts, and others which live but a single year or a fraction even of one year, and yet the long-lived and the short-lived may be of the same size. It is evident, therefore, that size is not in itself properly a measure of the length of life.[2] Another supposition, which at first sounds very attractive, is that which explains the duration of life by the rate of wear, of the using up, of the wearing out, of the body. This theory has been particularly put forward by Professor Weissmann, who in his writings calls it the *Abnutzungstheorie*—the theory of the wearing out of the body. But the body does not really wear out

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[1] But there are some species of fish which outlive whales; thus the European carp is said to live more than a century.

[2] See Appendix No. IV, F. A. Lucas's letter.

in that sense. It goes on performing the functions for a long time, and after each function is performed the body is restored, and we do not find at death that the parts have worn out. But, as we have seen, we do find at death that there has been an extensive cytomorphosis, cell-change, and that the living material, after having acquired its differentiation, passes now in one part, now in another, then in a third, to a yet further stage, that of degeneration, and the result of degeneration, or atrophy, as the case may be, is that the living protoplasm loses its living quality and becomes dead material, and necessarily the functional activity ceases. We must, it seems to me, conclude that longevity, the duration of life, depends upon the rate of cytomorphosis. If that cytomorphosis is rapid, the fatal condition is reached soon, if it is slow, the fatal condition is postponed. And cytomorphosis in various species and kinds of animals must proceed at different rates and at different speeds at different ages. Birds grow up rapidly during their period of development; the cell-change occurs at a high speed, far higher than that which occurs in man, probably, during his period of development. But after the bird has acquired its mature development, it goes on almost upon a level for a long time; the bird which becomes mature in a single year may live for a hundred or even more. There can be during these hundred years but a very slow rate of change. But in a mammal, a dog or a cat, creatures of about the same bulk as some large birds, we find that the early development is at a slower rate. The mammals take a much longer period to pass through their infancy and reach their maturity, but after they have reached their maturity they do not sustain themselves so long. Their later cytomorphosis occurs at a higher speed than the bird's. This is a field of study which we can only recognise the existence of at present, and which needs to be explored before, to any general, or even to a special scientific, audience, any promising hypotheses can be presented. Definite conclusions are of course still more remote.

Next as regards death. The body begins its development from a single cell, the number of cells rapidly increases, and they go on and on increasing through many years. Their whole succession we may appropriately call a cycle. Each of our bodies represents a cell cycle. When we die, the cycle of cells gives out, and, as I have explained to you in a previous lecture, the death which occurs at the end of the natural period of life is the death which comes from the breaking down of some essential thing—some essential group of members of this cell cycle; and then the cycle itself collapses. But the death is the result of changes which have been going on through the successive generations of cells making up this cycle. There are unicellular organisms; these also die; many of them, so far as we can now determine, never have any natural death, but there are probably others in which natural death may occur. It is evident that the death of a unicellular organism is comparable to the death of one cell in our own bodies. It is not properly comparable to the death of the whole body, to the ending-up of the cell cycle. August Weissmann was led to a series of erroneous notions concerning death by his failure to distinguish between the death of a cell and the death of a cycle of cells. Let him serve as a warning to us. Is there anything like a cell cycle among the lower organisms? among the protozoa, as the lowest animals are called? It has been maintained by a French investigator, by the name of Maupas, that such a cycle does exist, that even in these low organisms there is a cell which begins the development, and that gradually the loss in the power of cell multiplication goes on until the cycle gives out and has to be renewed by a rejuvenescent process, and this rejuvenating process he thinks he has found in the so-called conjugating act of these animals, in which there occurs a curious migration of the nucleus of one individual into the cell body of another. Whether he is right or not remains still to be determined. It means much that Professor G. N. Calkins, one of the world authorities on protozoa and easily the foremost American master of this branch of zoölogy, thinks that cyclical development rules the protozoa, each cycle ending with natural death. You will recognise, I hope, from what I have said, that we have now some kind of measure of what constitutes old and young. We can observe the difference in the proportion of protoplasm and nucleus, the increase or diminution, as the case may be, of one or the other.

If it be true that there is among protozoa, among unicellular animals, anything comparable to the gradual decline in the growth power which occurs in us, we shall expect it to be revealed in the condition of the cells—to see in those cells which are old an increase in the proportion and in the differentiation of their protoplasm, and consequently a diminution in the relative amount of nucleus. That subject is now being investigated, and we shall probably know, within a few years at least, something positive in this direction. At present we are reduced to posing our question. We must wait patiently for the answer.

The scientific man has many occasions for patience. He has to make his investigations rather where he can than where he would like to. Certain things are accessible to our instruments and methods of research at the present time, but other things are entirely hidden from us and inaccessible at the present. We are indeed, more perhaps than people in any other profession of life, the slaves of opportunity. We must do what we can in the way of research, not always that which we should like most to do. Perhaps a time will come when many of the questions connected with the problems of growing old, which we can now put, will be answered, because opportunities which we have not now will exist then. Scientific research offers to its devotees some of the purest delights which life can bring. The investigator is a creator. Where there was nothing he brings forth something. Out of the void and the dark, he creates knowledge, and the knowledge which he gathers is not a precious thing for himself alone, but rather a treasure which by being shared grows; if it is given away it loses nothing of its value to the first discoverer, but acquires a different value and a greater usefulness that it adds to the total resources of the world. The time will come, I hope, when it will be generally understood that the investigators and thinkers of the world are those upon whom the world chiefly depends. I should like, indeed, to live to a time when it will be universally recognised that the military man and the government-maker are types which have survived from a previous condition of civilisation, not ours; and when they will no longer be looked upon as the heroes of mankind. In that future time those persons who have really created our civilisation will receive the acknowledgment which is their due. Let these thoughts dwell long in your meditation, because it is a serious problem in all our civilisation to-day how to secure due appreciation of the value of thought and how to encourage it. I believe every word spoken in support of that great recognition which is due to the power of thought is a good word and will help forward toward good results.

In all that I have said, you will recognise that I have spoken constantly of the condition of the living material. If it is in the young state it has one set of capacities. If it is differentiated, it has, according to the nature of its differentiation, other kinds of capacities. We can follow the changing structure with the microscope. We can gain some knowledge of it by our present chemical methods. Fragmentary as that knowledge is, nevertheless, it suffices to show to us that the *condition of the living material is essential and determines what the living material can do.* I should like to insist for a moment upon this conception, because it is directly contrary to a conception of living material which has been widely prevalent in recent years, much defended and popularly presented on many different occasions. The other theory, the one to which I cannot subscribe, may perhaps be most conveniently designated by the term—the theory of life units. It is held by the defenders of this faith that the living substance contains particles, very small in size, to which the vital properties are especially attached. They look at a cell and find that it has water, or water containing a small amount of salts in solution, filling up spaces between the threads of protoplasm. Water is not alive. They see in the protoplasm granules of one sort and another, in plants chlorophyll, in animals perhaps fat or some other material. That is not living substance, and so they go, striking out from their conception of the living material in the cell one after another of these component parts until they get down to something very small, which they regard as the life unit. I do not believe these life units exist. It seems to me that all these dead parts, as this theory terms them, are parts of the living cell. They are factors which enable the functions of life to go on. Other conditions are also there, and to no one of them does the quality of life properly attach itself. Of life units there is an appalling array. The most estimable of them, in my opinion, are the life units which were hypothetically created by Charles Darwin in his theory of pangenesis. He assumed that there were small particles (gemmules) thrown off from different portions of the body circulating throughout the body, gathering sometimes in the germ cells. These particles he assumed to take up the qualities of the different parts of the body from which they emanated, and by gathering together in immense numbers in the germ cells to accomplish the hereditary transmission. We know now that this theory is not necessary, that it is not the correct theory. But at the time that Darwin promulgated it, it was a perfectly sound, defensible theory, a theory which no one considering fairly the history of biological knowledge ought to criticise unfavourably. It was a fine mental achievement, but I should like also to add that of all the many theories of life units, this of Darwin is the only one which seems to me intellectually entirely respectable. Of supposed structural life units there is a great variety. Besides the gemmules of Darwin, there were the physiological units of Herbert Spencer. Professor Haeckel, the famous German writer, has structural life units of his own which he terms plastidules; he gave his theory the charming alliterative title of perigenesis of the plastidules; the rhythm of it must appeal to you all, though the hypothesis had better be forgotten. Then came Nägeli, the great botanist, who spoke of the Idioplasma-Theilchen. Then Weisner, also a botanist, who spoke of the plassomes. Our own Professor Whitman attributed to his life units certain other essential qualities and called them idiosomes. A German zoölogist, Haacke, has called them gemmules. Another German writer, a Leipzig anatomist, Altmann, calls them granuli. Now these different life units, of which I have read you briefly the names, are not identical according to these authors. Everybody else's life units are wrong, falsely conceived, and endued with qualities which they do not combine. Here is a curious assemblage of "doxies," and each writer is orthodox and all the others are heterodox; and I find myself viewing them all from the standpoint of my "doxy," that of the structural quality of the living matter, and, therefore, interpreting every one of these conceptions as heterodox, not sound doctrine, but something to be rejected, condemned, and fought against. These theories of life units have filled up many books. Among the most ardent defenders of the faith in life units is Professor Weismann, whose theories of heredity many of you have heard discussed; though I doubt if many of you, unless you recall what I said previously, are aware of the fact that the essential part of Weismann's doctrine was the adoption of the theory of germinal continuity originated by Professor Nussbaum, whose name by a strange injustice has been too seldom heard in these discussions.

Weismann has gone much farther in the elaboration of the conception of life units than any of the other writers. He thinks the smallest of the life units are biophores. A group of biophores brought together constitutes another order of life units which he calls determinants; the determinants are again grouped and form ids; and the ids are again grouped and form idants. If you want to accept any theory of life units, I advise you to accept that of Weismann, for it offers a large range for the imagination, and has a much more formidable number of terms than any other.

I want to pass now to an utterly different line of study, the question of psychological development. If it be true that the development is most rapid at first, slower later, we should expect to find proof of that rate in the progress of mental development. In other words, we should expect to find that the baby developed faster than the child mentally, that the child developed faster than the young man, and the young man faster than the old. And do you not all instinctively feel immediately that the general assertion is true? In order, however, that you may more fully appreciate what I believe to be the fact of mental development going on with diminishing rapidity, I should like to picture to you briefly some of the things which the child achieves during the first year of its life.[1] When the child is born, it is undoubtedly

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[1] I am indebted to Dr. Benjamin Rand of Harvard University for guidance to the literature upon the subject of the mental development of children. The account in the text is the result of reworking the recorded data, so as to elucidate the relation of the child's mental progress to its age, none of the

supplied with a series of the indispensable physiological functions, all those which are concerned with the taking in and utilising of food. The organs of digestion, assimilation, circulation, and excretion are all functionally active at birth. The sense organs are also able to work. Sense of taste and of smell are doubtfully present. It is maintained that they are already active, but they do not show themselves except in response to very strong stimulation. Almost the only additional faculty which the child has is that of motion, but the motions of the new-born baby are perfectly irregular, accidental, purposeless, except the motions which are connected with the function of sucking, upon which the child depends for its nourishment. The instinct of sucking, the baby does have at birth. It might be described as almost the only equipment beyond the mere physiological working of its various organs. But at one month we find that this uninformed baby has made a series of important

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authorities I have consulted having presented the matter with special reference to the age rate. I have drawn chiefly from the following publications :

Compayré "La psychologie de l'enfant," *Revue philosophique*, vi., 1878, 464–481.

Ch. Darwin, "Biographical Sketch of an Infant," *Mind*, ii., 1877, 285–294.

Louise Hogan, *Study of a Child*, New York, 1898.

Kussmaul, *Seelenleben des neugeborenen Menschen*, 1896.

Kathleen Moore, "Mental Development of a Child," *Psychol Review*, Supplement, Oct., 1896.

Oppenheim, *The Development of a Child*, New York, 1898.

Wm. Preyer, *The Mind of the Child.* Translated by H. W. Brown. 2 vols. One of the most important and suggestive works on the subject.

M. W. Shinn, *The Biography of a Baby*, Boston, 1900. An excellent book, both authoritative and readable.

Amy E. Tanner, *The Child*, New York, 1904.

discoveries. It has learned that there are sensations, that they are interesting; it will attend to them. You all know how a baby of one month will stare; the eyes will be fastened upon some bright and interesting object. At the end of a month the baby shows evidences of having ideas and bringing them into correlation,—association, as one more correctly expresses it,—because already after one month, when held in the proper position in the arms, it shows that it expects to be fed. There is, then, already evidence and trace of memory. At two months much more has been achieved. The baby evidently learns to expect things. It expects to be fed at certain times; it has made the great discovery of the existence of time. And it has made the discovery of the existence of space, for it will follow to some extent the bright light; it will hold its head in a certain position to catch a sound apparently from one side; or to see in a certain direction. The sense of space and time in the baby's mind is, of course, very imperfect, doubtless, at this time, but those two non-stuff realities about which the metaphysicians discuss so much, the two realities of existence which are not material, the baby at this time has discovered. Perhaps, had some great and wonderfully endowed person existed who preserved the memory of his own psychological history, of his development during babyhood, we should have been spared the gigantic efforts of the metaphysicians to explain how the notions of space and time arose. Without knowing how, the baby has acquired them, and has already become a rudimentary metaphysician. We see, also, at the end of the third month, that the baby has made another remarkable discovery. It has found not merely that its muscles will contract and jerk and throw its parts about, which surely was earlier a great delight to it; but that the muscles can contract in such a way that the movement will be directed; there is a co-ordination of the muscular movements. I should like to read to you just these three or four lines from Miss Shinn, who has given perhaps the best story of the development of a baby which has yet been written. This is not merely my opinion, but also the opinion of my psychological colleagues at Cambridge whom I consulted before venturing to express the idea before you, and I find that they take the view that Miss Shinn's book, which is charmingly written, is really done with such precision and understanding of the psychological problems involved that it may fairly be called the best of the books treating of the mental development of a baby. Miss Shinn says, referring to the condition of the child at the end of two months—"Such is the mere life of vegetation the baby lived during the first two months; no grown person ever experienced such an expansion of life — such a progress from power to power in that length of time." She is not thinking of senescence, as we have been thinking of it, but she makes precisely the assertion, which seems to me to be true, that the baby in two months has accomplished an amount of development which no adult is capable of. And now at three months we find another great discovery is made by the baby, that it is possible to bring the sensations which it receives into combination with the movements which it makes. It learns to co-ordinate its sensory impressions and its motor responses. We hardly realise what a great rôle this adjustment, between what our muscles can do and what our senses tell us, plays in our daily life. It is the fundamental thing in all our daily actions, and though by habit we perform it almost unconsciously, it is a thing most difficult to learn. Yet the baby has acquired the art, though he only gradually gets to be perfect in it. Again we see, at the end of the fourth month, that the baby begins to show some idea of another great principle—the idea that it can do something. It shows evidence of having purpose in what it does. Its movements are no longer purely accidental. At four months we find yet another equally astonishing addition to the achievements of this marvellous baby. He makes the amazing discovery that the two sides of an object are not separate things, but are parts of the same. When a face, for instance, disappears by a person's turning around, that face, to a baby of one month, probably simply vanishes, ceases to exist: but the baby at four months realises that the face and the back of the head belong to the same object. He has acquired the idea of objects existing in the world around him. That is an enormous achievement, for this little baby has no instructor; he is finding out these things by his own unaided efforts.

Then at five months begins the age of handling when the baby feels of everything. It feels urgently of all the objects which it can get hold of and perhaps most of all of its own body. It is finding that it can touch its various own parts and that when its hands and parts of its own body come in contact it has the double sensations, and learns to bring them together and thereby is manufacturing in its consciousness the conception of the *ego*, personal, individual existence, another great metaphysical notion. Descartes has said, "*Cogito, ergo sum*"—" I think, therefore I am." The baby, if he had written in Descartes's place, would have said, " I feel, therefore I am." The first five months constitute the first period of the baby's development. Its powers are formed, and the foundations of knowledge have been laid. The second period is a period of amazing research, constant, uninterrupted, untiring; renewed the instant the baby wakes up, and kept up until sleep again overtakes it. In the six months' baby we find already the notion of cause and effect. You see he is dealing mostly in metaphysical things, getting the fundamental concepts. That there is such an idea as cause and effect in the baby's mind is clearly shown by the progress of its adaptive intelligence. It evidently has now distinct purposes of its own. It shows clearly at this age also another thing which plays a constant and important rôle in our daily life. It has the consciousness of the possibilities of human intercourse; it wants human companionship. And with that the baby's equipment to start upon life is pretty well established. It has discovered the material universe in which it lives, the succession of time, the nature of space, cause and effect, its own existence, its ego and its relationship with other individuals of its own species. Do we get at any time in our life much beyond this? Not very much; we always use these things, which we learn in the first six months, as the foundation of all our thought. By eight months, baby is upon the full career of experiment and observation. Everything with which the baby comes in contact interests him. He looks at it, he seizes hold of it, tries to pull it to pieces, studies its texture, its tensile strength, and every other quality it possesses. Not satisfied with that, he will turn and apply his tongue to it, putting it in his mouth for the purpose of finding out if it has any taste. In doing this, hour after hour, with unceasing zeal, never interrupted diligence, he rapidly gets acquainted with the world in which he is placed. At the same time he is making further experiments with his own body. He begins to tumble about; perhaps learns that it is possible to get from one place to another by rolling or creeping, and slowly he discovers the possibility of locomotion, which you know by the end of the year will have so far perfected itself that usually at twelve months the baby can walk. During this period of from five months to twelve the baby is engaged upon a career of original research, unaided much by anybody else, getting doubtless a little help and, of course, a great deal of protection, but really working chiefly by himself. How wonderful it all is! Is any one of us capable of beginning at the moment we wake to carry on a new line of thought, a new series of studies, and to keep it up full swing, with unabated pace, all day long till we drop asleep? Every baby does that every day.

When we turn to the child who goes to school, behold how much that child has lost. It has difficulties with learning the alphabet. It struggles slowly through the Latin grammar, painfully with the subject of geometry, and the older it gets the more difficult becomes the achievement of its study. The power of rapid learning, which the baby has, is clearly already lessened.

The introduction of athletics affords a striking illustration of the decline of the learning power with the progressing years. When golf first came in it was considered an excellent game for the middle-aged; and you have all watched the middle-aged man play. He was so awkward, he could not do it. Day after day the man of forty, fifty, or even older, would go to the golf field, hoping each time to acquire a sure stroke, but never really acquiring it. The young man learned better, but the good golf players are those who begin as children, twelve and fourteen years of age, and in a few months become as expert and sure as their fathers wished to become, but could not. In bicycling it was the same. Eight lessons was considered the number necessary to teach the intelligent adult to ride a wheel. Three for a child of eight. And an indefinite number of lessons, ending in failure, for a person at seventy. It would have been scientifically interesting to have kept an exact record of the period of time which it took at each age to learn bicycling, but I think enough has been said to convince you that if we could acquire such a measure of psychological development as would enable us to express its rate in figures, we should be able to construct a curve like the curve which I showed you in the third lecture illustrating the decline in the rate of growth, and we should see that during the early years of life the decline in the power of learning was extremely rapid, during childhood less rapid, during old age very slow. But the great part of the decline would occur during early years.

Here we see the principle of stability, in maturity, which we see also illustrated in structure and growth. The mind acquires its development; it retains that development in the adult a long time. But surely there comes a period when the exercise of the mind is difficult. It requires a great effort to do something new and unaccustomed. A sense of fatigue overwhelms us. I believe that this principle of psychological development, paralleling the career of physical development, needs to be more considered in arranging our educational plans. For if it be true that the decline in the power of learning is most rapid at first, it is evident that we want to make as much use of the early years as possible—that the tendency, for instance, which has existed in many of our universities, to postpone the period of entrance into college is biologically an erroneous tendency. It would be better to have the young man get to college earlier, graduate earlier, get into practical life or into the professional schools earlier, while the power of learning is greater.

Do we not see, in fact, that the new ideas are indeed for the most part the ideas of young people? As Dr. Osler, in that much-discussed remark of his, has said, the man of forty years is seldom the productive man. Dr. Osler also mentioned the amiable suggestion of Trollope in regard to men of sixty, which has been so extremely misrepresented in the newspaper discussions throughout the country, causing biologists much amusement. But I think that Dr. Osler probably took a far too amiable view of mankind, and that in reality the period when the learning power is nearly obliterated is reached in most individuals very much earlier. Permit me to read to you a quotation from a lecture which I delivered last year (1906) before the Harvey Society:

> "It may be true that that age (40) marks in intellectual men usually a transition or the point where the accumulated losses which have been occurring from birth on reveal their effects clearly, but in the great majority of men comparative mental fixity surely occurs at a much earlier period. If you will allow me to wander for a moment from the strict discussion of our immediate theme, I should like to refer to what may be called the theory of permanent mental fatigue. The organic changes which go on in the nervous system diminish its pliability and there comes a time when the individual finds it exceedingly difficult to bring his mind into any unaccustomed form of activity. How completely we are mastered by this difficulty is often hidden, I believe, from our

recognition and from that of our friends, because we have acquired certain habits of activity which we are able to keep up, but we are not able without ever-increasing difficulty to turn to new forms of mental activity, or in other words, to learn new things. When we grow old we may still continue to do well the kind of thing which we have learned to do, whether it be paying out bills at a bank or paying out a particular set of scientific ideas to a class of students. If we try to overstep the limits of our acquired expertness we find that we are held up by this sense of permanent mental fatigue. Usually this condition comes about gradually, but I have known, as I presume you all have, several cases in which it has appeared suddenly, where a man who up to a certain time was fond of mental exertion suddenly ceased to be mentally active. We have probable illustrations of this in the careers of well-known scientific men. I think the theory of permanent mental fatigue, in connection with the theory of gradual decline which we are considering this evening, could be usefully developed and might well be utilised by the psychologists in their studies."

As in every study of biological facts, there is in the study of senescent mental stability the principle of variation to be kept in mind. Men are not alike. The great majority of men lose the power of learning, doubtless some more and some less, we will say, at twenty-five years. Few men after twenty-five are able to learn much. They who cannot, become day-labourers, mechanics, clerks of a mechanical order. Others probably can go on somewhat longer, and obtain higher positions; and there are men who, with extreme variations in endowment, preserve the power of active and original thought far on into life. These of course are the exceptional men, the great men.

We have lingered so long together studying phenomena of growth, that it is natural to allude to one more, which is as singular as it is interesting, namely, the increase in size of Americans. It was first demonstrated by Dr. Benjamin A. Gould in his volume of statistics derived from the records of the Sanitary Commission—a volume which still remains the classic and model of anthropometric research. Any one, however, can observe that the younger generation of to-day tends conspicuously to surpass its parents in stature and physical development. How to explain the remarkable improvement we do not know. Our discovery of the fact that the very earliest growth is so enormously rapid, makes that earliest period especially important. If the initial growth can be favoured, a better subsequent development presumably would result. In brief, I find myself led to the hypothesis that the better health of the mothers secures improved nourishment in the early stages of the offspring, and that the maternal vigour is at least one important immediate cause of the physical betterment of the children. Much is said about the degeneracy of the American race, but the contrary is true—the American race surpasses its European congeners in physical development.

You will naturally wish to ask, before I close the series of lectures, two questions. One, how can rejuvenation be improved? the other, how can senescence be delayed? These questions will strike every one as very practical. But the first, I fear, is not an immediately practical question, but rather of scientific interest, for we must admit that the production of young individuals is, on the whole, very well accomplished and much to our satisfaction. But in regard to growing old, in regard to senescence, the matter is very different. There we should, indeed, like to have some principle given to us which would retard the rate of senescence and leave us for a longer period the enjoyment of our mature faculties. I can, as you have readily surmised by what I have said to you, present to you no new rule by which this can be accomplished, but I can venture to suggest to you that in the future deeper insight into these mysteries probably awaits us, and that there may indeed come a time when we can somewhat regulate these matters. If it be true that the growing old depends upon the increase of the protoplasm, and the proportional diminution of the nucleus, we can perhaps in the future find some means by which the activity of the nuclei can be increased and the younger system of organisation thereby prolonged. That is only a dream of the possible future. It would not be safe even to call it a prophecy. But stranger things and more unexpected have happened, and perhaps this will also.

I do not wish to close without a few words of warning explanation. The views which I have presented before you in this series of lectures I am personally chiefly responsible for. Science consists in the discoveries made by individuals, afterwards confirmed and correlated by others, so that they lose their personal character. You ought to know that the interpretations which I have offered you are still largely in the personal stage. Whether my colleagues will think that the body of conceptions which I have presented are fully justified or not, I cannot venture to say. I have to thank you much, because between the lecturer and his audience there is established a personal relation, and I feel very much the compliment of your presence throughout this series of lectures, and of the very courteous attention which you have given me.

To recapitulate—for we have now arrived at the end of our hour—it must be said first that all of the conclusions presented are based upon the laws of cytomorphosis, in other words, of the change in structure which occurs not only in a single cell, but progressively in successive generations of cells. We can formulate the following laws of cytomorphosis:

*First*, cytomorphosis begins with an undifferentiated cell.

*Second*, cytomorphosis is always in one direction, through progressive differentiation and degeneration towards the death of the cells.

*Third*, cytomorphosis varies in degree characteristically for each tissue (hence in the adult higher animals nearly all stages of cytomorphosis may co-exist).

We may add that reversed cytomorphosis is not known to occur, or, in other words, differentiated material cannot be restored to the undifferentiated condition.

Finally, if my arguments before be correct, we may say that we have established the following four laws of age :

*First*, rejuvenation depends on the increase of the nuclei.

*Second*, senescence depends on the increase of the protoplasm, and on the differentiation of the cells.

*Third*, the rate of growth depends on the degree of senescence.

*Fourth*, senescence is at its maximum in the very young stages, and the rate of senescence diminishes with age.

As the corollary from these, we have this—natural death is the consequence of cellular differentiation.

# APPENDICES

# APPENDIX I. GROWTH OF RABBITS.

THE data which I have collected concerning the growth of rabbits have not been published hitherto, and are therefore printed here. It is from the average of the percentage increments that Figures 35 and 36 were constructed.

There are certain precautions in making weighings, not only of rabbits but also of other animals, which were found necessary. As soon as a litter was born and the amniotic fluid dried off from the fur of the young, each individual was weighed, the sex noted, and an exact description of all the markings, which do not alter after birth, written down. The litter was numbered, and the date of birth and the parentage, or at least the maternal parentage, recorded.

To identify the rabbits they were marked with spots of nitrate of silver. It may be mentioned in passing that the Guinea-pigs, of which there was a large number raised, can usually be individually identified by their natural markings. I found it a great convenience to give mnemonic names to all the pigs of which I followed the growth, so that the name would suggest the appearance of the individual pig. For the most part the names referred directly to the marking, for instance, " Brown rump," "Saddle back," " Snout," etc.,—but often the allusion was more remote, as for instance, " Hypocrite," whose head, seen from one side, appeared entirely black, from the other, entirely white. The record having been started, the next thing was to enter in a diary all the dates during the remainder of the year upon which the litter in question was to be weighed.[1] The plan adopted after a little experience was to weigh each individual every day up to 40 days, then every fifth day up to 215

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[1] The apparatus devised for calculating the required dates mechanically is described in Appendix VI.

days, and then after every thirtieth day, and to avoid accidental variations, also five days before and five days after each thirtieth day: for instance, the months being assumed at 30 days, the animals would be weighed for the eighth month at 240, also at 235 and 245 days, and the next set for nine months, 265, 270, and 275, and so on to the end of the second year after birth, at which age the observations were stopped. Of no individual have I an absolutely complete series of weights, but of a good many the series are nearly complete. A very few of my animals died from disease.

GROWTH OF RABBITS. A, MALES

| Age Days | Total Weight Grams | Obs. | Average | Increase Over Last Measurement | Average Daily Increase | Daily Per Cent. Increase | Av. Daily Per Cent. Increase |
|---|---|---|---|---|---|---|---|
| 0 | 201.3 | 4 | 50.3 | | | | |
| 1 | 238.9 | 4 | 59.7 | 9.4 | 9.4 | 18.5 | 17.6 |
| 2 | 272.6 | 4 | 68.1 | 8.4 | 8.4 | 14.1 | |
| 3 | 344.9 | 4 | 86.2 | 18.1 | 18.1 | 26.6 | |
| 4 | 402.3 | 4 | 100.6 | 14.4 | 14.4 | 16.7 | |
| 5 | 452.2 | 4 | 113.0 | 12.4 | 12.4 | 12.3 | |
| 6 | 287.0 | 2 | 143.5 | 30.5 | 30.5 | 26.9 | 13.5 |
| 7 | 622.5 | 4 | 155.6 | 12.1 | 12.1 | 8.4 | |
| 8 | 708.1 | 4 | 177.0 | 21.4 | 21.4 | 13.8 | |
| 9 | 786.6 | 4 | 196.6 | 19.6 | 19.6 | 11.1 | |
| 10 | 844.6 | 4 | 211.1 | 14.5 | 14.5 | 7.4 | |
| 11 | 922.0 | 4 | 230.5 | 19.4 | 19.4 | 9.2 | 15.6 |
| 12 | 993.2 | 4 | 248.3 | 17.8 | 17.8 | 7.7 | |
| 13 | 683.0 | 2 | 341.5 | 93.2 | 93.2 | 37.5 | |
| 14 | 1121.2 | 4 | 280.3 | —61.2 | —61.2 | —17.9 | |
| 15 | 794.0 | 2 | 397.0 | 116.7 | 116.7 | 41.6 | |
| 16 | 1265.0 | 4 | 316.2 | —80.8 | —80.8 | —20.4 | 10.1 |
| 17 | 1356.0 | 4 | 339.0 | 22.8 | 22.8 | 7.2 | |
| 18 | 922.0 | 2 | 461.0 | 122.0 | 122.0 | 36.0 | |
| 19 | 1479.5 | 4 | 369.9 | —91.1 | —91.1 | —19.8 | |
| 20 | 1090 | 2 | 545.0 | 175.1 | 175.1 | 47.3 | |
| 21 | 1627 | 4 | 406.7 | —138.3 | —138.3 | —25.4 | 6.6 |
| 22 | 1122 | 2 | 561.0 | 154.3 | 154.3 | 37.9 | |
| 23 | 1798 | 4 | 449.5 | —111.5 | —111.5 | —19.9 | |
| 24 | 1202 | 2 | 601.0 | 151.5 | 151.5 | 33.7 | |
| 25 | 642 | 1 | 642.0 | 41.0 | 41.0 | 6.8 | |
| 26 | 1401 | 3 | 467.0 | —175.0 | —175.0 | —27.3 | 5.3 |
| 27 | 1297 | 2 | 648.5 | 181.5 | 181.5 | 38.9 | |
| 28 | 2215 | 4 | 553.7 | —94.8 | —94.8 | —14.6 | |
| 29 | 1410 | 2 | 705.0 | 151.3 | 151.3 | 27.3 | |
| 30 | 1439 | 2 | 719.5 | 14.5 | 14.5 | 2.1 | |

### ·GROWTH OF RABBITS. A, MALES—(*Continued*)

| Age Days | Total | | Average | Increase Over Last Measurement | Average Daily Increase | Daily Per Cent. Increase | Av. Daily Per Cent. Increase |
|---|---|---|---|---|---|---|---|
| | Weight Grams | Obs. | | | | | |
| 31 | 2502 | 4 | 625.5 | —94.0 | —94.0 | —13.1 | 3.1 |
| 32 | 1530 | 2 | 765.0 | 139.5 | 139.5 | 22.3 | |
| 33 | 1564 | 2 | 782.0 | 17.0 | 17.0 | 2.2 | |
| 34 | 1575 | 2 | 787.5 | 5.5 | 5.5 | .7 | |
| 35 | 1627 | 2 | 813.5 | 26.0 | 26.0 | 3.3 | |
| 36 | 1683 | 2 | 841.5 | 28.0 | 28.0 | 3.4 | 5.5 |
| 37 | 2914 | 4 | 728.5 | —113.0 | —113.0 | —13.4 | |
| 38 | 1830 | 2 | 915.0 | 186.5 | 186.5 | 25.6 | |
| 39 | 1842 | 2 | 921.0 | 6.0 | 6.0 | .7 | |
| 40 | 3108 | 4 | 777.0 | —144.0 | —144.0 | —15.6 | |
| 45 | 3304 | 4 | 826.0 | 49.0 | 9.8 | 1.3 | 1.6 |
| 50 | 2071 | 2 | 1035.5 | 209.5 | 41.9 | 5.1 | |
| 55 | 3881 | 4 | 970.2 | —65.3 | —13.1 | —1.3 | |
| 60 | 4167 | 4 | 1041.7 | 71.5 | 14.3 | 1.5 | |
| 65 | 4465 | 4 | 1116.2 | 74.5 | 14.9 | 1.4 | |
| 70 | 4969 | 4 | 1242.2 | 126.0 | 25.2 | 2.3 | 1.0 |
| 75 | 5519 | 4 | 1379.7 | 137.5 | 27.5 | 2.2 | |
| 80 | 4013 | 3 | 1337.7 | —42.0 | —8.4 | —.6 | |
| 85 | 2690 | 2 | 1345.0 | 7.3 | 1.5 | .1 | |
| 90 | | | | | | | |
| 95 | 3120 | 2 | 1560.0 | 215.0 | 21.5 | 1.6 | 1.0 |
| 100 | 3195 | 2 | 1597.5 | 37.5 | 7.5 | .5 | |
| 110 | 3555 | 2 | 1777.5 | 180.0 | 18.0 | 1.1 | |
| 120 | 3836 | 2 | 1918.0 | 140.5 | 14.0 | .8 | |
| 150 | 4268 | 2 | 2134.0 | 216.0 | 7.2 | .4 | .3 |
| 165 | 4517 | 2 | 2258.5 | 124.5 | 8.3 | .4 | |
| 180 | 4570 | 2 | 2285.0 | 26.5 | 1.8 | .1 | |
| 195 | 4812 | 2 | 2406.0 | 121.0 | 8.1 | .4 | |
| 210 | 4954 | 2 | 2477.0 | 71.0 | 4.7 | .2 | |
| Months | | | | | | | |
| 8 | 5052 | 2 | 2526.0 | 49.0 | 1.6 | .07 | —.4 |
| 9 | 4812 | 2 | 2406.0 | —120.0 | —4.0 | —1.3 | |
| 10 | 4795 | 2 | 2397.5 | —8.5 | —.3 | —.01 | |

## GROWTH OF RABBITS. B, FEMALES, NOT LITTERING WHILE YOUNG

| Age Days | Total Weight Grams | Total Obs. | Average | Increase Over Last Measurement | Average Daily Increase | Daily Per Cent. Increase | Av. Daily Per Cent. Increase |
|---|---|---|---|---|---|---|---|
| 0 | 242.8 | 5 | 48.6 | | | | |
| 1 | 275.9 | 5 | 55.2 | 6.6 | 6.6 | 13.6 | 16.0 |
| 2 | 310.3 | 5 | 62.1 | 6.9 | 6.9 | 12.5 | |
| 3 | 391.5 | 5 | 78.3 | 16.2 | 16.2 | 26.1 | |
| 4 | 431.7 | 5 | 86.3 | 8.0 | 8.0 | 10.2 | |
| 5 | 507.2 | 5 | 101.4 | 15.1 | 15.1 | 17.5 | |
| 6 | 252.0 | 2 | 126.0 | 24.6 | 24.6 | 24.2 | 11.4 |
| 7 | 657.5 | 5 | 131.5 | 5.5 | 5.5 | 4.4 | |
| 8 | 746.6 | 5 | 149.3 | 17.8 | 17.8 | 13.5 | |
| 9 | 806.5 | 5 | 161.3 | 12.0 | 12.0 | 8.0 | |
| 10 | 866.8 | 5 | 173.4 | 12.1 | 12.1 | 7.1 | |
| 11 | 922.7 | 5 | 184.5 | 11.1 | 11.1 | 6.4 | 15.3 |
| 12 | 1012.2 | 5 | 202.4 | 17.9 | 17.9 | 9.7 | |
| 13 | 576.0 | 2 | 288.0 | 85.6 | 85.6 | 42.3 | |
| 14 | 1236.5 | 5 | 247.3 | —40.7 | —40.7 | —14.1 | |
| 15 | 653.0 | 2 | 326.5 | 79.2 | 79.2 | 32.0 | |
| 16 | 1257.0 | 5 | 251.4 | —75.1 | —75.1 | —23.0 | 10.5 |
| 17 | 1314.0 | 5 | 262.8 | 11.4 | 11.4 | 4.5 | |
| 18 | 783.0 | 2 | 391.5 | 128.7 | 128.7 | 48.9 | |
| 19 | 1421 | 5 | 284.2 | —107.3 | —107.3 | —27.4 | |
| 20 | 850 | 2 | 425.0 | 140.8 | 140.8 | 49.5 | |
| 21 | 1612 | 5 | 322.4 | —102.6 | —102.6 | —24.1 | 8.4 |
| 22 | 923 | 2 | 461.5 | 139.1 | 139.1 | 43.1 | |
| 23 | 1785 | 5 | 357.0 | —104.5 | —104.5 | —22.6 | |
| 24 | 992 | 2 | 496.0 | 139.0 | 139.0 | 38.9 | |
| 25 | 529 | 1 | 529.0 | 33.0 | 33.0 | 6.7 | |
| 26 | 1507 | 4 | 376.7 | —152.3 | —152.3 | —28.8 | 6.8 |
| 27 | 1098 | 2 | 549.0 | 172.3 | 172.3 | 45.7 | |
| 28 | 2251 | 5 | 450.2 | —98.8 | —98.8 | —18.0 | |
| 29 | 1203 | 2 | 601.5 | 151.3 | 151.3 | 33.6 | |
| 30 | 1222 | 2 | 611.0 | 9.5 | 9.5 | 1.6 | |
| 31 | 2570 | 5 | 514.0 | —97.0 | —97.0 | —15.9 | 4.7 |
| 32 | 1313 | 2 | 656.5 | 142.5 | 142.5 | 27.7 | |
| 33 | 2670 | 5 | 534.0 | —122.5 | —122.5 | —18.7 | |
| 34 | 1367 | 2 | 683.5 | 149.5 | 149.5 | 28.0 | |
| 35 | 1398 | 2 | 699.0 | 15.5 | 15.5 | 2.3 | |
| 36 | 1461 | 2 | 730.5 | 31.5 | 31.5 | 4.5 | .3 |
| 37 | 3073 | 5 | 614.6 | —115.9 | —115.9 | —15.9 | |
| 38 | 1621 | 2 | 810.5 | 195.9 | 195.9 | 31.9 | |
| 39 | 1606 | 2 | 803.0 | —7.5 | —7.5 | —.9 | |
| 40 | 3160 | 5 | 632.0 | —171.0 | —171.0 | —21.3 | |
| 45 | 3522 | 5 | 704.4 | 72.4 | 14.5 | 2.3 | 2.4 |
| 50 | 1872 | 2 | 936.0 | 231.6 | 46.3 | 6.6 | |
| 55 | 4039 | 5 | 807.8 | —128.2 | —25.6 | —2.7 | |
| 60 | 4452 | 5 | 890.4 | 82.6 | 16.5 | 2.0 | |
| 65 | 4908 | 5 | 980.4 | 90.0 | 18.0 | 2.0 | |

## GROWTH OF RABBITS. B, FEMALES NOT LITTERING WHILE YOUNG—(*Continued*)

| Age Days | Total |  | Average | Increase Over Last Measurement. | Average Daily Increase | Daily Per Cent. Increase | Av. Daily Per Cent. Increase |
|---|---|---|---|---|---|---|---|
|  | Weight Grams | Obs. |  |  |  |  |  |
| 70 | 5286 | 5 | 1057.2 | 76.8 | 15.4 | 1.6 | 1.0 |
| 75 | 5668 | 5 | 1133.6 | 76.4 | 15.3 | 1.4 |  |
| 80 | 5964 | 5 | 1192.8 | 59.2 | 11.8 | 1.0 |  |
| 85 | 6362 | 5 | 1272.4 | 79.6 | 15.9 | 1.3 |  |
| 90 | 2528 | 2 | 1264.0 | —8.4 | —1.7 | —0.1 |  |
| 95 | 5839 | 4 | 1459.7 | 195.7 | 39.1 | 3.5 | 1.6 |
| 100 | 4626 | 3 | 1542.0 | 82.3 | 16.5 | 1.1 |  |
| 110 | 5055 | 3 | 1685.0 | 143.0 | 14.3 | .9 |  |
| 120 | 5494 | 3 | 1831.3 | 146.3 | 14.6 | .9 |  |
| 150 | 6094 | 3 | 2031.3 | 200.0 | 6.7 | .4 | .4 |
| 165 | 6682 | 3 | 2227.3 | 196.0 | 13.1 | .6 |  |
| 180 | 7134 | 3 | 2378.0 | 150.7 | 10.0 | .5 |  |
| 195 | 6934 | 3 | 2311.3 | —66.7 | —4.4 | —.2 |  |
| 210 | 7597 | 3 | 2532.3 | 221.0 | 14.7 | .6 |  |
| Months |  |  |  |  |  |  |  |
| 8 | 5504 | 2 | 2752.0 | 219.7 | 7.3 | .3 | .1 |
| 9 | 5694 | 2 | 2847.0 | 95.0 | 3.2 | .1 |  |
| 10 | 5300 | 2 | 2650.0 | —197.0 | —6.6 | —.2 |  |

# APPENDIX II. GROWTH OF CHICKENS.

THE data which I have collected concerning the growth of chickens have not been published hitherto, and are therefore printed here. It was from the percentage increments of these tables that Figures 33 and 34 were constructed.

GROWTH OF CHICKENS. A. MALES

| Age Days | Total | | Average | Increase Over Last Measurement | Average Daily Increase | Daily Per Cent. Increase | Av. Daily Per Cent. Increase |
|---|---|---|---|---|---|---|---|
| | Weight Grams | Obs. | | | | | |
| 1 | 93 | 2 | 46.5 | | | | |
| 2 | 92 | 2 | 46.0 | —.5 | —.5 | —1.1 | 3.9 |
| 3 | 95 | 2 | 47.5 | 1.5 | 1.5 | 3.3 | |
| 4 | 103 | 2 | 51.5 | 4.0 | 4.0 | 8.4 | |
| 5 | 108 | 2 | 54.0 | 2.5 | 2.5 | 4.9 | |
| 6 | 120 | 2 | 60.0 | 6.0 | 6.0 | 11.1 | 9.0 |
| 7 | 137 | 2 | 68.5 | 8.5 | 8.5 | 14.2 | |
| 8 | 139 | 2 | 69.5 | 1.0 | 1.0 | 1.5 | |
| 9 | 146 | 2 | 73.0 | 3.5 | 3.5 | 5.2 | |
| 10 | 165 | 2 | 82.5 | 9.5 | 9.5 | 13.0 | |
| 11 | 180 | 2 | 90.0 | 7.5 | 7.5 | 9.1 | 6.0 |
| 12 | 187 | 2 | 93.5 | 3.5 | 3.5 | 3.9 | |
| 13 | 189 | 2 | 94.5 | 1.0 | 1.0 | 1.1 | |
| 14 | 207 | 2 | 103.5 | 9.0 | 9.0 | 9.5 | |
| 15 | 220 | 2 | 110.0 | 6.5 | 6.5 | 6.3 | |
| 16 | 255 | 2 | 127.5 | 17.5 | 17.5 | 15.9 | 6.5 |
| 17 | 248 | 2 | 124.0 | —3.5 | —3.5 | —2.7 | |
| 18 | 268 | 2 | 134.0 | 10.0 | 10.0 | 8.1 | |
| 19 | 288 | 2 | 144.0 | 10.0 | 10.0 | 7.5 | |
| 20 | 298 | 2 | 149.0 | 5.0 | 5.0 | 3.5 | |
| 21 | 316 | 2 | 158.0 | 9.0 | 9.0 | 6.0 | 5.1 |
| 22 | 320 | 2 | 160.0 | 2.0 | 2.0 | 1.3 | |
| 23 | 346 | 2 | 173.0 | 13.0 | 13.0 | 8.1 | |
| 24 | | | | | | | |
| 25 | | | | | | | |
| 26 | | | | | | | |
| 27 | 399 | 2 | 199.5 | 26.5 | 6.6 | 3.8 | 3.7 |
| 28 | 418 | 2 | 209.0 | 9.5 | 9.5 | 4.8 | |
| 29 | 422 | 2 | 211.0 | 2.0 | 2.0 | .9 | |
| 30 | 444 | 2 | 222.0 | 11.0 | 11.0 | 5.2 | |

GROWTH OF CHICKENS. A, MALES—(*Continued*)

| Age Days | Total Weight Grams | Total Obs. | Average | Increase Over Last Measurement | Average Daily Increase | Daily Per Cent. Increase | Av. Daily Per Cent. Increase |
|---|---|---|---|---|---|---|---|
| 31 | 494 | 2 | 247.0 | 25.0 | 25.0 | 11.3 | 5.2 |
| 32 | 524 | 2 | 262.0 | 15.0 | 15.0 | 6.1 | |
| 33 | 533 | 2 | 266.5 | 4.5 | 4.5 | 1.7 | |
| 34 | 564 | 2 | 282.0 | 15.5 | 15.5 | 5.8 | |
| 35 | 570 | 2 | 285.0 | 3.0 | 3.0 | 1.1 | |
| 36 | 600 | 2 | 300.0 | 15.0 | 15.0 | 5.3 | 4.2 |
| 37 | 606 | 2 | 303.0 | 3.0 | 3.0 | 1.0 | |
| 38 | 661 | 2 | 330.5 | 27.5 | 27.5 | 9.1 | |
| 39 | 662 | 2 | 331.0 | .5 | .5 | .1 | |
| 40 | 700 | 2 | 350.0 | 19.0 | 19.0 | 5.7 | |
| 42 | 737 | 2 | 368.5 | 18.5 | 9.2 | 2.6 | 2.2 |
| 44 | 788 | 2 | 394.0 | 25.5 | 12.7 | 3.4 | |
| 46 | 815 | 2 | 407.5 | 13.5 | 6.7 | .8 | |
| 48 | 849 | 2 | 424.5 | 17.0 | 8.5 | 2.1 | |
| 50 | 881 | 2 | 440.5 | 16.0 | 8.0 | 1.9 | |
| 52 | 926 | 2 | 463.0 | 22.5 | 11.0 | 2.5 | 2.7 |
| 54 | 984 | 2 | 492.0 | 29.0 | 14.5 | 3.1 | |
| 56 | | | | | | | |
| 58 | | | | | | | |
| 60 | 1127 | 2 | 563.5 | 71.5 | 11.9 | 2.4 | |
| 62 | 1194 | 2 | 597.0 | 33.5 | 16.7 | 2.9 | 2.8 |
| 64 | 1182 | 2 | 591.0 | —6.0 | —3.0 | —.5 | |
| 66 | 1297 | 2 | 648.5 | 57.5 | 28.7 | 4.8 | |
| 68 | 1318 | 2 | 659.0 | 10.5 | 5.2 | .8 | |
| 70 | 1400 | 2 | 700.0 | 41.0 | 20.5 | 3.1 | |
| 72 | | | | | | | |
| 74 | 1552 | 2 | 776.0 | 76.0 | 19.0 | 2.7 | 2.1 |
| 76 | | | | | | | |
| 78 | | | | | | | |
| 80 | 1692 | 2 | 846.0 | 70.0 | 11.7 | 1.5 | |
| 82 | 1853 | 2 | 926.5 | 80.5 | 40.2 | 4.7 | 2.3 |
| 86 | 1974 | 2 | 987.0 | 60.5 | 15.1 | 1.6 | |
| 90 | 2056 | 2 | 1028.0 | 41.0 | 10.2 | 1.0 | |
| 94 | | | | | | | |
| 98 | 2408 | 2 | 1204.0 | 176.0 | 22.0 | 2.1 | |
| 102 | 2705 | 2 | 1352.5 | 148.5 | 37.1 | 3.1 | 1.5 |
| 106 | 2783 | 2 | 1391.5 | 39.0 | 9.7 | .7 | |
| 110 | 2869 | 2 | 1434.5 | 43.0 | 10.7 | .8 | |
| 120 | 3185 | 2 | 1592.5 | 158.0 | 15.8 | 1.1 | 1.0 |
| 125 | 3450 | 2 | 1725.0 | 132.5 | 26.5 | 1.7 | |
| 130 | 3452 | 2 | 1726.0 | 1.0 | .2 | .1 | |
| 135 | 3636 | 2 | 1818.0 | 92.0 | 18.4 | 1.1 | |
| 140 | 3840 | 2 | 1920.0 | 102.0 | 20.4 | 1.1 | |
| 192 | 4897 | 2 | 2448.5 | 528.5 | 10.2 | .5 | .3 |
| 197 | 5025 | 2 | 2512.5 | 64.0 | 12.8 | .5 | |
| 202 | 4965 | 2 | 2482.5 | —30.0 | —6.0 | —.2 | |
| 335 | 5552 | 2 | 2776.0 | 293.5 | 2.2 | .09 | .1 |
| 341 | 5559 | 2 | 2779.5 | 3.5 | .6 | .02 | |
| 351 | 5475 | 2 | 2737.5 | —42.0 | —4.2 | —.1 | |

GROWTH OF CHICKENS. B, FEMALES

| Age Days | Total | | Average | Increase Over Last Measurement | Average Daily Increase | Daily Per Cent. Increase | Av. Daily Per Cent. Increase |
|---|---|---|---|---|---|---|---|
| | Weight Grams | Obs. | | | | | |
| 0 | 39 | 1 | 39 | | | | |
| 1 | 326 | 8 | 40.7 | | | | |
| 2 | 321 | 8 | 40.1 | —.6 | —.6 | —1.5 | 4.2 |
| 3 | 330 | 8 | 41.2 | 1.1 | 1.1 | 2.7 | |
| 4 | 352 | 8 | 44.0 | 2.8 | 2.8 | 6.8 | |
| 5 | 383 | 8 | 47.9 | 3.9 | 3.9 | 8.9 | |
| 6 | 419 | 8 | 52.4 | 4.5 | 4.5 | 9.4 | 8.6 |
| 7 | 468 | 8 | 58.5 | 6.1 | 6.1 | 11.6 | |
| 8 | 475 | 8 | 59.4 | .9 | .9 | 1.5 | |
| 9 | 504 | 8 | 63.0 | 3.6 | 3.6 | 6.1 | |
| 10 | 577 | 8 | 72.1 | 9.1 | 9.1 | 14.4 | |
| 11 | 610 | 8 | 76.2 | 4.1 | 4.1 | 5.7 | 5.8 |
| 12 | 633 | 8 | 79.1 | 2.9 | 2.9 | 3.8 | |
| 13 | 668 | 8 | 83.5 | 4.4 | 4.4 | 5.6 | |
| 14 | 710 | 8 | 88.7 | 5.2 | 5.2 | 6.2 | |
| 15 | 764 | 8 | 95.5 | 6.8 | 6.8 | 7.7 | |
| 16 | 880 | 8 | 110.0 | 14.5 | 14.5 | 15.2 | 7.1 |
| 17 | 876 | 8 | 109.5 | —.5 | —.5 | —.5 | |
| 18 | 938 | 8 | 117.2 | 7.7 | 7.7 | 7.0 | |
| 19 | 995 | 8 | 124.4 | 7.2 | 7.2 | 6.1 | |
| 20 | 1071 | 8 | 133.9 | 9.5 | 9.5 | 7.6 | |
| 21 | 1116 | 8 | 139.5 | 5.6 | 5.6 | 4.2 | 5.0 |
| 22 | 1139 | 8 | 142.4 | 2.9 | 2.9 | 2.1 | |
| 23 | 1082 | 7 | 154.6 | 12.2 | 12.2 | 8.6 | |
| 24 | | | | | | | |
| 25 | | | | | | | |
| 26 | 144 | 1 | 144.0 | —10.6 | —3.5 | —2.3 | 5.4 |
| 27 | 1356 | 8 | 169.5 | 25.5 | 25.5 | 17.7 | |
| 28 | 1416 | 8 | 177.0 | 7.5 | 7.5 | 4.4 | |
| 29 | 1448 | 8 | 181.0 | 4.0 | 4.0 | 2.3 | |
| 30 | 1519 | 8 | 189.9 | 8.9 | 8.9 | 4.9 | |
| 31 | 1656 | 8 | 207.0 | 17.1 | 17.1 | 9.0 | 5.5 |
| 32 | 1733 | 8 | 216.6 | 9.6 | 9.6 | 4.6 | |
| 33 | 1787 | 8 | 223.4 | 6.8 | 6.8 | 3.1 | |
| 34 | 1908 | 8 | 238.5 | 15.1 | 15.1 | 6.8 | |
| 35 | 1985 | 8 | 248.1 | 9.6 | 9.6 | 4.2 | |
| 36 | 2057 | 8 | 257.1 | 9.0 | 9.0 | 3.6 | 3.8 |
| 37 | 2114 | 8 | 264.2 | 7.1 | 7.1 | 2.8 | |
| 38 | 2254 | 8 | 281.7 | 17.5 | 17.5 | 6.6 | |
| 39 | 2303 | 8 | 287.9 | 6.2 | 6.2 | 2.2 | |
| 40 | 2394 | 8 | 299.2 | 11.3 | 11.3 | 3.9 | |
| 42 | 2572 | 8 | 321.5 | 22.3 | 11.1 | 3.7 | 2.5 |
| 44 | 2742 | 8 | 342.7 | 21.2 | 10.6 | 3.3 | |
| 46 | 2841 | 8 | 355.1 | 12.4 | 6.2 | 1.8 | |
| 48 | 2634 | 7 | 376.3 | 21.2 | 10.6 | 3.0 | |
| 50 | 3064 | 8 | 383.0 | 6.7 | 3.3 | .9 | |

## GROWTH OF CHICKENS. B, FEMALES—(*Continued*)

| Age Days | Total | | Average | Increase Over Last Measurement | Average Daily Increase | Daily Per Cent. Increase | Av. Daily Per Cent. Increase |
|---|---|---|---|---|---|---|---|
| | Weight Grams | Obs. | | | | | |
| 52 | 3209 | 8 | 401.1 | 18.1 | 9.0 | 2.3 | 3.4 |
| 54 | 3430 | 8 | 428.7 | 27.6 | 13.8 | 3.4 | |
| 56 | | | | | | | |
| 58 | 426 | 1 | 426.0 | —2.7 | —.7 | —.1 | |
| 60 | 3973 | 8 | 496.6 | 70.6 | 35.3 | 8.2 | |
| 62 | 4255 | 8 | 531.9 | 35.3 | 17.6 | 3.5 | 2.4 |
| 64 | 4274 | 8 | 534.2 | 2.3 | 1.1 | .2 | |
| 66 | 4639 | 8 | 579.9 | 45.7 | 22.8 | 4.3 | |
| 68 | 4861 | 8 | 607.6 | 27.7 | 13.8 | 2.4 | |
| 70 | 5021 | 8 | 627.6 | 20.0 | 10.0 | 1.6 | |
| 72 | | | | | | | |
| 74 | 5538 | 8 | 692.2 | 64.6 | 16.1 | 2.4 | 2.5 |
| 76 | | | | | | | |
| 78 | 707 | 1 | 707.0 | 14.8 | 3.9 | .5 | |
| 80 | 5398 | 7 | 771.1 | 64.1 | 32.0 | 4.5 | |
| 82 | 6592 | 8 | 824.0 | 52.9 | 26.9 | 3.4 | 1.7 |
| 86 | 6924 | 8 | 865.5 | 41.5 | 10.4 | 1.2 | |
| 90 | 7093 | 8 | 886.6 | 21.1 | 5.3 | .5 | |
| 94 | | | | | | | |
| 98 | 8173 | 8 | 1021.6 | 135.0 | 16.9 | 1.9 | |
| 102 | 8981 | 8 | 1122.6 | 101.0 | 25.2 | 2.5 | 1.5 |
| 106 | 9552 | 8 | 1194.0 | 71.4 | 17.8 | 1.6 | |
| 110 | 9742 | 8 | 1217.7 | 23.7 | 5.9 | .5 | |
| 115 | | | | | | | |
| 120 | 10593 | 8 | 1324.1 | 106.4 | 10.6 | .9 | .8 |
| 125 | 9831 | 7 | 1404.4 | 80.3 | 16.1 | 1.2 | |
| 130 | 11492 | 8 | 1436.5 | 32.1 | 6.4 | .5 | |
| 135 | 12087 | 8 | 1510.9 | 74.4 | 14.9 | 1.0 | |
| 140 | 12456 | 8 | 1557.0 | 46.1 | 9.2 | .6 | |
| 192 | 15786 | 8 | 1973.2 | 416.2 | 8.0 | .5 | .5 |
| 197 | 16546 | 8 | 2068.2 | 95.0 | 19.0 | 1.0 | |
| 202 | 16551 | 8 | 2068.9 | .7 | .1 | .00 | |
| 335 | 17276 | 8 | 2159.5 | 90.6 | .7 | .03 | .2 |
| 341 | 16985 | 8 | 2123.1 | —36.4 | —6.1 | —.3 | |
| 351 | 17535 | 8 | 2191.9 | 68.8 | 6.9 | .3 | |

## APPENDIX III. DEATH OF PROTOZOA

IN 1877 I pointed out that a Protozoon cannot be directly compared with a Metazoan (*Proceedings Boston Society of Natural History*, April 18th, p. 170), and in 1879 formulated this opinion more clearly. Since each Metazoon consists of many successive generations of cells, it really is a cell cycle, and can only be homologised with a cycle of protozoan generations, not with any single Protozoon, which is but a single cell. Hence it follows that the death of an individual Protozoon is not homologous with the death of an individual multicellular animal.

Weismann committed the fundamental error of assuming the complete homology of the two forms of death, and thus reached the false conclusion that Protozoa are all certainly potentially immortal. The error is all the more important because without assuming its truth the whole speculative structure of germ plasm hypotheses cannot stand. As Oskar Hertwig has already expounded in the first part of his *Zeit und Streitfragen* the dependence of Weismann's "Keimplasm" doctrines upon the incorrect hypothesis of Protozoon immortality, it is unnecessary to discuss the matter further.

Concerning Weismann's notions about death a few words may be added. His view was first published in 1882, in his essay *Ueber die Dauer des Lebens*, and it has been again advocated in his article *Ueber Leben und Tod* (1884), and has been defended by him subsequently.[1] Weismann missed the real problem, which is whether Protozoa like Metazoa develop in senescent cell cycles. My position is unchanged, and is clearly presented by the following quotation from an article in the *American Naturalist*:

"He [Weismann] misses the real problem. The following

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[1] E. g., *Biologisches Centralblatt.*, iv., p. 690.

reasoning leads to this decision. Protozoa and Metazoa consist of successive generations of cells ; in the former the cells separate ; in the latter they remain united ; the death of a Protozoon is the annihilation of a cell, but the death of a Metazoon is the dissolution of the union of cells. Such a dissolution is the result of time, that is to say, of the period necessary to the natural duration of life, and we call it, therefore, 'natural death.' Moreover, we know that natural death is brought about by gradual changes in the cells until, at last, certain cells, which are essential to the preservation of the whole, cease their functions. Death, therefore, is a consequence of changes which progress slowly through successive generations of cells. These changes cause senescence, the end of which is death. If we wish to know whether death, in the sense of natural death, properly so called, occurs in Protozoa or not, we must first possess some mark or sign, by which we can determine the occurrence or absence of senescence in unicellular organisms.

"Around this point the whole discussion revolves. Certainly a simpler and more certain conclusion could hardly be drawn than that the death of a Metazoon is not identical, *i.e.*, homologous, with the death of a single cell. Weismann tacitly assumed precisely this homology, and bases his whole argument on it. In all his writings upon this subject, he regards the death of a Protozoon as immediately comparable with the death of a Metazoon. If we seek from Weismann for the foundation of this view we shall have only our labour for our pains. Starting from this view Weismann comes to the strictly logical conclusion that the Protozoa are immortal. This is a paradox ! In fact, if one compares death in the two cases, from Weismann's standpoint, then we must assume a difference in the causes of death, and conclude that the cause in the case of the Protozoa is external only, while in the Metazoa it is internal only, for, of course, we may leave out of account the accidental deaths of Metazoa. If we approach the problem from this side, we encounter the following principal question : Does death from inner causes occur in Protozoa? Weismann gives a negative answer to this question, with his assertion that unicellular organisms are immortal. The assertion remains, but the proof of the assertion is lacking. In order to justify the assertion, it must be demonstrated that there does not occur in Protozoa a true senescence, showing itself gradually through successive generations of cells. Has Weismann furnished this demonstration? Certainly not. He has, strictly speaking, not discussed the subject. It is clear that we must first determine whether natural death from senescence occurs in Protozoa or not, before we can pass to a scientific discussion of the asserted immortality of unicellular beings. The problem cannot be otherwise apprehended. Weismann has not thus conceived it, therefore the judgment stands against him: *he misses the real problem.*"

E. Maupas[1] has maintained that among unicellular animals loss of vitality (senescence) and actual rejuvenation could be demonstrated. He was the first to follow a colony of Protozoa through a long series of generations with a view to determining the changes in the life cycle. His conclusion is that there is an actual exhaustion of the cells going on with the progress of the generations, and that conjugation must occur to effect "réjeunissement" (rejuvenescence) otherwise the cells of the cycle die off. Similar experiments have been made in this country by G. N. Calkins,[2] who likewise concludes that the development of Protozoa is cyclical, the end of the cycle coming through senile degeneration of the cells, and new cycles beginning by a rejuvenation effected by conjugation. If these conclusions are correct we must expect to find proof of cyclical development in other Protozoa.

Maupas and Calkins leave a fundamental question undecided.

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[1] E. Maupas, *Archives de Zool. Expér.*, *i.*, 299; *i.*, 427 (1883); vi., 165 (1888); vii., 149 (1889).

[2] G. N. Calkins, "Studies in the Life History of Protozoa," *Arch. für. Entwickelungs mechanik*, xv., 139–186, also *Biol. Bulletin*, iii., 192–205, and *Journ. Exp. Zool.*, i., 423–461 (1904). A comprehensive and later presentation of Calkins's views on the protozoan life cycle is given by him in chapter xvii. of the first volume of Osler's *Modern Medicine* (1907); see especially pp. 361–367.

If it be admitted that the mark of senescence in the Metazoa is increase in the proportion of protoplasm, and the mark of rejuvenation increase of the nuclei, then we must expect similar variations in the protozoa, if there be true senescence and rejuvenation among them. It is probable that the observations to decide this question can be made without serious difficulty, and indeed I think they will soon be successfully accomplished.

Professor Richard Hertwig has also developed views concerning the death of Protozoa, which are certainly interesting, suggestive, and important and have been summarised by the author in a special article.[1] He accepts the views of Calkins as to "*depression*" among Protozoa, but thinks that a further explanation is necessary to explain senescence among Metazoa. I quote from p. 23 of reprint: "Die Teilungsfähigkeit der Zellen eines ausgewachsenen Menschen oder Tieres ist also nicht erloschen, sie ist nur nicht im Stande sich zu betätigen; sie ist zurückgehalten. . . . Mit anderen worten die Zellen eines hochentwickelten Tieres teilen sich nicht, weil sie den Wachsthumsgesetzen des Ganzen unterworfen sind, wie ein jeder von uns den Gesetzen des Staates." I agree with Professor Hertwig that the inhibition of growth plays an extremely important rôle in the higher animals, but as this whole volume argues, I think that cytomorphosis produces true senescence of individual cells, and that this senescence is more fundamental and essential than the inhibitory control.

The paper by M. Hartmann[2] on Death, I have not seen. From a review of it in the *Zoologisches Centralblatt.*, 1907, 543, I infer that he has revived the idea that reproduction is the cause of death. He is said to maintain that natural death does occur among the protozoa. The review cited says: "Das Resultat seiner Erörterungun fasst unser Autor dahin zusammen dass allen Protozoen (Protisten ueberhaupt) ein natürlicher Tod zukommt und dieser ausnahmslos mit der Fortpflanzung zusammenfällt."

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[1] R. Hertwig, "Über die Ursache des Todes," Beilage zur *Allgemeinen Zeitung*, Dez. 12 u. 13, 1906.

[2] M. Hartmann, *Tod und Fortpflanzung*, München, 1906.

## APPENDIX IV. LONGEVITY OF ANIMALS

AUGUST WEISMANN in his essay on *Lebensdauer* has collected many data in regard to the longevity of animals. It is by far the best compilation of the sort known to me.

Mr. F. A. Lucas, Curator of the Brooklyn Museum, has given me some additional facts, and by his courtesy I am allowed to publish the following quotation from a letter which he addressed to me on November 27, 1907:

"So far as we know the Aldabra tortoises have reached the greatest age—from ninety to one hundred and fifty years. Of this we may be positive. Carp 'are said' 'to have lived over a hundred years,' and I should not be surprised if this were true. I doubt much if any mammals attain such an age. Until I went to Newfoundland in 1903 I had credited the whale with living to a very great age, but my examination of the many specimens I saw there leads me to doubt this. I discussed the matter a little in *Nature* and in *Science*, but the gist of the matter is this—if whales lived indefinitely there should be an indefinite number of sizes, whereas the animals fall into comparatively few groups as regards size, and I now doubt if the whale lives much more than twenty-five years, though this is a mere guess. Observations made on the Pribilof Islands during the past ten years show that the fur seals probably do not reach the age of twenty years with which they have been credited and the fur seal is a fairly large mammal. Even in regard to reptiles, which have been supposed to grow very slowly and almost indefinitely, recent observations have shown that the Galapagos tortoise and our own alligator may grow quite rapidly."

# APPENDIX V. THEORY OF LIFE

THE abstract of the paper on the theory of life, referred to on p. viii., is here reprinted because it still indicates the starting point of the studies, the results of which are given in the current volume. So little have we gained since 1879 in our comprehension of the basic phenomena of living things that were I to rewrite the abstract in accordance with present knowledge I should not change it essentially. The vitalistic hypothesis still seems to me scientifically the best.

## ON THE CONDITIONS TO BE FILLED BY A THEORY OF LIFE. BY CHARLES SEDGWICK MINOT, of Boston, Mass.

[ABSTRACT.]

It has been so often asserted that the essential nature of life cannot be discovered by man, that the remark has become commonplace. It would seem that this assertion is merely the assumption of haste, and is based only upon our present ignorance of vital properties. It should rather be said that the main object of all botanical and zoölogical studies is ultimately to discover the vital principle. The conviction that such is the end of biological research has led me for several years past to endeavour to sort out those vital phenomena which are most universal, in order to determine what are the principal and essential functions of living bodies. Such a labour cannot add much that is new to science, but it forced me to the conclusion that the favourite speculations of the present time concerning the origin and nature of life as explained by science were superficial and even crude, principally because they were not based upon a careful examination of the phenomena to be explained. In order to avoid erroneous opinions I have deferred publication for a long time, during which, however, no very essential improvement of the outline I had drawn has occurred to me. To deal with such difficult and dangerous questions with complete success requires more knowledge and judgment than I possess; I hope, therefore, to be allowed to publish what follows rather as opinions I deem plausible, than as conclusions I believe certain. Of one thing, however, I feel sure—that it is useless to discuss the opposing claims of conscious automatism, the mechanical theory of life and a vital principle, until we decide what are really the vital phenomena to be explained.

All the higher animals and plants are known to consist of colonies of cells. There are beside many unicellular animals and plants. Of late years there have been described a large number of organisms stated to consist solely of protoplasm. It is on these discoveries that the various protoplasm theories of life have been founded. Many popular articles have been written beginning with the assertion that protoplasm is a simple, jelly-like mass, and ending with the conclusion that life depends solely on the mechanical properties of protoplasm. I think it cannot be too seriously regretted that respectable periodicals have published so many of such articles, because all but the ignorant know that protoplasm is not jelly-like, and not simple; on the contrary, it consists of many and various chemical compounds, and from recent investigations it has become probable that it never exists as a homogeneous mass, but always contains numerous vacuoles, each enclosing some distinct substance or substances, liquid or solid; this structure explains the appearance of the so-called protoplasmatic network. Moreover, protoplasm probably cannot permanently maintain its life when separated from a nucleus.[1] The number of protoplasmatic animals supposed to be without nuclei has rapidly diminished,—especially as the nucleus of the

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[1] By this I mean only, that *all* vital functions cannot be performed, because to some of them the nucleus is necessary. Of course protoplasm may remain alive when separated from the nucleus, but the possibility of reproduction is probably lost.

Foraminiferæ has been discovered, and the unicellular nature of the Infusoria established. To say that all the supposed protoplasmatic animals have a nucleus is not yet safe, but it must not be forgotten that in many cases the nucleus is discoverable when properly searched for with the aid of nice histological methods, and that those cases where it has not been found as yet are all cases of uncertainty, partly because careful observations have not been made, partly because the objects themselves are too minute. The probability, therefore, is against the separate existence of protoplasm, and is in favour of the universal presence of the nucleus. This view is strengthened by the discovery of the real nature of Bathybius.

A cell must, therefore, be regarded as the unit of life, and the problem we are considering becomes to determine the general properties and functions of cells. I reason chiefly upon the basis of zoölogy, that branch of biology which alone I have studied scientifically. The principal peculiarities of cells, as thus determined, I consider to be as follows :

1. *Irritability.* When some motion strikes the cell it may simply act mechanically or give rise to peculiar effects which occur only in living matter. Nothing but some mode of motion ever acts as a stimulus. The effect produced by stimuli is a sensation. The stimuli may come from the outside or from the inside of the cell. The ultimate effects of the irritation may be inhibited,—that is delayed or prevented by the cell itself.

2. *The power of doing work*, or developing in response to a stimulus, or from some other cause, a certain amount of motion or energy. The work done may be mechanical, electrical, calorific, or even luminiferous. The power of doing work cannot be sustained indefinitely, hence the phenomena of fatigue or exhaustion, and recovery.

3. *To set free energy by chemical changes ;* each cell must be supposed to maintain a vortex by which matter is continually drawn in from the outside, the elements re-combined, and finally *in part* ejected, while the shape of the vortex or cell is preserved.

4. *Growth.* The cell retains permanently a portion of the matter drawn in by the vortex.

5. *Multiplication.* The cell cannot grow beyond a certain limit, but instead of further enlargement it divides. (The budding of Infusoria is only a peculiar form of cell division.)

6. *Senescence.* With each successive generation of cells the power of growth diminishes. Were this otherwise, the growth of each individual at any given time would be in geometrical progression. This loss of power I term senescence.

7. *Rejuvenation.* The effects of senescence are overcome by some of the cells separating in character from the rest, and giving rise to peculiar bodies, the eggs and spermatozoa. A new cycle of cell generations is thus formed. In each cycle there is a slow senescence terminating in the formation of a new cycle by the rejuvenating influence of the sexual products.

8. *Material continuity of life.* The actual continuity of living matter is unbroken in consequence of the nature of cell division and of the origin of the sexual products. We cannot, therefore, yet conceive the origin of life, especially as all attempts to demonstrate spontaneous generation have been unconvincing.

9. *Heredity.* Every cell inherits the qualities of its parents, though imperfectly. The resemblance of an animal to its parent is due to the fact that a given cell of the parent cycle transmits an influence to the child cycle, tending to cause a similar cell to be developed in the same place and at the same time in the offspring. Heredity is imperfect, both inherently and from the effects of external circumstances.

10. *Direct influence of external circumstances.* This has now become established in several cases.

11. *Predetermined union of cells.* When the cells of one cycle unite to form an animal, they arrange themselves definitely in three sets (germ layers), at least in the higher metazoa.

12. *Vital union of cells.* Some of the cells of each set are united by means of the nerves into a common neural union or association, each member of which loses some of its originality and independence as an individual cell, and becomes able to affect the

other members of the union both in their growth, nourishment, and sensations.

13. *Teleological mechanism.* This principle has been recently clearly formulated by Pflüger—a need causes its own satisfaction, *e.g.*, the need of digestion produced by the presence of food causes the secretion of the digestive fluids.

14. *Memory.* Man knows by introspection that he has memory; we attribute it to the higher animals by common consent, and there is no reason for denying its existence in the lower forms. Real memory implies consciousness, otherwise it cannot be known that the sensation refers to the past.

15. *Habit.* This may be best defined as unconscious memory. It seems to me a grave error to identify habit and real memory. Habit implies that acts become easier if repeated.

16. *Consciousness.* Our knowledge of this, as of memory, is introspective, and is attributable to animals for the same reasons.

17. *Free will.* If there be such a thing it must of course be entered here.

These are the essential categories of the phenomena of animal life, and as they are all performed by colonies of cells, they must be the work of the units of such colonies, or in other words each one of these properties is that of a cell. There are reasons for thinking that unicellular animals have the same properties. To summarise, every cell performs all functions:

1. Responds to stimuli.
2. Maintains the vortex.
3. Grows and divides.
4. Inherits, varies, and bequeaths.

Further, each cell probably has

5. A sexual power, usually dormant.
6. Consciousness.
7. Memory.
8. Habit.

To explain life we must discover why it displays itself only in a physical basis composed of various albumenoid molecules, imbibed with water and certain salts, and commingled with other complex organic compounds, all disposed in a definite order; why this basis divides into distinct masses, cells, grouped each around a distinct body, the nucleus; why chemical and physical events take place in a particular order in each cell, the regulating power being within the cell itself; why senescence and rejuvenation take place; and finally the sources of consciousness, memory, and habit. No mechanical explanation, or theory of conscious automatism suffices, but a vital force is the only reasonable hypothesis; the nature of that force is, for the present, an entire mystery, and before we can expect to discover it we must settle what are the phenomena to be explained by it.

[From the *Proceedings* of the American Association for the Advancement of Science, vol. xxviii., Saratoga Meeting, August, 1879.]

# APPENDIX VI. THE AGE-RECKONER

IN making records of growth it is advantageous to weigh the animals at definite ages, using the same ages in all cases. As it is somewhat laborious to calculate the proper dates for an animal born on a given day, the age-reckoner, herewith figured, was devised. It does away with all calculation, for after setting the machine for a given birth-date, all the dates on which weighings are to be made can be read off at once. The apparatus as shown in the figure consists of two metal wheels close together on a single axle. The rims of the wheels are broad and each one bears 365 lines, one for each day in the year. The right-hand wheel is inscribed with the months and days of the month, for example, "*Nov.*" marks November 1st, the numbers below November 5th, 15th, and 25th. "*Dec.*" marks December 1st. This wheel which bears the dates may be called the "*calendar wheel*," and is attached permanently upon the axis. The left or "*age wheel*" can be revolved without turning the axis, so that it can be set with its zero line opposite any date on the calendar wheel; it can then, by means of the set screw seen in the figure, be clamped to the axle, and both wheels will then revolve together. Upon the age wheel the ages are marked, for every ten days up to 210, thereafter every thirty for five months. Obviously after the age wheel has been set with its zero at the date of birth and been clamped, all the ages selected for weighing will fall opposite the proper dates, and may be read off by simply revolving the two wheels.

It was the usual practice as soon as an animal (or litter) was born to set the age-reckoner, and then copy down from it on a sheet of paper all the dates for weighing the animal during the ensuing year. Then in a diary all the animals of whatever sort to be weighed were entered for each day, thus reducing the chance of omissions.

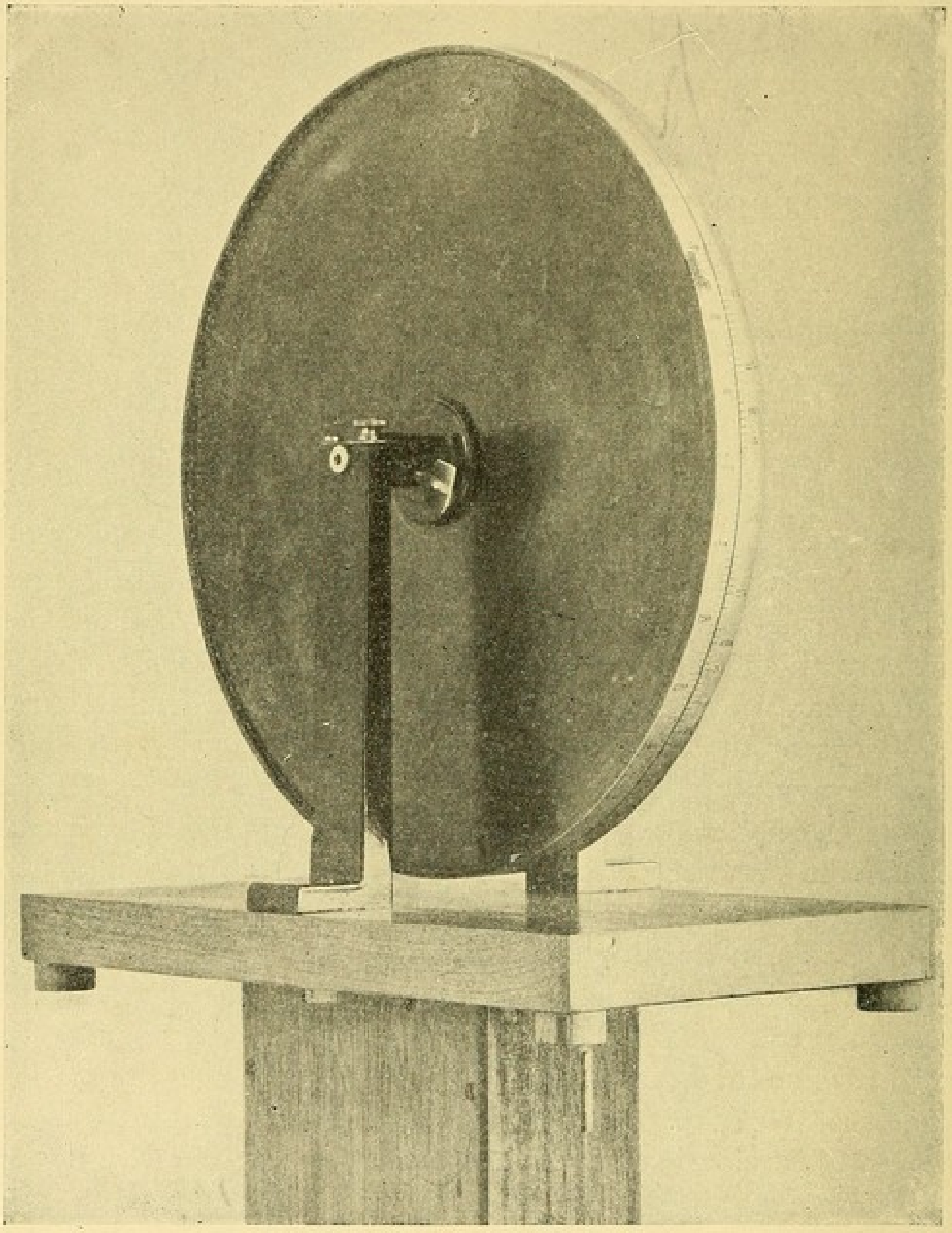

FIG. 73. AGE-RECKONER.

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