THE CELL

INTRODUCTION

"*Every animal appears as a sum of vital units*, each of which bears in itself the complete characteristics of life." VIRCHOW.[1]

Among the milestones of modern scientific progress the cell-theory of Schleiden and Schwann, enunciated in 1838–39, stands forth as one of the commanding landmarks of the nineteenth century. Its importance is not to be judged by its original form; as first outlined it was but a rude sketch, in many respects faulty and distorted. Its announcement nevertheless marked a turning point in the advance of biology, opening a new point of view for the study of living organisms, and revealing the outlines of a fundamental common plan of organization that underlies their endless external diversity. The cell-theory thus became a perennial source of fruitful researches which down to our own day have continued to press forward into always expanding fields of discovery. Long ago it became evident that the key to every biological problem must finally be sought in the cell; for every living organism is, or at some time has been, a cell. Applied by Goodsir, Virchow and their successors to the analysis of organic functions, the cell-theory opened far-reaching new vistas of progress in physiology and pathology and revolutionized our views of vital action, in health and in disease. It was the guide of Remak, Nägeli, Kölliker, and other immediate followers of Schleiden and Schwann, in those pioneer microscopical researches which ultimately demonstrated that cell-division constitutes the central phenomenon in organic reproduction, genetic continuity and heredity. Thirty years later it was the cell-theory that cleared the way for a remarkable group of investigators, including Fol, Auerbach, Bütschli, O. Hertwig, Van Beneden, Flemming, Strasburger and Carnoy, who laid the foundations for the new science of cytology and solved at last the ancient riddle of the fertilization of the egg and the beginnings of the individual life. Followed up especially by Boveri and his successors these researches provided the basis for a detailed analysis of heredity and development that stands among the most remarkable achievements of our time. Every field of biological research has been illuminated by the cell-theory. In respect to the range and diver-

[1] *Cellularpathologie*, 1858, p. 12.

sity of the phenomena which it has brought under a single point of view it is surpassed by no other of the great generalizations of biology, and equaled only by the theory of organic evolution. By force of habit we still continue to speak of the cell "theory" but it is a theory only in name. In substance it is a comprehensive general statement of fact and as such stands to-day beside the evolution-theory among the foundation-stones of modern biology.

The cell-theory and the evolution-theory are now closely affiliated; but the historian of biology is struck by the fact that for a long time they did not come within hailing distance of each other. The theory of evolution originally grew out of the study of natural history and took definite shape long before the finer structure of living bodies was made known. A century ago, in the time of Lamarck and Cuvier, naturalists had but the vaguest notions concerning the finer details of internal organization. They were mainly concerned with more obvious characters of living things; with forms, colors, habits, distribution; with gross anatomy, organogeny and morphological classification. Long afterwards it was in the main the study of such characters that led to the Darwinian revolution. The study of cells and their activities seemed at first to have little connection with all this. The convergence between the study of cells (cytology) and that of heredity and evolution (genetics) was set on foot more than forty years after Schleiden and Schwann, and it is still in the full tide of its advance.

In tracing the main outlines of this movement we may conveniently divide the history of the subject since Schleiden and Schwann into three periods. The first, from 1840 to 1870, was a time of foundation, during which the fundamental outlines of the cell-theory were marked out and the principles of genetic continuity became more clearly defined. The second, extending from 1870 to 1900, included a development of cytology and cellular embryology which gave more definite form to our general ideas concerning the physical basis of heredity and the mechanism of development. The third period, opening with the rediscovery of Mendel's laws of heredity in 1900, includes those modern and more searching inquiries into the mechanism of sex and heredity which find their fullest expression in the so-called chromosome-theory of heredity. These periods are separated by no sharply drawn boundaries; they are but different phases of a single movement. We approach it by a statement of the most elementary facts from which it proceeded.[1]

[1] Schleiden and Schwann are universally and rightly recognized as the founders of the cell-theory; but like every other great generalization it was preceded by a long series of earlier investigations, beginning with the memorable microscopical studies of Leeuwenhoek, Malpighi, Grew and Hooke in the latter half of the seventeenth century.

Wolff, in the *Theoria generationis* (1759), clearly recognized the "spheres" and "vesicles" composing the embryonic parts both of animals and of plants, though he did not grasp their real nature or mode of origin. His conclusions were developed by Mirbel, Sprengel and Treviranus early in the

In all higher plants and animals the body may be resolved into a vast assemblage of extremely minute structural units, known as *cells* out of which, or their products, every part is built (Figs. 1, 2). The substance of the skin, of

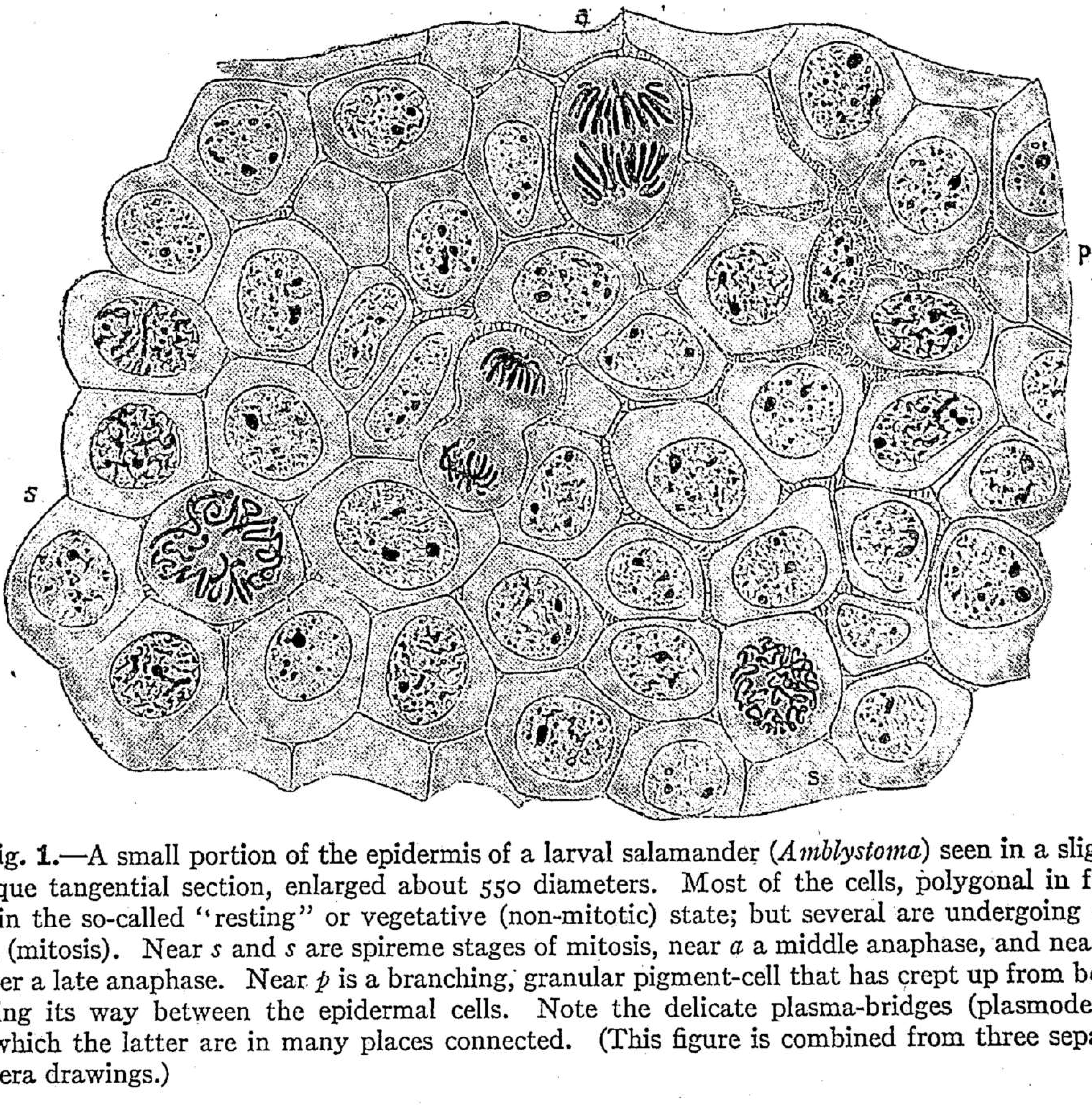

Fig. 1.—A small portion of the epidermis of a larval salamander (*Amblystoma*) seen in a slightly oblique tangential section, enlarged about 550 diameters. Most of the cells, polygonal in form, are in the so-called "resting" or vegetative (non-mitotic) state; but several are undergoing division (mitosis). Near *s* and *s* are spireme stages of mitosis, near *a* a middle anaphase, and near the center a late anaphase. Near *p* is a branching, granular pigment-cell that has crept up from below, forcing its way between the epidermal cells. Note the delicate plasma-bridges (plasmodesmis) by which the latter are in many places connected. (This figure is combined from three separate camera drawings.)

the brain, of the blood, the bones, muscles or of any tissue, is shown by the microscope to be composed of innumerable minute bodies, as if it were a colony or congeries of organisms more elementary than itself (*cf.* p. 101).

nineteeenth century; and nearly at the same time Oken (1805) foreshadowed the cell-theory in the form that it assumed with Schleiden and Schwann. His conception of "Bläschen" and of "Urschleim" was, however, hardly more than a lucky guess. A still closer approximation to the truth, prior to Schleiden and Schwann, appears in the works of Meyen, von Mohl, Raspail and Dutrochet and others. "The cells of plants," writes Meyen in 1830, "appear either singly, so that each one forms a single individual, as in the case of some algæ and fungi, or they are united together in greater or smaller masses to constitute a more highly organized plant. Even in this case each cell forms an independent, isolated whole; it nourishes itself, it builds itself up, and elaborates the raw nutrient materials which it takes up, into very different substances and materials." (Quoted from O. Hertwig, *The Cell*, English Trans., p. 3.) This passage might almost have been written at the present day. Such statements, however, were insufficiently based, and served only to pave the way for the real founders of the cell-theory.

Among other immediate predecessors or contemporaries of Schleiden and Schwann should be especially mentioned: Robert Brown, who discovered the cell-nucleus (1831, published in 1833);

By the early botanists these bodies were casually designated as "cells" (Robert Hooke, 1665), and this name was ultimately adopted by nearly all observers. It was an unlucky term; for later studies proved that cells do not in general have the form of hollow chambers, as the name suggests, but are typically solid bodies. The cell is largely composed of *protoplasm*, a complex mixture of substances, commonly of viscid consistency, and having the general properties of a colloidal system. Early recognized as the active living part of the organism, and later (1868) happily characterized by Huxley as the "physical basis of life," protoplasm is now universally recognized as the immediate substratum of all forms of vital activity.[1] Endlessly diversified in the details of their form and structure cells possess a characteristic common type of organization and may be treated as elementary organic units out of which and their products the body is built. In higher animals and plants (*Metazoa*, *Metaphyta*) the body is *multicellular*, consisting of a great number of such units, while in the lowest organisms or *Protista*, it is unicellular, consisting of but a single cell (Fig. 3). All such organisms, of which a multitude are known, are of microscopic size. They display a wonderful diversity of structural and physiological type. Some are plants (desmids, diatoms, bacteria, etc.), others animals (rhizopods, ciliates) while in still others (flagellates) the boundary between animals and plants becomes hard to define, so that many of these forms are claimed by botanists and zoölogists alike.

Both structurally and physiologically the multicellular organism suggests an aggregate or colony of unicellular ones; whether this be literally true or not the analysis of biological phenomena is made definite and effective by the conception that the cell constitutes a primary organic unit both of

Dujardin, who emphasized the physiological importance of protoplasm ("sarcode") in Protista; Purkinje, Valentin, Johannes Müller, Henle, Unger, Nägeli and the early investigators of protoplasm enumerated beyond. The significance of Schleiden's and Schwann's work lies in the thorough and comprehensive way in which the problem was studied, the philosophic breadth with which the conclusions were developed, and the far-reaching influence which they thus exercised upon subsequent research. In this respect it is hardly too much to compare the *Mikroskopische Untersuchungen* with the *Origin of Species*.

More detailed accounts of the history of research during this period will be found in the works mentioned at the end of this Introduction, especially those of Heidenhain and O. Hertwig. See also Gerould ('22).

[1] The word protoplasm is due to Purkinje (1840) who applied it to the formative substance of the animal embryo and compared it with the "granular material" of the cambium in plants. It was afterwards independently used by H. von Mohl (1846) to designate the contents of the plant-cell. The fundamental significance of protoplasm in the cells of higher organisms, its identity with the "sarcode" (Dujardin) of Protista, and its essential similarity in animals and plants were gradually made known by numerous researches between 1840 and 1870. Among the most important of these were the classical works of De Bary and of Max Schultze; but beside them stand many others of high interest, in particular those of Unger, von Mohl, and Cohn among botanists, and of Virchow, Kölliker and Beale among zoölogists. These early works have been reviewed by many writers. Accounts of them, with literature lists, will be found in the works cited in the preceding footnote.

structure and of action.[1] In the unicellular body all the vital activities are performed by one such unit. In the multicellular plant or animal each function, and hence the life of the organism as a whole, has at its root a multitude of cell-activities. The more complex life of the higher plant or animal arises through the specialization of the cells, this way or that, for the better performance of particular functions; hence that "physiological division of labor" which, as in organized human society, leads to higher

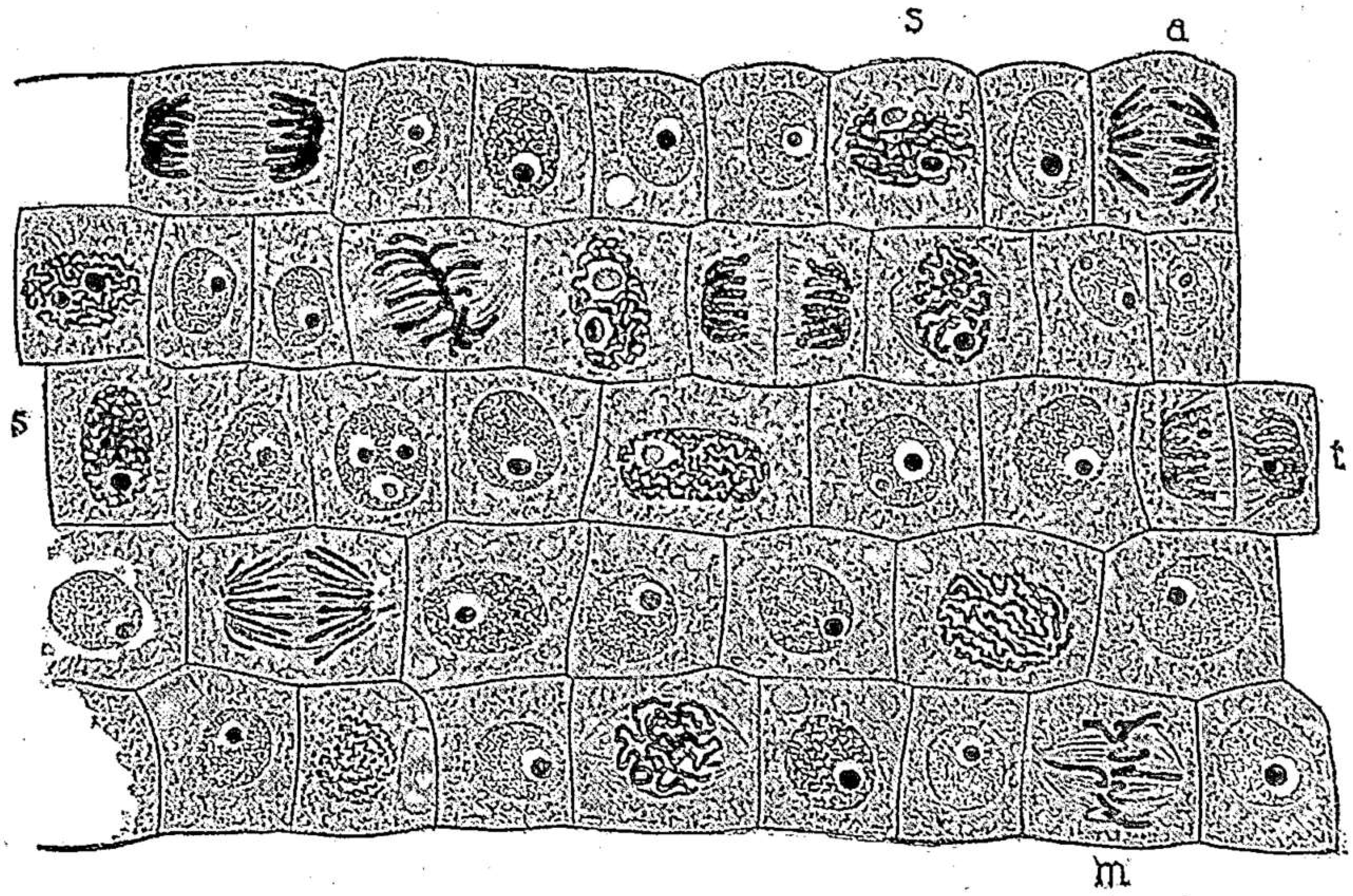

Fig. 2.—Group of cells from the meristem or embryonic tissue of the growing root-tip of the onion, as seen in longitudinal section. Like the preceding figure this is combined from a number of separate camera drawings, several stages of mitosis having been brought together. At *a*, *a* are seen anaphase-figures, at *s*, *s* spiremes, at *m* a metaphase, and at *t* an early telophase.

functional efficiency. On such considerations was based the famous comparison of the multicellular body to a "cell-state," due especially to Virchow (1858) though foreshadowed by Schwann and other early writers, and later elaborated by Milne Edwards, Haeckel and many others. This conception of the multicellular organism brought about a revolution in the prevailing views of vital action, and gave as great an impetus to physiology and pathology as to morphology. As we now can see, it requires some qualification, especially as applied to the phenomena of growth; but the conviction of its essential truth has survived all criticism, and as measured by its continued fruitfulness, it still stands among the most important generalizations of modern biology.

[1] *Cf.* p. 101. "It is to the cell that the study of every bodily function sooner or later drives us. In the muscle-cell lies the problem of the heart-beat and that of muscular contraction; in the gland-cell reside the causes of secretion; in the epithelial cell, in the white blood-cell, lies the problem of the absorption of food, and the secrets of the mind are hidden in the ganglion-cell." (Verworn, *Allgemeine Physiologie*, p. 53, 1895.)

Equally momentous was the influence of the cell-theory on embryology, where it first was brought to bear upon the problem of heredity. Prior to the cell-theory all attempts to comprehend the mechanism of development and heredity had been futile. Aristotle, it is true, and long afterwards Harvey (1651), had firmly grasped the principle of epigenesis or progressive new-formation in development: but neither of these great embryologists had the smallest real conception of the nature of the germ or of the mechanism of its development. The seventeenth and eighteenth centuries witnessed a speculative controversy concerning the nature of development which constitutes one of the most picturesque episodes in the history of biology.[1] It was precipitated by the doctrine of *preformation* or "*evolution*," which arose in the latter part of the seventeenth century. This assumed, in opposition to the teaching of Aristotle and Harvey, that the germ-cell (egg or sperm) contains an embryo fully formed in miniature, as the bud contains the flower or the chrysalis the butterfly. Development is merely the unfolding or "evolution" of a preëxisting germ; inheritance the handing down from parent to child of an infinitesimal reproduction of its own body. This doctrine was advocated by some of the most eminent naturalists and physiologists of the time. One group of these writers considered the preformed germ to be borne by the sperm and to be introduced by it into the egg; another that it is from the first contained within the egg and is merely awakened to its development by the sperm. Thus arose two contending schools, on one side the *spermatists* or *animalculists*, including Leuwenhoek, Hartsoeker, Boerhave and Leibnitz, on the other the *ovists*, among whom were numbered Swammerdam, Malpighi, Haller and above all Bonnet. By this eminent French naturalist (1720–1793) the theory of preformation was consistently worked out to its logical limit in the theory of *encasement*, the embryo itself being conceived as containing eggs including embryos for the next generation, these other eggs and embryos in turn, and so on *ad infinitum* like an unending series of boxes, one within another; hence the term "*emboîtement*." This conclusion, evidently, was but a logical *tour de force*, hardly to be taken seriously, as Bonnet himself in the end frankly admitted; its mere statement, indeed, carries its own refutation. The controversy was in fact wholly futile, for spermatists and ovists alike received their *coup de grâce* through the work of Caspar Friederich Wolff (1759), who brought forward a renewed and masterly demonstration that the fertilized egg does not at the beginning contain any preformed germ but gives rise to the embryo little by little by the progressive production of new parts previously non-existent as such. Biologists therefore gradually returned

[1] A fuller account of this will be found in O. Hertwig, *Lehrbuch der Entwicklungsgeschichte*, 9te Aufl. 1910. See also Whitman ('94a, '94b).

to the views of the fathers of embryology, and in the end universally accepted the fact that development, in its external aspects at least, is not a

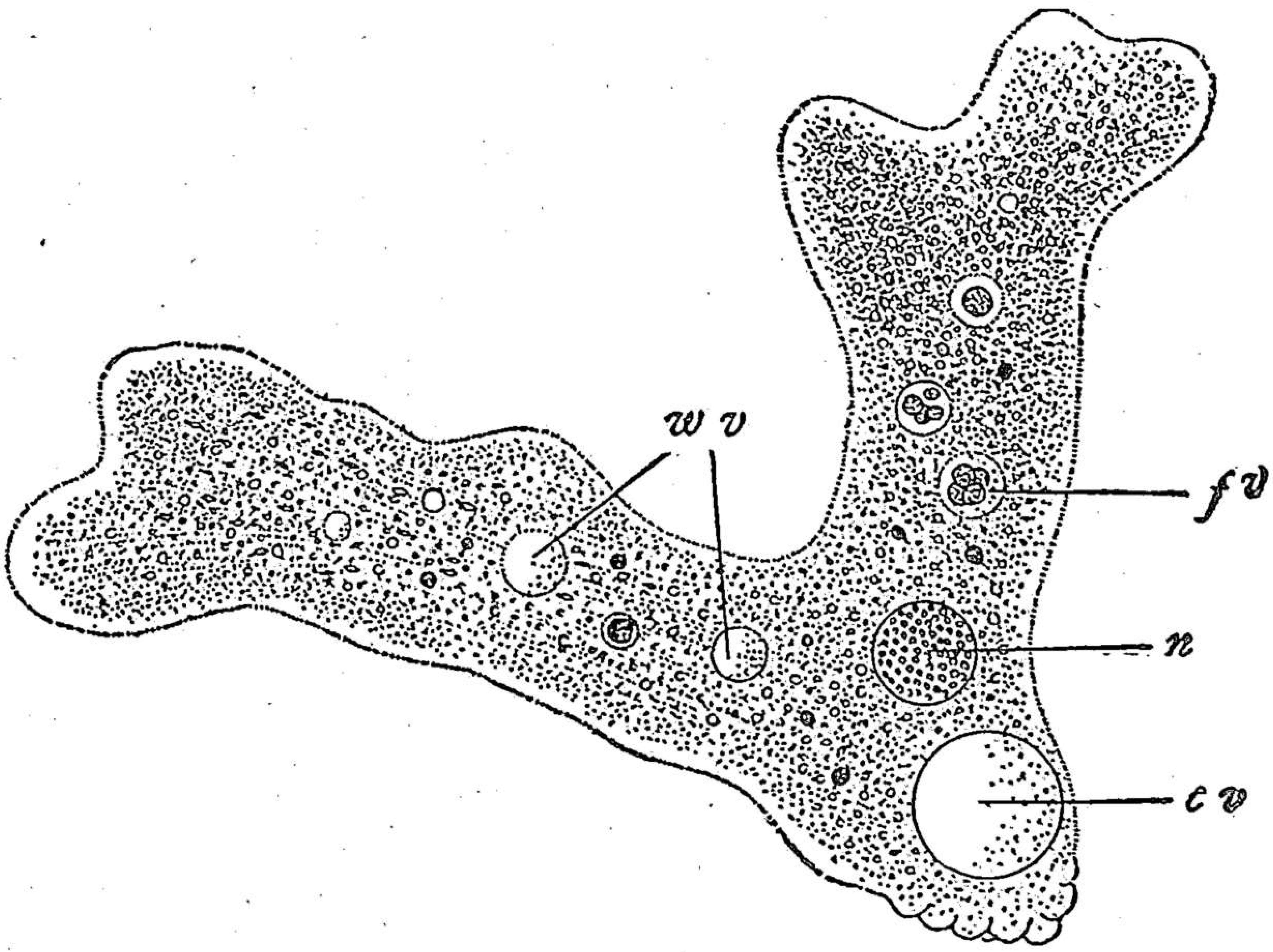

Fig. 3.—*Amœba Proteus*, an animal consisting of a single naked cell, × 280. (From Sedgwick and Wilson's Biology.)
n. The nucleus; *w. v.* Water-vacuoles; *c. v.* Contractile vacuole; *f. v.* Food-vacuole.

process of "evolution" or unfolding but one of progressive new-formation, or *epigenesis*.[1]

This result provided the foundation for modern embryology; but for nearly a century after Wolff the actual nature of the egg and the mechanism of its development remained in the dark. The way towards a solution of the mystery was first opened by the proof that *the egg is a single cell*, like other kinds of cells in every essential respect. This fact had been recognized by Schwann, but was not at first generally accepted. Its demonstration by Gegenbaur (1861) and many later observers constituted the first solid advance towards a true view of heredity, making manifest the wonderful fact that a single cell may contain within its microscopic compass the total heritage of even the most complex adult individual. So far as the egg is concerned the problem of heredity thus took on perfectly definite shape; but in respect to paternal inheritance the mystery remained as impenetrable as before. It was soon to be dispelled. Since the time of Leeuwenhoek (1677) it had been known that the sperm or fertilizing fluid contains innumerable minute bodies, endowed with the power of active movement, and therefore regarded by the early observers as parasitic animalcules or

[1] A critical analysis of Wolff's remarkable work is given by Wheeler ('98) and by O. Hertwig ('10).

infusoria—hence the term *spermatozoa* (sperm-animals) by which the sperms are still often called. As long ago as 1786, however, the experiments of Spallanzani proved that the fertilizing power must lie in the sperms, not in the liquid in which they swim, because the spermatic fluid loses its power when filtered. Spallanzani himself, it is true, did not thus interpret his results, but concluded, strangely enough, that the fertilizing effect was due to the seminal fluid in which the sperms swim.[1] The correct conclusion seems first to have been drawn by Prévost and Dumas (1824), who in addition to repeating Spallanzani's experiments performed many others demonstrating that "The prolific principle resides in the spermatic animalcules."[2] Shortly after the appearance of Schwann's great work Kölliker demonstrated (1841) that the sperms arise by the transformation of cells in the testis; obviously, therefore, they are not parasites but, like the ovum, form a part of the parent organism. In 1865, finally, the final proof was attained by Schweigger-Seidel and La Valette St. George that the sperm does not consist of a nucleus alone, as Kölliker believed, but contains also cytoplasm. It was thus shown to be, like the egg, a single cell, peculiarly modified in structure and of extreme minuteness, yet morphologically equivalent to other cells.[3]

One all-important point remained undetermined, namely, the history of the sperm in fertilization. In the time of Schleiden and Schwann it was supposed by some leading observers that the sperm might affect the egg merely by contact-action or by carrying to it a catalytic agent (Kölliker, Bischoff); and it was for a time believed, even by such observers as Bütschli, Van Beneden and Strasburger, that the sperm completely disintegrates as it enters the egg or fuses with its surface-layer.[4] On the other hand, an important group of observers had conjectured that the sperm must actually penetrate the egg, though unable to demonstrate the fact with certainty. This view, long ago adopted by Leeuwenhoek, Hartsoeker and other "spermatists," was reasserted by Prévost and Dumas (1824), and later by other observers (1840–1855) who observed the presence of sperms inside the egg-membrane (Barry, Meissner, Keber) or in contact with the egg. Newport (1854) seems first to have actually described the entrance of the sperm (in the frog), and in the following year it was also described by Pringsheim in the green alga *Œdogonium*. The first demonstrative evidence of the fact, with a full and detailed account of the process of pene-

[1] See F. R. Lillie ('16, '19).

[2] Cited from Lillie.

[3] The discovery of the sperm is often accredited to Ludwig Hamm, described as a pupil of Leeuwenhoek (1677), but he seems to have done no more than call the attention of Leeuwenhoek to the subject. Hartsoeker afterward claimed the merit of having seen them as early as 1674 (Allan Thomson) but his observations were not made known until after those of Leeuwenhoek.

[4] See O. Hertwig ('17, p. 31).

tration, was however given by Fol (1879) in the sea-urchin egg, while at the same time it was described in lower plants by Schmitz. In the meantime O. Hertwig ('75) had traced the fate of the sperm within the egg; and while he had not actually seen the process of penetration his work left no doubt of the fundamental fact that fertilization is accomplished by a single sperm that enters the egg.

We retrace our steps in order to consider earlier investigations on the origin of cells. In this all-important question is involved the central problem of development and heredity, as gradually became clear in the course of the first two decades after Schleiden and Schwann. Several earlier observers had observed the origin of cells by the division of preëxisting cells, in particular the botanists, Brogniart (1827), Meyen (1830), Mirbel (1835) and von Mohl (1835); and this mode of cell-formation was also recognized in limited measure by the authors of the cell theory, though only with considerable hesitation. Its fundamental significance was obscured for a time by the erroneous conclusion of Schleiden and Schwann that cells most commonly arise *de novo* by a process of "free cell-formation," new cells making their appearance by crystallizing, as it were, out of a continuous and formless matrix or "cytoblastema." The problems thus raised engaged the efforts of investigators more and more seriously in the period between 1840 and 1860,[1] under the lead especially of Unger, von Mohl and Nägeli on the botanical side, and of Kölliker, Remak and Virchow, on the zoölogical. In the end the long series of investigations set on foot at this time overturned the theory of free cell-formation, and finally established the conclusion that every cell arises by the division of a preëxisting cell, and in no other way. This conclusion (as Heidenhain has pointed out) was clearly stated already by Kölliker in his classical work on the embryology of cephalopods (1844) and extended by him to both plants and animals; but this observer later admitted the occurrence also of free cell-formation. The universality of cell-division was first definitely maintained by Remak and by Virchow whose celebrated aphorism *omnis cellula e cellula* (1855)[2] has become a household word in every modern laboratory. Echoes of free cell-formation, it is true, have now and then continued to be heard, even down to our own day, but have always been a product of error. To-day, therefore, we may with complete confidence repeat Remak's remark (1852) that the origin of cells *de novo* is no more credible than the spontaneous generation of life.

It is here that the full significance of the cell-theory for heredity and

[1] For accounts of the early literature see Remak (1855), Flemming (1882), Sachs (1890). A more recent detailed and critical review is given in Heider ('00).

[2] *Arch. für Path. Anat.*, VIII, p. 23.

development first dawns upon us. If the cells of the body always arise by division of preëxisting cells, all must be descended by division from the original germ-cell as their common ancestor; and such is the observed fact. The first step in development consists in the division of the egg into two cells, which then divide in turn to form four, eight, sixteen and so on in more or less regular progression (Fig. 4). Step by step the egg thus splits up into a multitude of cells which build up the body of the embryo, and finally of the adult. This process, known as the *cleavage* or *segmentation*

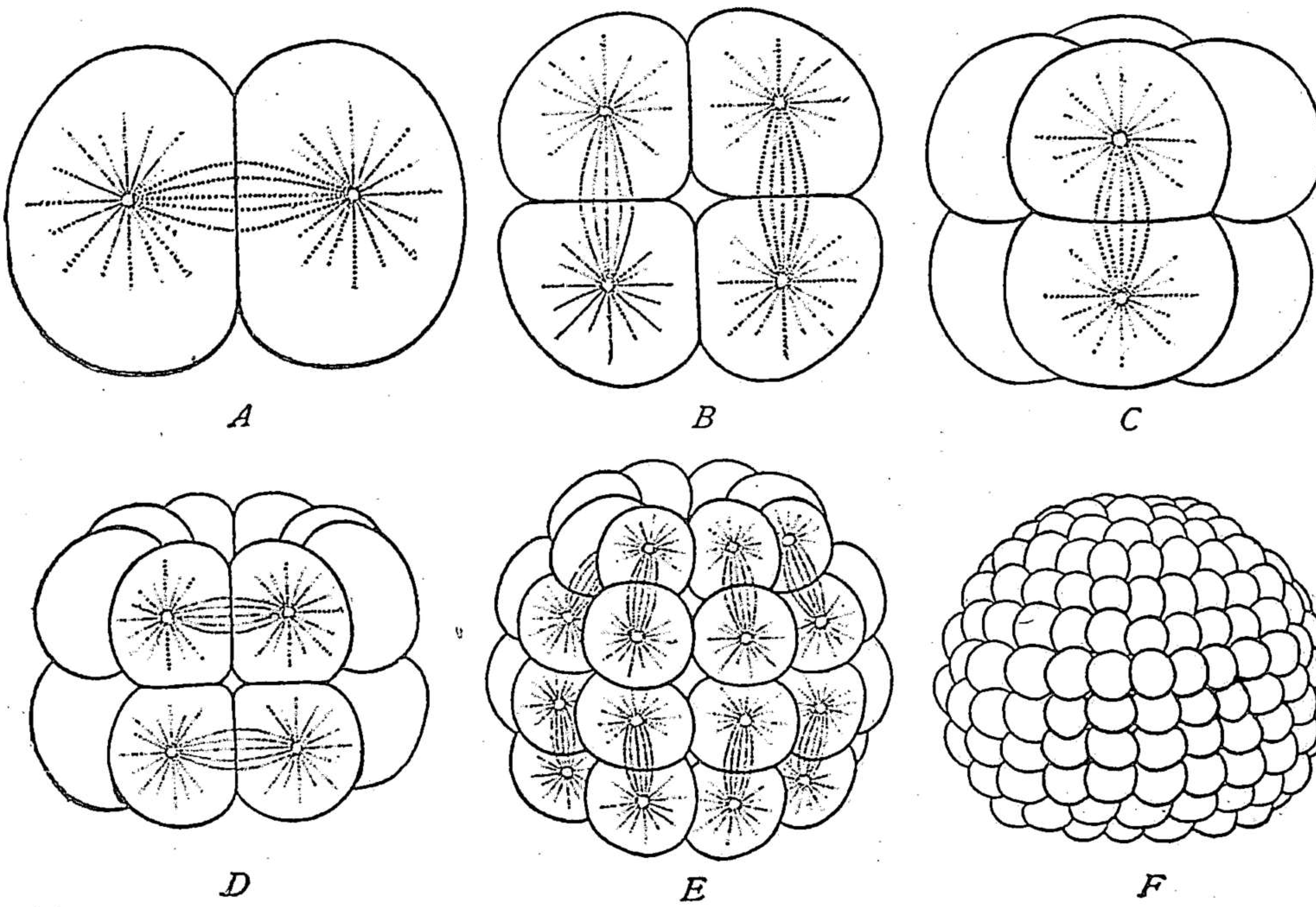

Fig. 4.—Cleavage of the ovum in the holothurian *Synapta* (slightly schematized). [After SELENKA.]
A–E. Successive cleavages to the 32-cell stage. *F*. Blastula of 128 cells.

of the egg, was observed long before its meaning was understood. It seems to have been first definitely described by Prévost and Dumas (1824) in the case of the frog's egg, though earlier observers had seen it; but at that time neither the egg nor its descendants were known to be cells. Its true meaning was first fully deciphered by Kölliker and Remak in the first decade after Schleiden and Schwann, though important contributions in the same direction were made at that time by Bergmann, Bischoff, Martin Goodsir and Barry. This critical point once made clear, the dominating significance of cell-division in the history of life began to stand forth in its true proportions. It became manifest that cleavage is but an infinitesimal part of a greater series of cell-divisions that has no assignable limits in the past or future. The germ-cell arises by division of a cell preëxisting in the body of the parent, and in its turn divides to form the body of the offspring and also new germ-cells for coming generations; and so on without end. Embryologists thus arrived at the conception, vividly set forth by Virchow in 1858,[1] of an unbroken series of cell-divisions that extends backwards from our own day throughout the entire past history of life. So far as we know, life under existing conditions never arises *de novo*. It is a *continuum*, a never-ending stream of protoplasm in the form of cells, maintained by assimilation, growth and division. The individual is but a passing eddy in the flow which vanishes and leaves no trace, while the general stream of life goes forwards.

Heredity thus appears as a consequence of the genetic continuity of cells by division, and the germ-cells constitute its physical basis. With this result before us we may formulate the problem of development with greater precision. If the egg contains no preformed embryo, what does it transmit? Such was the question which, in the seventies and eighties of the last century, first brought the cell-theory to closer quarters with the problems of heredity and development. Among many speculative attempts to answer it we here refer only to Darwin's celebrated hypothesis of pangenesis (1868) which assumed the germ-cells to be reservoirs of minute germs or "gemmules," originally thrown off by the cells of the body or soma, later transported to the germ-cells and there held in reserve. During the development of the embryo the gemmules were supposed to determine the production of (or actually to develop into) somatic cells like those from which they arose. Darwin thus assumed (in accordance with a notion even now widely prevalent) that the parent literally transmits its characters to the offspring, and thus sought to explain the heredity of "acquired" or "somatogenic" characters, at that time generally accepted as a fact. Pangenesis was, however, a purely speculative construction, devoid of any actual basis of observed fact. It received no support from later experimental tests by Galton and others. It was therefore gradually abandoned,[2] leaving the internal cell-mechanism of heredity as hidden as before.

The early eighties brought forth certain theoretical writings which grew out of cytological researches then in progress and in consequence of which the whole problem took on a different aspect. In 1883 appeared the first

[1] See quotation from Virchow's *Cellularpathologie*, at p. 114.

[2] Darwin's theory must not be confused with the "intracellular pangenesis" of De Vries (1889), which, though modeled upon Darwin's conception, differed wholly from it in respect to heredity. De Vries accepted Darwin's fundamental conception of gemmules (which he calls *pangens*) as minute organized units, capable of independent growth and division, and responsible for particular heredity qualities; but denied the transportal of pangens from cell to cell, and hence from somatic to germ-cells. This view, subsequently adopted by many other writers, received an elaborate theoretical development in Weismann's well-known work on the *Germ Plasm* (1885).

of Weismann's memorable series of essays which did so much to illuminate the problem of heredity and to bring it into closer relations with microscopical research. The way for Weismann's main conclusion was prepared by Nussbaum (1880), who emphasized the genetic continuity of the germ-cells from generation to generation, urging that during development the fertilized egg divides to produce on the one hand the cell-material of the individual body, on the other the cells by which the characters of the species are maintained.[1] From this as a starting point Weismann's analysis led him to a bold challenge of the entire Lamarckian principle on which Darwin's theory of pangenesis had been based. "I do not propose to treat of the whole problem of heredity, but only of a certain aspect of it,—the transmission of acquired characters, which has been hitherto assumed to occur. In taking this course I may say that it was impossible to avoid going back to the foundation of all phenomena of heredity, and to determine the substance with which they must be connected. In my opinion this can only be the substance of the germ-cells; and this substance transfers its hereditary tendencies from generation to generation, at first unchanged, and always uninfluenced in any corresponding manner by that which happens during the life of the individual which bears it. If these views be correct, all our ideas upon the transformation of species require thorough modification, for the whole principle of evolution by means of exercise (use and disuse) as professed by Lamarck, and accepted in some cases by Darwin, entirely collapses" (Essays, 1885).

Nussbaum and Weismann thus held, in opposition to the prevailing view, that the child does not inherit its characters from the parental *body*, but from the *germ-cell*, and the latter in turn does not owe its characteristics to the body which bears it, but to its *descent from a preëxisting germ-cell of the same kind* (Fig. 5); so far as heredity is concerned the body is merely a carrier of germ-cells, held in trust for coming generations. Thus regarded, the individual appears as an evanescent by-product; it is but an incident,—almost, we might say, an accident.[2] So far as the species is concerned the germ-cells alone are of consequence, for they alone live on, carrying with them, as it were, the traditions of the race from which they have sprung, and handing them on in turn to generations still unborn. To the layman this often appears as a paradox, and even among biologists it long remained a subject of controversy. Time has demonstrated, however, that it simplifies and illuminates the whole problem in remarkable degree and, for the present at least, offers the only intelligible conception of heredity. Upon it is

[1] See quotation at p. 256.

[2] "It has, I believe, been often remarked that a hen is only an egg's way of making another egg" (Samuel Butler).

founded the whole modern science of genetics, and it has given a powerful impetus to the study of cytology and embryology, lending new interest to the study of the germ-cells and their transformations during development. These problems, obviously, are inseparable from the cytological problems offered by cells in general. We now therefore return to those remarkable researches, on the internal organization of cells, the structure of protoplasm

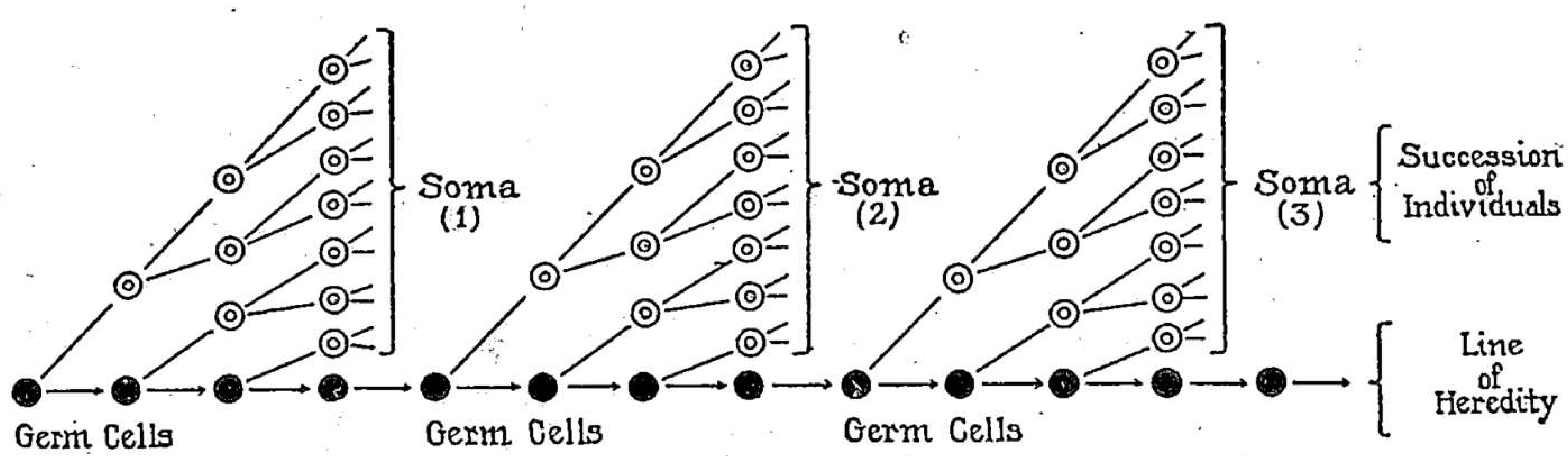

Fig. 5.—Diagram illustrating the Nussbaum-Weismann theory of heredity. In each generation the germ-cell (black) gives rise on the one hand to the body or soma, on the other to new germ-cells. The line of heredity is thus seen to be always through the germ-cells, not through the soma.

and nucleus, and the mechanism of cell-division and fertilization, which mark the opening of the second period in the history of our subject.

It is here that we see cytology first emerging from the earlier histology and embryology. The advance guard of the movement was led by Schneider ('73), Fol ('73, '75, '79), Bütschli ('73, '76) and Auerbach ('74), soon reënforced by O. Hertwig ('75–'78), Van Beneden ('75, '76), Strasburger ('75–'79) and Flemming ('79, '82). During the eighties it gained full headway under the leadership especially of Van Beneden, Flemming, Strasburger and Boveri whose cytological observations on the germ-cells were closely affiliated with the theoretical writings of Nägeli, Weismann, O. Hertwig, Strasburger, Roux and DeVries (p. 14). We can at this point barely mention the most important of the advances of this period.

One of the most fundamental of the discoveries of the time was Oscar Hertwig's demonstration of the fate of the sperm within the egg (1875). Other observers had paved the way by showing that, at the time of fertilization, the egg contains *two nuclei* that fuse together or become closely associated before development begins.[1] Hertwig, in his work of 1875 and subsequently ('77, '78, '84, etc.), paralleled and supplemented by that of Fol ('77, '79) demonstrated in the eggs of the sea-urchin (*Toxopneustes lividus*) that *one of these nuclei belongs to the egg, while the other is derived from the sperm.* This result was soon extended to the fertilization of higher

[1] An exhaustive review of the earlier literature will be found in Fol ('79) Mark ('81) and Flemming ('82). See also Rabl ('15), O. Hertwig ('17), and F. R. Lillie ('19).

plants by Strasburger ('77) and ultimately by many observers to higher organisms generally. *In every case an essential phenomenon of normal fertilization is the union or close association of a sperm-nucleus, of paternal origin, with an egg-nucleus, of maternal origin, to form the primary nucleus of the embryo. This nucleus, known as the cleavage- or segmentation-nucleus, gives rise by division to all the nuclei of the body; hence every nucleus of the child may contain nuclear substance derived from both parents;* and this gave the first basis for the conclusion, independently announced in 1884–1885 by Hertwig and by Strasburger, that it is the cell-nucleus which carries the physical basis of heredity.[1]

Meanwhile the way for a more precise study of these phenomena had been prepared by investigations upon indirect cell-division, or mitosis (karyokinesis) of which a detailed account will be given in the second chapter of this work. The most essential result was the discovery that the nucleus typically divides by spinning out its substance into elongate threads (spireme) which *split lengthwise,* shorten and thicken to form *chromosomes.* Many observers contributed to this discovery and its development, foremost among them Flemming ('82) and Strasburger ('80, '82), who showed that the phenomena are fundamentally similar in animals and plants. This was followed by the final proof, brought forward by Van Beneden ('83) and by Heuser ('84) that in plants and animals alike the longitudinal halves of each split chromosome separate from each other and pass into the two respective daughter-nuclei. The nucleus, therefore, does not undergo a mere mass-division but a meristic division of its entire substance. The great theoretic interest of this fact was indicated by Wilhelm Roux (1883), while almost at the same moment Nägeli (1884) developed his interesting theory of the *idioplasm,* a hypothetical substance assumed to be present in every cell and possessing specific properties by virtue of which the hereditary characters of the species are determined. By Hertwig and Strasburger this conception and that of Roux were blended in a single and coherent theory by the assumption that the *idioplasm is identical with the nuclear substance or chromatin.*

The cytological discoveries of this period reached their climax in the splendid researches of Edouard Van Beneden ('83–'84, '87) on the history of the nuclei during the fertilization of the egg of the nematode *Ascaris megalocephala,* which demonstrated that *the chromosomes of the offspring are derived in equal numbers from the nuclei of the two conjugating germ-cells, and hence equally from the two parents.* This fundamental discovery opened

[1] The more modern form of this conclusion is outlined elsewhere (*cf.* p. 916). Haeckel expressed the same thought as early as 1866; but this was no more than a lucky guess. "The internal nucleus provides for the transmission of hereditary characters, the external plasma on the other hand for accommodations or adaptations to the external world" (*Gen. Morph.,* pp. 287–289).

remarkable new possibilities for the detailed analysis of the nuclear organization and the cytological study of heredity and development. Weismann instantly grasped its importance and was the first to emphasize its far-reaching significance. To him, therefore, above all others, belongs the credit for having placed the keystone between the study of cytology and that of heredity, thus finally bringing the cell-theory and the evolution-theory into organic connection.

The subsequent history of cytology in its relation to genetics can only be rightly apprehended in the light of other lines of inquiry that were initiated during this period. One of these, a logical sequel to the pioneer studies of Kölliker, Remak, and Hofmeister, was the foundation of cellular embryology through the work of C. O. Whitman on the early development of leeches (1878), of Rabl on that of snails (1879), and that of Van Beneden and Julin on ascidians (1884). These researches demonstrated that the cleavage of the ovum, in some animals at least, is a perfectly ordered process, in which every individual cell in the early stages of development may possess a definite morphological value in the building of the body. This led in later years to numerous studies in cell-lineage devoted to the task of tracing out the formation of the embryonic body cell by cell; while efforts to test these results of observation by means of experiment created experimental embryology. In the latter field, the early leaders were especially Pflüger, Roux, Chabry and Driesch (1883–92); but the earlier work of Newport (1854–55), should also here be mentioned. Nearly at the same time, O. and R. Hertwig (1886–89) initiated experimental studies on the chemical environment of the egg and the conditions of artificial hybridization which had an important influence upon the later course of cellular biology. In later years, these studies were followed by many fruitful experimental researches on the chemical physiology of the germ-cells and their development; among the most interesting of the results was Loeb's discovery (1899) that the unfertilized egg may experimentally be caused to develop by purely chemical or physical stimulus, without the action of a sperm-cell ("artificial parthenogenesis"). The Hertwigs' studies likewise led to experimental researches on hybridization and merogony, particularly by Boveri, which yielded results fundamentally important to our conceptions of the internal mechanism of development, and contributed in an important way to the development of experimental cytology.

The third period in the history of our subject opened in 1900 with the rediscovery of Mendel's long forgotten laws of heredity (1865) by the independent work of DeVries, Correns and Tschermak. This momentous discovery produced an effect almost as far reaching in cytology as in genetics because of the remarkable new questions that it raised concerning the maturation of the germ-cells. The fact had long been recognized that every sexually produced organism is of double or *diploid* hereditary constitution, a condition obviously traceable to its origin from a zygote formed by the union of two germ-cells (gametes) respectively of maternal and paternal origin. Mendel and his successors brought forward specific experimental proof that the zygote and its product (*i. e.*, the diploid organism) unites in itself two corresponding sets of qualities ("factors," "units," "genes," etc.), likewise of maternal and paternal origin respectively, while the gametes are of single or *haploid* constitution, containing but a single such set of qualities. This result, evidently, is exactly parallel to Van Beneden's earlier discovery that the gametes contain a single or haploid group of chromosomes, which is made double or diploid by the act of fertilization. More especially, Mendel found in hybrids that in the case of any pair of corresponding or homologous qualities (such as two colors, *C* and *c*) in respect to which the parents differ, half the gametes of the hybrid receive one member of this pair (*C*) and half the other (*c*). This is the essential fact (segregation) at the basis of Mendel's first "law"; and, as Mendel clearly perceived, it can only mean that at some period in the history of the gametes the two members of each such pair are separated or disjoined so as to pass into different gametes. Mendel found, finally, that different pairs of qualities (*Aa*, *Bb*, *Cc*) behave independently of one another during segregation, (independent or free assortment) so that all possible recombinations of them may appear in the gametes and zygotes (Figs. 102, 105).

These fundamental discoveries resulted from purely genetic experiments having no direct reference to the cytological problems involved. In the meantime, however, cytologists had independently demonstrated that the general history of the chromosomes during the life-cycle runs so exactly parallel to that of the Mendelian phenomena that both may in large degree be formulated in the same terms. This was first clearly set forth by Sutton (1902–03) and by DeVries ('03), who offered the first complete demonstration that the behavior of the chromosomes may offer a mechanical (or at least mechanistic) explanation of Mendel's laws.[1] Taken together these advances marked the advent of a new era in both cytology and genetics and opened the way for many new lines of progress. Prominent among them were investigations on the determination of sex and the phenomena of linkage which demonstrated that both are in conformity with Mendel's laws. That sex-determination is connected with the chromosomes was suggested by McClung (1901–02) and established by the direct observations of Stevens

[1] Important data necessary for this conclusion had already been brought forward, especially by Montgomery, Boveri, and Guyer, and the cytological explanation of Mendel's laws was indicated nearly at the same time by Boveri and by Cannon (see p. 926).

and of Wilson in 1905. In respect to linkage, numerous researches, especially by Morgan and his followers, have demonstrated that the hereditary units are linked together in groups equal in number to the chromosomes. Followed out in great detail and in many directions these researches have removed every doubt concerning the intimate connection of the chromosomes with the determination of development generally, and have provided a remarkably effective means for the detailed analysis of the intricate and puzzling problems of genetics.

The determinative action of the nucleus in development was thus finally placed beyond doubt, but probably no investigator would to-day maintain that the nucleus or the chromosomes are the sole agents of heredity. On the contrary, both cytological and experimental research have clearly demonstrated that the protoplasm (cytoplasm) plays an important part in development. This has been directly proved on the cytological side by experiments on the development of egg-fragments by Boveri, Driesch, Fischel and later investigators, while indirectly the same conclusion is indicated by genetic experiments on the part of Correns, Toyama and others. With reference to this problem much interest has been aroused in recent years by cytological studies on the *mitochondria* or *chondriosomes*, cytoplasmic structural elements now widely believed to play an important part in the chemical activities of cells and perhaps also in differentiation; by some authors, accordingly (Benda, Meves) they have been regarded as representing a mechanism of "cytoplasmic heredity" comparable in importance with that represented by the chromosomes. This view, still very far from substantiation, remains a subject of controversy and must be taken with proper scepticism; but in spite of its doubtful status it should be kept clearly in view in all cytological discussions of these problems. To some extent, perhaps, our conclusions concerning the chromosomes have thus far been more definite and frutiful because we are able to follow their history more readily.

The present work has been written by a student of embryology and cytology, with especial reference to the cell considered as the physical basis of heredity and development. It is plain that any treatment of this subject must be based on our knowledge of cells generally, but neither can we, on the other hand, go very far into the minutiæ of histology, cell-physiology, biophysics and biochemistry. The order of treatment has been determined by practical rather than by strictly logical considerations. The first two chapters offer a general elementary sketch of cell-structure and cell-division, the third a preliminary outline of the phenomena of reproduction and of the life-cycle as related to the physiological problems of syngamy. The morphological aspects of these problems are treated in some detail in the succeeding chapters, the fourth considering the structure and origin of the gametes, the fifth their union in syngamy or fertilization, and the sixth their maturation and the phenomena of meiosis or the reduction and segregation of the chromosomes. The seventh chapter offers a brief outline of the related phenomena displayed in the sexual processes of lower organisms, where we may seek for indications of their historical origin.

These seven chapters offer a general foundation for the study of more specific problems of cytology and genetics, and of the more general ones involved in the phenomena of development. The eighth chapter includes a brief outline of certain chemical and physiological cell-phenomena that are of importance for the subsequent analysis; the ninth an account of some general problems and theories of cell-organization.

The tenth chapter deals with the cytological basis of sex-production and serves as an introduction to the eleventh and twelfth chapters which give some account of the organization and individuality of the chromosomes and their relation to various specific problems of genetics and to heredity in general. The last two chapters deal with the cell in development, considering some of the problems of cleavage, localization and differentiation from the standpoint of the cytologist, together with an outline of current theories of development and heredity.

LITERATURE. INTRODUCTION.[1]

(See also Literature I, II, V, XIII, XIV, etc.)

Auerbach, L., '74. Organologische Studien. *Breslau.*
Beale, L. S., '61. On the Structure of the Simple Tissues of the Human Body: *London.*
Boveri, Th., '87–'90. Zellenstudien, I–III (see General List).
Carnoy, J. B., '84. La biologie cellulaire: *Lierre.*
Delage, Yves, '03. La structure de protoplasm, les théories sur l'hérédité et les grandes problèmes de la biologie générale: *Schleicher, Paris*, 2nd Ed.
Flemming, W., '82. Zellsubstanz, Kern und Zelltheilung: *Leipzig.*
Id., '79–'82. Beiträge zur Kenntnis der Zelle, etc.: (See II).
Fol, H., '79. Recherches sur la fécondation et la commencement de l'hénogénie: *Mém. Soc. phys. et d'Hist. Nat. Genève.*, XXVI.
Gerould, J. H., '22. The Dawn of the Cell-Theory: *S. M.*, XIV.
Grew, Nehemiah, 1682. The Anatomy of Plants: *London.*
Haecker, V., '99. Praxis und Lehre der Zellen- und Befructungs-lehre: *Jena.*
Haecker, V., '11. Allgemeine Vererbungslehre: *Vieweg, Braunschweig.*

[1] The list includes for the most part earlier works or more recent ones in which the earlier literature is reviewed. For explanation of the abbreviations, see p. 1145. Compare general literature list at the end.

For additional earlier works see especially the historical introductory chapters in Heidenhain's *Plasma und Zelle* ('07, '11), O. Hertwig's *Handbuch der Entwicklungslehre* ('06), the same author's *Allgemeine Biologie*, 5th ed. ('20), Lillie's *Problems of Fertilization* ('19) and Sharp's *Introduction to Cytology* ('21).

Harvey, Wm., 1651. Exercitationes de Generatione Animalium: *London;* Trans. in Sydenham Soc., X, '47.
Heidenhain, M., '07. '11. Plasma und Zelle I, II: *Fischer, Jena.*
Henle, J., 1841. Allegemeine Anatomie: *Leipzig.*
Henneguy, L. F., '03. Leçons sur la Cellule: *2nd Ed. Schleicher, Paris.*
Hertwig, O., '75, '77, '78 (see V).
'84. Das Problem der Befruchtung und der Isotropie des Eies, eine Theorie der Verebung: *J. Z.*, XVIII.
'93, '98. Die Zelle und die Gewebe: *Fischer, Jena.*
'01, '06. Die Entwicklungslehre im 16 bis 18 Jahrhundert: *Handb. der vergleichenden experimentellen Entwicklungslehre der Wirbeltierre*, I, 1, 1, *Fischer, Jena.*
'17. Documente zur Geschichte der Zeugungslehre, etc., *A. M. A.*, XL.
'20. Allgemeine Biologie, 5te Auflage: *Fischer, Jena.*
Hertwig, O. and R., '87. Ueber den Befruchtungs- und Theilungsvorgang des thierischen Eies unter den Einfluss äusserer Agentien: *J. Z., N. F.*, XIII.
Hofmeister, '67. Lehre von der Planzenzelle: *Leipzig.*
Hooke, Robt., 1665. Mikrographia, or some physiological Descriptions on minute Bodies by magnifying Glasses: *London.*
Huxley, T. H., '53. Review of the Cell-theory: *Brit. and Foreign Med. Chir. Review*, XII.
V. Kölliker, A., '85. Die Bedeutung der Zellkerne für die Vorgänge der Veverbung: *Z. W. Z.*, XLII.
Lillie, F. R., '19. Problems of Fertilization: *Univ. Chi. Press.*
Locy, W. A., '15. Biology and its Makers: 3rd Ed., *New York.*
Malpighi, M., 1675. Anatome Plantarum.
Mark, E. L., '81. Maturation, Fecundation and Segmentation of *Limax campestris: Bull. Mus. Comp. Zoöl. Harvard*, VI.
Nägeli, C., 84. Mechanisch-physiologische Theorie der Abstammungslehre: *München u. Leipzig*, '84.
Prévost and Dumas, 1824. Nouvelle théorie de la génération: *A. S. N.*, 1.
Rabl, C., '06. (See XIV.)
'15. Edouard Van Beneden, etc.: *A. M. A.*, LXXXVIII.
Remak, R., '50–'55. Untersuchungen über die Entwicklung der Wirbelthiere: *Berlin.*
Sachs, J., '90. History of Botany: Trans. *Oxford.*
Schleiden, M. J., '38. Beiträge sur Phytogenesis: *Müller's Archiv.* Trans. in *Sydenham Soc.*, XII, London, '47.
Schwann, Th., '39. Mikroscopische Untersuchungen über die Uebereinstimmung in der Struktur und dem Wachsthum der Thiere und Pflanzen: *Berlin.* Trans. in *Sydenham Soc.*, XII, London, '47.
Strasburger, E., '75, '08. Zellbildung und Zelltheilung: 1st and 3rd Ed., *Jena.*
'84. Neue Untersuchungen über den Befruchtungsvorgang, etc.: *Jena.*
'07. Die Ontogenie der Zelle seit 1875: *P. R. B.*
'10. The Minute Structure of Cells in Relation to Inheritance: In *Darwin and Modern Science.*
Tyson, James, '78. The Cell Doctrine: *Philadelphia.*
Van Beneden, E., '83,–'84. Recherches sur la maturation de l'œuf, la fécondation et la division cellulaire: *A. B.*, IV (dated 1883, issued 1884. See Rabl, '15).

Virchow, R., '58. (See also '55). Die Cellularpathologie in ihrer Begründung auf physiologische und pathologische Gewebelehre: *Berlin.*

Waldeyer, W., 88. Ueber Karyokinese und ihre Beziehung zu den Befruchtungsvorgängen: *A. M. A.*, XXXII (trans. in *Q. J.*, XXX).

Weismann, A., '82–'88. Essays on Heredity, 1st and 2nd series: Trans. Oxford, '89, '92, '04. The Evolution Theory (Trans. by Thomson): *London.*

Wheeler, W. M., '98. Caspar Friedrich Wolff and the Theoria Generationis: *W. H. L.*

Whitman, C. O., '78. The Embryology of *Clepsine: Q. J.*, XVIII.
'94. (a) Evolution and Epigenesis: (b) Bonnet's Theory of Evolution: *Woods Hole Biol. Lect.*, 1894.

Wilson, E. B., '96, '00. The Cell in Development and Inheritance, 1st and 2nd Editions: *Macmillan, New York.*
'09. The Cell in Relation to Heredity and Evolution: In *Fifty Years of Darwinism: N. Y.*

Wolff, Caspar Friedrich, 1759. Theoria Generationis.