The Cell-theory: a Restatement, History, and Critique

Part IV. The Multiplication of Cells

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SUMMARY

In the first half of the nineteenth century it was commonly supposed that new cells arose either *exogenously*, outside pre-existing cells, or *endogenously*, from small rudiments that appeared within pre-existing cells and gradually grew larger. The theory of exogeny had been founded by Wolff (1759), and was supported especially by Link (1807), Schwann (1839), and Vogt (1842). The theory of endogeny, which had been hinted at by various writers in early times, obtained the backing of a very large literature. Its chief advocates were Raspail (1825, &c.), Turpin (1827, &c.), Schleiden (1838), Kölliker (1843–4), and Goodsir (1845).

That cells do not arise exogenously or endogenously, but are produced by the division of pre-existing cells, was at last realized by the convergence of studies made in three separate fields, as follows:

(1) Trembley (1746, &c.), Morren (1830, 1836), Ehrenberg (1830, 1832, 1838), and others noticed how protists multiply.

(2) Dumortier (1832), Mohl (1837), and Meyen (1838) watched the partitioning of the cells of filamentous algae.

(3) Several observers studied the cleavage of eggs and at last revealed that this was a process of cell-division (Prévost and Dumas (1824), von Siebold (1837), Barry (1839), Reichert (1840), Bagge (1841), Bergmann (1841–2)).

Nägeli (1844, 1846) also made an important study of cell-division in all the main groups of plants (except bacteria), but used an unfortunate nomenclature that tended to obscure the true nature of the process.

Remak (1852 and 1855) and Virchow (1852, 1855, 1859) made general statements to the effect that division is the standard method by which cells multiply. The writings of Remak on this subject were much more weighty than those of Virchow.

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Introduction

WE are concerned here with the proposition that *cells always arise, directly or indirectly, from pre-existent cells, usually by binary fission*; that is to say, with Proposition III in the formulation of the cell-theory adopted in this series of papers.

With a few exceptions the early cytologists appear not to have been very inquisitive about the way in which cellular structure developed: they were content to describe what they saw at a particular moment in time. About the beginning of the nineteenth century, however, attention began to be focused on the subject of the multiplication of cells. Unfortunately several false theories were promulgated at that time and gained a good deal of acceptance, so that when the truth began to be disclosed towards the middle of the century, by the convergence of unconnected studies, the new discoveries had to contend against firmly established errors. To give a realistic history of the discovery of the actual method by which cells multiply, it is necessary at the outset to present a rather full account of the erroneous views, which were expounded by such distinguished investigators as Wolff, Sprengel, L. C. Treviranus, Raspail, Schleiden, Schwann, and Kölliker. There is a special reason why the exact nature of the errors should be understood. As we have already seen in this series of papers, it happens from time to time that someone alights casually on a particular passage in an old book or journal and attributes a discovery to the author of it, when critical reading and thorough preliminary knowledge would have shown that the writer of the passage actually held entirely mistaken opinions. A careful history of such opinions is necessary if credit is to be restricted to those who really deserve it.

A study of the very extensive literature of the subject reveals that there are three main methods by which cells have been supposed to multiply. These will here be called *exogeny*, *endogeny*, and *division*. By exogeny I mean the origin of new cells outside existing ones; by endogeny, the growth of new cells from small rudiments within an existing cell; and by division, the carving up of an existing cell into two or more smaller ones.

The following classification of the theories of cell-multiplication will be used in the present paper:

Exogeny
- by partitioning
- by vacuolation
- from granules

Endogeny
- with migration from the protoplast
- without migration

Cell-division
- by partitioning

with constriction of the cell-wall
with formation of entirely new cell-walls
in the absence of cell-walls (division of the naked protoplast).

This classification is intended to be as logical, precise, and self-explanatory as possible, but the meaning of its terms must be more fully explained below. These terms were not used by the originators of the several theories or by their adherents. As we shall see, some of the terms used by the early students of the subject are in fact inappropriate, and would confuse the account given here.

It may be remarked at the outset that while exogeny and endogeny are unreal, the various methods of division mentioned in the classification occur in nature.

The present paper deals with the history of the discovery of the methods of cell-multiplication down to the time of general acceptance of the views summarized in the phrase, *Omnis cellula e cellula.* In the next paper in the series it will be necessary to tell the story of the discoveries culminating in the generalization, *Omnis nucleus e nucleo.* The derivation of cell from cell and nucleus from nucleus will lead us back to the cell that originates a new individual. To complete the discussion of Proposition III it will therefore be necessary in the succeeding paper to show how it was discovered that the fertilized ovum is a cell formed by the fusion of two cells.

THE SUPPOSED ORIGIN OF CELLS BY EXOGENY

In Grew's little book, *The anatomy of vegetables begun* (1672), there is an interesting passage bearing on the subject of the origin of cells. It has already been mentioned in Part I of this series of papers (Baker, 1948) that Grew demonstrated the cellular nature of plant-embryos, and he must have realized that the adult plant contains an immensely greater number of cells (or 'Pores', as he often called them). He does not mention this subject specifically, but it seems to have been at the back of his mind when he wrote these words: 'In the *Piths* of many Plants, the greater Pores have some of them lesser ones within them, and some of them are divided with cross Membranes: And betwixt their several sides, have, I think, other smaller Pores visibly interjected' (p. 79). Thus Grew seems to have thought that new cells might originate in various ways. Visible interjection of new pores between the sides of old ones must presumably mean the origin of new cells by exogeny, but unfortunately he gives no details that would enable us to classify this supposed method of cell-multiplication more exactly. These words of Grew constitute the earliest reference to the problem of the multiplication of cells. I have already called attention to them elsewhere (1951, 1952*b*).

Exogeny by partitioning

The supposed origin of cells by exogenous partitioning is illustrated diagrammatically in fig. 1. A space between existing cells enlarges; partitions begin to appear in this space; they become more evident; new cells thus originate, and these enlarge.

The opinion that cells multiply by exogenous partitioning was put forward by Link (1807, p. 31). He later repeated his opinion that new cells originate in this way (1809–12, vol. 1, p. 7). He received little support, however, from subsequent writers, though Mirbel's *développement inter-utriculaire* and *super-utriculaire* (1835, p. 369) may perhaps fall into this category of theories. Mirbel's ideas were confused at the time by his firm belief that the whole of

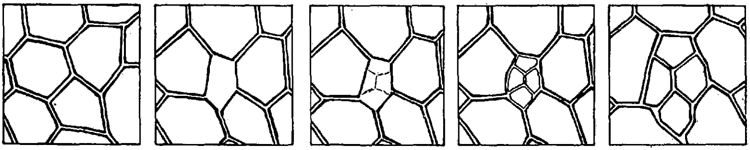


FIG. 1. Diagram of exogeny by partitioning. In this and in all the succeeding diagrams (figs. 2–6), the earliest stage is represented in the square on the left side, and the sequence of events is shown in the remaining squares from left to right across the figure.

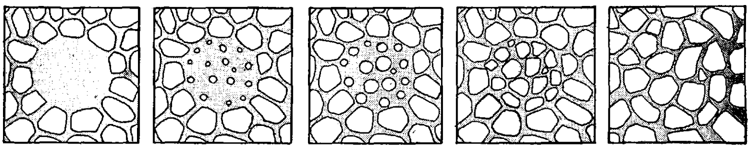


FIG. 2. Diagram of exogeny by vacuolation. The solid intercellular substance is shaded.

the 'membranous tissue' (that is, all the cell-walls) of a plant was perfectly continuous (see Baker, 1952*a*, p. 160), and the meaning of what he wrote on the subject of cell-multiplication is not clear.

Exogeny by vacuolation

This is represented in fig. 2. Between the cells there is a homogeneous, solid or semi-solid substance. In places where there is much of this substance, minute vacuoles sometimes appear in it. These enlarge and transform themselves into new cells resembling the old.

Grew seems to have thought that cells might originate in some such way as this. He remarks (1682, p. 49) that when the sap penetrates into the seed, the liquid internal parts of the latter become coagulated into a solid; a process of 'Fermentation' transforms the coagulum 'into a *Congeries* of *Bladders*: For such is the *Parenchyma* of the whole *Seed*'.

It was Wolff (1759), however, who described exogeny by vacuolation most explicitly. His erroneous views on this subject formed the basis for his theory of epigenesis. He believed that the growing parts of plants were formed of a 'pure, homogeneous, glassy substance' (*pura æquabilis vitrea substantia*, p. 13);

in another place he calls it a 'delicate, solid substance' (*substantia tenera solida*, p. 17). This material permitted the passage of nutritious fluids (p. 17). Minute holes (*punctula*, p. 19), widely separated from one another, were formed in it from blebs (*bullulae*, p. 17) of nutritious fluid; these holes swelled to become cells (*vesiculae*, p. 15; *cellulae*, p. 19). The glassy substance remained as the *interstitia* between them (p. 8). 'Leaves therefore grow for the most part by the interposition of new vesicles between the old, though partly indeed also by the enlargement of the [existing] vesicles' (p. 14).

Wolff did not homologize the *globuli* constituting the blastoderm of the developing hen's egg with the *vesiculae* or *cellulae* of plants. On the contrary, he thought that the material composed of globules, despite its lack of homogeneity, was the counterpart of the glassy interstitial substance of plants; and

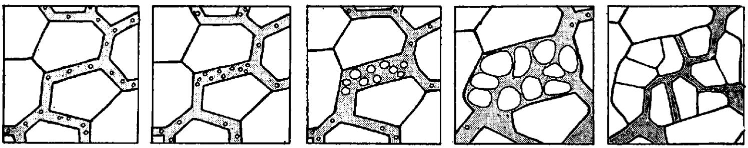


FIG. 3. Diagram of exogeny from granules. The intercellular fluid is shaded.

he thought that the cellular parts of the embryo (the *cellulosa animalis*)—that is, the viscera and vessels—were laid down epigenetically *in* this substance formed of globules (pp. 72, 75).

If one is to hold a balanced view of the history of the epigenesis-preformation controversy, it is necessary to grasp firmly what Wolff's views on the subject of cell-multiplication really were. The opinion, so commonly expressed, that Wolff was essentially right and Bonnet wrong, cannot be substantiated by a study of their writings. I have discussed this matter elsewhere (Baker, 1952*b*, pp. 183–6).

Exogeny from granules

This is represented in fig. 3. Small granules originate in the intercellular fluid; they expand, press upon one another, and become new cells.

It was from a study of the cotyledons in the germination of the seed that Sprengel (1802, pp. 89–90) derived his opinion that new plant cells originated from granules that subsequently enlarged. The granules in the cotyledons were in fact presumably starch-grains. It would appear that in his opinion the cell-forming granules sometimes originated inside and sometimes outside pre-existing cells, but unfortunately he is not explicit on this point. L. C. Treviranus adopted Sprengel's view (1806, pp. 2, 6–10, 14–16). He says that the intercellular spaces of plants contain a fluid that sometimes precipitates fine granules; these grow into *Blasen* or cells. For him, indeed, the purpose of the intercellular fluid (*Saft*) was to produce new cells: it carried the granules wherever new cellular tissue was to be formed. It did not surprise him that the granules that were to become cells were sometimes seen within cells, because he believed that there was free communication between the intercellular fluid and the cavities of the cells, through apertures in the cell-walls.

Rudolphi (1807, p. 35) considered that the intercellular fluid could form new *Bläschen.* He supported Sprengel in general, but gave no particulars.

After a long period of eclipse, the theory of exogeny from granules was reintroduced in the eighteen-thirties and became famous through its promulgation, in a modified form, by Schwann. Valentin (1835, p. 194) first gave a curious account of the origin of the pigment of the chorioid coat of the eye of birds and mammals. Colourless, transparent bodies that he called by the misleading names of *Pigmentkörperchen* and *Pigmentbläschen* appeared first, and the actual globules of pigment subsequently developed in aggregations round each of them. Four years later (1839, p. 133), Valentin announced that the *Pigmentbläschen* were in fact nuclei, and that cells containing pigment were formed round the nuclei after the latter had appeared. This led to a dispute with Schwann (1839, p. 264) about priority.

Schwann, as is well known, considered that new cells originate in a structureless substance which he called the *Cytoblastema* (1839, p. 45) or *Cytoblastem* (p. 112 and elsewhere). This substance, he supposed, sometimes existed within pre-existing cells, but in animals it was usually extracellular (pp. 203–4). Its consistency differed in different cases. It was often fluid, but might also be solid: the matrix of cartilage was an example of it. Schwann's general scheme of cell-formation was as follows (1839, pp. 207–12). The first object to appear in the previously homogenous *Cytoblastem* was the nucleolus. A clump of granules next appeared round this; these then resolved themselves into a pellucid nucleus with a clear boundary, which sometimes took the form of a distinct membrane. The nucleus grew. When it had reached a certain size, a substance derived from the *Cytoblastem* was deposited on it in the form of a layer. Either the whole of this layer, or the outer part of it only, was the future cell-wall (*Membran*). The nucleus adhered to the cell-wall in one place, but elsewhere a fluid appeared between the two and separated them; this fluid, the *Zelleninhalt*, increased in volume. The typical nucleated cell was thus produced. The nucleus in most cases was eventually absorbed and disappeared.

In forming his opinions about the origin of cells, Schwann was undoubtedly much influenced by Schleiden, though he placed the *Cytoblastem* of animal cells, as a general rule, outside pre-existing cells, while Schleiden regarded cell-formation in plants as endogenous (see below, p. 416).

The exogenous origin of cells in a *Cytoblasteme*, as he called it, was reiterated by Vogt in his book on the development of the obstetric toad, *Alytes* (1842). Vogt distinguished between *Cytoblasteme primäre*, or intercellular material that had never formed part of a cell, and *Cytoblasteme secondäre*, formed of material that had previously composed cells and had subsequently become structureless (p. 125). He held that cell-formation started in *Alytes* when cleavage was finished (pp. 9–10, 25). In the *Cytoblasteme* (whether primary or secondary) a nucleus originated, and round this a cell (pp. 117–19); sometimes the cell originated first (pp. 119–20). Vogt does not describe the details of the process, but the nucleolus was not the first object to appear (p. 118).

It is a remarkable fact that so late as 1849, Virchow instituted a comparison between the origin of a crystal from its mother-liquor, and a cell from the *Blastem*. 'Both the mother-liquor and the *Blastem* are amorphous substances, from which bodies of definite shape arise by aggregation of atoms' (1849, pp. 8–9). The difference lay in the substance of the crystal being already present in the liquor, while chemical change was necessary for the differentiation of the cell.

The Supposed Origin of Cells by Endogeny

Endogeny with migration from the protoplast

Fig. 4 represents the origin of a new cell in a filamentous alga by this hypothetical method. In such a form as this there are no intercellular spaces,

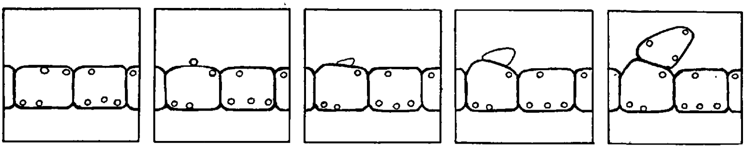


FIG. 4. Diagram of endogeny with migration from the protoplast.

and exogeny is therefore scarcely possible. The cells contain granules. These have the property of being able to migrate through the cell-wall and grow into new cells; in these, new granules appear endogenously, which are capable of repeating the process.

L. C. Treviranus supposed that this method of cell-multiplication occurred in certain algae. He considered that the new tubes (*Schläuchen*) of the water-net, *Hydrodictyon*, arose from granules that were present on (*an*) the walls of the old tubes (1806, p. 3). He did not give particulars of the original positions of the granules, but what he saw were probably the pyrenoids, which are very evident in this plant. He derived the new cells of filamentous algae from the chloroplasts originally situated within pre-existing cells (1811, p. 6).

Kieser's writings (1814, pp. 105, 219) on cell-multiplication are not very explicit. He derived new cells from the small globules that are found in the *sève* contained in the intercellular spaces. He appears to have supposed that these globules originated within cells. Turpin (1829, p. 181) considered that Kieser's globules must have originated within cells; he allowed that they might perhaps develop into new cells in the intercellular spaces, in certain cases. As we shall see, however (p. 415), Turpin thought that new cells usually developed within pre-existing cells, and that no migration took place.

Endogeny without migration

According to this theory, which was supported by a formidable literature, small granules originate within a pre-existing cell (fig. 5); these granules enlarge at the expense of the contents of the pre-existing cell, until they touch one another and take on the usual characters of cells. The cell-wall of the mother-cell eventually disappears.

Grew's remark, quoted above (p. 409), that 'the greater Pores have some of them lesser ones within them', suggests that he may have envisaged this as a possible method of cell-multiplication. The theory, however, was first put forward in concrete form by Sprengel, in his account of the germination of the bean-seed (1802). He gives an illustration of cells of the cotyledon, with small granules or vesicles within them (his plate I, fig. 2), and he remarks, 'The small vesicles that still float in the fluid of the cell seem to have the

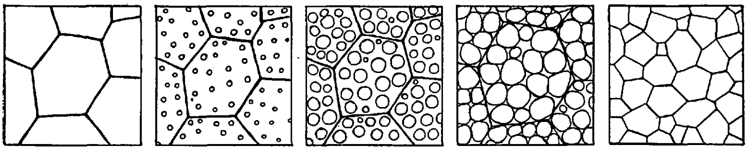


FIG. 5. Diagram of endogeny without migration.

character of future cells, and perhaps will become transformed into them subsequently' (p. 90). The granules or vesicles were actually starch-grains, the nature of which was not in the least understood at the time. In his book published in 1811, L. C. Treviranus also derived new cells from the granules contained inside the cells of the cotyledons of beans and peas (p. 4); in this later work he does not dogmatize as to the place of origin of these granules. Kieser (1814, p. 219) seems to have thought that the small globules that originate within cells and are the primordia of new cells, sometimes undergo their transformation without first passing out into the intercellular *sève*.

The theory of endogeny without migration flourished in the eighteen-twenties through the labours of Raspail and Turpin. From his studies of the germination of cereals, Raspail concluded that new cells arose from starch-grains, which enlarged within the cell that produced them until they touched one another, the mother-cell eventually bursting (1825, pp. 412–13). It is strange that the very man who discovered, by the iodine test, that these granules contain starch, should have been so misled about their fate. He elaborated his views in further communications. He imagined that each starch-grain contained within itself one or more globules, and that there were other exceedingly minute ones inside these (1827, p. 212, and his plate 2, fig. 22); this kind of *emboîtement* at the cellular level provided for repeated acts of cell-multiplication. He derived a whole leaf from a single cell, inside which two new cells arose endogenously and enlarged so as to fill all the space except what would become the midrib; globules arose within these two cells and enlarged to fill all the space except what would become the veins; and so on, till the final cellular structure of the mature leaf was achieved (1827, pp. 254–5, and his plate 4, fig. 4). He applied the same idea to the stems of plants

(p. 269) and to the tissues of animals (p. 304). He repeated his opinions on the endogenous origin of new cells, in his book on biochemistry (1833, pp. 85–86).

Turpin had completed his first paper on cell-multiplication by endogeny when he received Raspail's original communication on the subject (Turpin, 1827*a*, pp. 47–48). One may summarize his views, which he put forward at great length, by saying that he derived new cells from chromatophores and from colourless bodies which he believed to be of the same nature. He regarded *Pleurococcus naegelii*, so abundantly found on damp walls, as a solitary chromatophore. This plant, which he called a *globuline*, was for him a typical example of the most primitive organisms. The globuline contains within it a large number of smaller globulines, destined to reproduce the little organism (p. 25). Most plants, however, consist of colourless cells, which *contain* globulines; the latter are commonly green, but the starch-grains of the potato, for instance, are examples of white globulines (p. 42). Each globuline has the latent capacity to swell within its parent cell to form a new cell, losing its colour (if any) in the process (p. 41).

Turpin now investigated particular plants in the light of his ideas on cell-multiplication (1827*b*, 1828*a*). He derived new branches of *Enteromorpha* (which he called *Ulva*) from globulines situated within the cells. It is impossible to be certain of the real nature of these particular globulines; possibly they were zoospores. He gives a figure showing three branches of the plant that have originated from globulines all situated in a single cell (1828*a*; his plate 11, fig. 3).

In an extraordinary and tantalizing paper (1828*b*), Turpin mentions the great number of cases, both in simple microscopical plants and in the reproductive parts of higher forms, in which cells occur in aggregations of 2, 4, 8, or 16. He cites the pollen mother-cells of *Cobæa* (see below, p. 432). One would have thought that the idea of repeated binary fission would have forced itself on his imagination; but no, he thinks there is some unexplained tendency towards the germination of globulines in these particular numbers.

Turpin finally summarized his views at considerable length (1829), without adding anything of importance.

The ideas of Raspail were carried over into the embryology of animals by de Quatrefages (1834), in his study of the development of the pulmonate gastropods of fresh water. He thought that the early blastomeres or *globules* contained small similar bodies which grew and distended them, and that the process was repeated until a mass of cells had been produced, which took the form of the little mollusc (p. 115). Dumortier (1837), a student of the embryology of the same group of animals, appears to have held somewhat similar views. Misunderstanding the cleavage stages, he regarded the early embryo of *Limnaea* as being merely lobed and later facetted on the surface. He thought that cells appeared for the first time about a week after these stages. The cells that then appeared in the interior of the embryo he called *cellules primitives*. Inside each of these there arose eight or more *cellules secondaires*, indicated at first by certain *striatures obscures*. These secondary cells appear to have enlarged at the expense of material contained within the parent cell, until they filled it. (If, however, the striations divided the whole of the primary cell into secondary cells, the method should strictly be described as cell-division by partitioning (see below, p. 419).) The secondary cells subsequently enlarged until the primary cell burst, and only remnants of it were left. Only certain parts of the animal were formed of cells: the head was not (Dumortier, 1837, pp. 137 and 143–50, and his plate 4, fig. 16*a*).

The contributions of Schleiden to this subject must be considered in some detail, because they had a strong influence on contemporary opinion. He remarks (1838, p. 161) that new cells must either be formed outside the existing mass of tissue, or in its interior; if the latter, either in the intercellular spaces, or in the cells themselves; there is no fourth possibility (*quartum non datur*). The development of the plant occurs solely by the formation of cells within pre-existing cells and their subsequent expansion (pp. 163–5). He studied the development of new cells especially in the endosperm and pollen-tube. It may be remarked that he could scarcely have chosen an object of study more likely to lead him astray than the endosperm; for the development of a syncytium, with subsequent division into cells, does in fact bear some resemblance to the supposed process of endogeny without migration. The pollen-tube was almost as likely to lead to misinterpretation.

Schleiden gives a general account of the origin of new cells in these two situations. He describes the embryo-sack, in which the cells of the endosperm are to arise by endogeny, as a *Zelle* (p. 144). The first sign of impending cell-formation in the cytoplasm or *Gummi* of this cell, or of the pollen-tube, is the appearance of small mucus-granules. The nucleoli, larger and more sharply defined than the more numerous mucus-granules, are the next objects to appear. Schleiden calls them *Kernchen* (p. 145) or *Kerne der Cytoblasten* (p. 174); the descriptions and figures leave no doubt as to the correct interpretation of these names. It is unfortunate that in their translations of Schleiden's paper into English, both Francis (see Schleiden, 1841, p. 287) find Smith (see Schleiden, 1847, p. 238), overlooked what the original author said about the role of the nucleolus, apparently because they misread *Kernchen* as *Körnchen*; as a result, Schleiden's views have not till now been adequately represented to English readers. According to Schleiden himself (1838, p. 145), the nucleolus is the body round which the nucleus is formed, by the deposition in its immediate vicinity of a granular coagulum. (It is not clear whether the mucus-granules participate in this coagulum.) Schleiden called the nucleus the *Cytoblastus* (p. 139) or *Cytoblast* because he thought that its function was to produce the cell. According to his account (pp. 145–6) it grows larger, and a little blister, the rudiment of the future cell, appears on its surface. The contents of the blister are transparent. The appearance is rather like that of a watch-glass on a watch. The blister enlarges so as eventually to enclose the nucleus, except on one side. Its wall becomes stiffened into a jelly. When this process is complete, the blister has become a cell, the nucleus remaining enclosed in one place in its wall. The cell grows and assumes a regular shape as a result of the pressure of the other new cells surrounding it. The nucleus generally disappears after the cell has assumed its final form.

In his first paper on the cell-theory, Schwann (1838*a*) maintained that Schleiden's statements about the way in which cells multiply applied also to animals. He claimed to have found small cells within larger ones in the notochordal tissue and cartilage of the larvae of the spade-footed 'toad', *Pelobates*. In his book published the next year, he allowed that in animals new cells sometimes develop inside pre-existing ones, but he thought an exogenous origin much more usual (1839, pp. 45, 200, 203–4; see above, p. 412).

In his study of the earliest stages in the development of the rabbit, Barry concluded that two or more 'vesicles' (cells) originate within each pre-existing one (1839, p. 363). This is surprising, because he compares the early embryo with that of the frog; and he already knew, from the studies of Prévost and Dumas (1824), that in the latter animal the number of blastomeres increases by binary fission. Barry did not state clearly how he thought that cells multiply, although he mentioned the subject in several papers (1841, *a*, *b*, and *c*), which are unsatisfactory in more than one respect. He seems to have thought that the nucleus divides or fragments, and that each part of it grows to become a new cell.

Reichert considered that the blastomeres of amphibian eggs were formed endogenously within the uncloven egg, and smaller blastomeres endogenously within these, and so on: cleavage was merely the separation of blastomeres that were already present (1840, p. 7; 1841, p. 540).

Henle described what he thought to be a new cell arising endogenously round a nucleolus, within an existing (? human) cartilage-cell (1841, pp. 153–4 and his plate V, fig. 6). It is just possible that he was in fact observing a stage in cell-division.

Vogt considered that new cells sometimes arose within pre-existing cells, even on occasions within their nuclei (1842, pp. 126–7); but he thought that in animals exogeny was the more usual process (see above, p. 412). He regarded the nucleolus of the egg as a cell embedded in another cell, the nucleus, itself embedded in a third, the yolk (1842, p. 18).

A curious misapprehension prevented Kölliker from being among the first to understand the true nature of blastomeres. In his researches on the development of nematodes (1843), he got the fixed idea that the cells of the later embryo originate from what were really the nuclei of the earlier stages. These nuclei he called *Embryonalzellen*, to emphasize his opinion of their nature, and their nucleoli he regarded as nuclei (*Kerne*) (pp. 101–2). In some cases, in his view, there was no cleavage, but only a multiplication of the *Embryonalzellen*. Each of these produced two new small ones endogenously within it, and dissolved to set them free; the same process then happened repeatedly until all the numerous cells of the later embryo had been produced (p. 79). In other cases (e.g. in what he called *Ascaris nigrovenosa* (presumably another name for what is now called *Rhabdias bufonis*)), he described cleavage clearly enough, and gave excellent figures of it (his plate VI, figs. 21–23); but he totally misunderstood it. He knew that the blastomeres multiplied by division, but he was evidently not much interested in them, for he regarded them as mere spherical conglomerates of yolk-granules (pp. 105–6) round the all-important *Embryonalzellen,* which were going to multiply and produce the definitive cells.

In his general account of the multiplication of cells, published the next year in his book on the development of cephalopods (1844, pp. 141–57), he called the cells of adult animals *secondäre Zellen,* while nuclei were for him *primäre Zellen.* The nucleolus was the *Kern* of the primary cell. A blastomere was not a cell but an *Umhüllungskugel.* His views may be translated into modern terms as follows. In the early embryo, the nucleus of each blastomere ordinarily gives rise to two nuclei, by aggregation of material round the nucleoli. A substance which may be either granular or homogenous aggregates round each nucleus; the two aggregates separate from one another by a process involving the division of the original blastomere into two. This process continues until at last definitive cells are produced by the formation of cell-walls; these appear either round blastomeres, or else round nuclei. Kölliker also thought that a definitive cell might produce daughter-cells endogenously, apparently in the cytoplasm, and then degenerate to set them free. He also thought that new cells might arise within a mass of material formed by the fusion of cells.

Kölliker denied specifically that cells multiply by division. Having at last (1845) adopted a more acceptable nomenclature, he remarked without equivocation, 'Nothing whatever is known of a division of animal cells. Nuclei and cells multiply by endogenous procreation, nucleoli (*Kernchen*) by division' (p. 82). These are strange words from one who had observed cleavage so accurately.

In his old age, Kölliker claimed that in his book on the development of cephalopods (1844), he had made it very probable that all cells are the direct descendants of the blastomeres (Koelliker, 1899, p. 198). The truth is that in the book to which he refers he gave a confused and erroneous account of the way in which cells multiply, while the actual facts, as we shall see (pp. 430–1), had already been revealed by Bergmann in 1841–2.

J. Goodsir (1845, p. 2) regarded the nucleus as the source of successive broods of new cells, which grew within the mother-cell. It is not clear, however, whether he thought the new cells remained within the mother-cell or escaped from it. Goodsir attributed the discovery of the method by which cells multiply to Barry.

Beale (1865, pp. 241–2) appears to have been the last exponent of endogeny, though his remarks on the subject of the multiplication of cells are difficult to understand. He derived new 'elementary parts' (as he called cells) from minute particles, present (it would seem) within pre-existing cells. These particles enlarged, and meanwhile other similar particles might arise within them and also grow, and so on. This would be a clear example of endogeny without migration, but apparently the whole mass might divide and subdivide. When Beale reached these rather elusive conclusions, however, others had already discovered how cells actually multiply.

THE DISCOVERY OF CELL-DIVISION

Preliminary remarks

About the middle of the nineteenth century there occurred a profound change in the beliefs of biologists about the way in which cells multiply. This change cannot be more dramatically recorded than in two extracts from the writings of Virchow. The first is from an original paper published in 1849. The second is the corresponding passage in a book of his collected papers, published seven years later. In the following translation an attempt is made to reproduce the style of Virchow's early writings, which are reminiscent of Oken's *Naturphilosophie.*

'The cell, as the simplest form of life-manifestation that nevertheless fully represents the idea of life, is the *organic unity*, the indivisible living One' (1849, p. 8).

'The cell, as the simplest form of life-manifestation that nevertheless fully represents the idea of life, is the *organic unity*, the divisible living One' (1856, p. 22).

In a note added to the second publication (p. 27), Virchow tries to persuade us that when he wrote *untheilbare* in 1849, he used the term in a philosophical rather than a scientific sense. It is difficult to accept this. There had, in fact, been a revolution in thought. It is the purpose of the rest of this paper to tell the story of this revolution and of the events that led up to it.

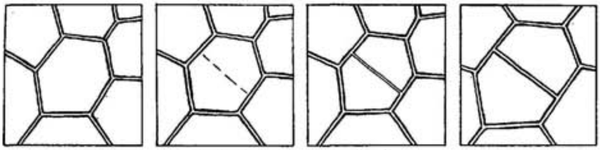
The early cytologists drew sharp distinctions between various methods of cell-division that seem to us to be very similar in all essential points. So sharp did these distinctions appear to them, however, that they would even describe cell-division while denying that cells ever divided. The difficulty is really verbal. They concentrated their attention on the cell-*wall*: this was for them the cell. If the wall did not divide, the cell did not divide, whatever might happen to its 'contents'.

Four methods of cell-division are illustrated diagrammatically in fig. 6.

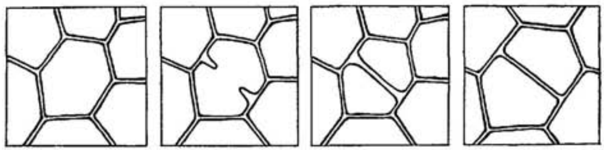
In *cell-division by partitioning*, a thin membrane appears across the middle of a cell. It thickens and is seen to be a double partition, continuous with the pre-existing cell-walls. A single cell has become two cells, each of half the original volume. These grow.

In *cell-division with constriction of the cell-wall*, the latter bends inwards on all sides near the middle of the cell; a continuation of this process results in the division of the whole cell, including its wall. The two new cells grow. This was regarded as genuine cell-division by the early cytologists. It was called *Theilung durch Abschnürung*.

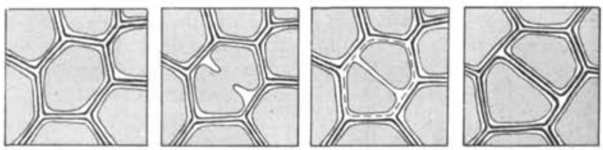
In *cell-division with formation of entirely new cell-walls*, the protoplasm divides into two or more parts inside the wall of the pre-existing cell. Each of these parts grows and acquires a complete new wall of its own, while the original wall disintegrates. This was the *Zellenbildung um Inhaltsportionen* of the early German cytologists. This name was given because the 'cells' (actually the



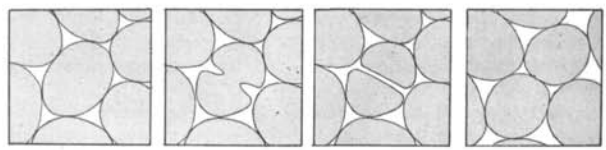
Cell-division by partitioning



Cell-division with constriction of the cell-wall



Cell-division with formation of entirely new cell-walls



Cell-division in the absence of cell-walls (division of the naked protoplast)

FIG. 6. Diagrams of methods of cell-division. In the two lower diagrams the protoplasts are shaded.

cell-walls) were formed afresh round portions of the cell 'contents' (protoplasm). In some cases the protoplasm divided up into numerous bodies that did not touch one another nor the wall of the mother-cell, and a new cell-wall was formed *separately* round each of these bodies. Since these new cell-walls were 'free' from each other, the name *freie Zellbildung* was used.

Cell-division with the formation of entirely new cell-walls shows a certain degree of resemblance to endogeny without migration. In endogeny, however, the new cells were supposed to originate as minute bodies that grew within the cytoplasm of the mother-cell, while in fact, of course, cells are first formed by the process of division, and growth is subsequent to this.

The endosperm is the classical site for the study of cell-division of this third type.

In *cell-division in the absence of cell-walls* (*division of the naked protoplast*) a furrow appears round the middle of a protoplast that has no cell-wall, and deepens until division is complete; the two resulting protoplasts then grow. This method of cell-division could not be envisaged until it was discovered that the cell-wall was not a necessary attribute of the cell. The history of that discovery was related in Part III of this series of papers (Baker, 1952).

Various different lines of research led up to the discovery that cells multiply by division into two or more parts. The chief of these were studies of protists, filamentous algae, and cleaving eggs. It would be possible to relate the story by concentrating first on examples of cell-division by partitioning, then on examples of division with constriction of the cell-wall, and so on; but the differences between the four methods result from such an unwarrantable overstressing of the cell-wall, that an unsatisfactory history would result. A far more logical arrangement will be to take each line of research separately. We shall begin with the results of researches on protists, for it was among these organisms that the process of cell-division was first witnessed.

The multiplication of protists

Leeuwenhoek saw ciliates coupled in pairs on several occasions (1681, p. 57; 1694, p. 198; 1697, p. 36; 1704, p. 1311). He interpreted the process in every case as one of copulation. Once he saw them actually come together in pairs *in conspectu meo* (1697, p. 36), and he must therefore have witnessed a stage in conjugation; but he does not give sufficiently accurate descriptions to make it certain whether he witnessed a stage in division on one or more of the other occasions. It is possible that he did (see especially 1694, p. 198). He himself, however, had no idea that ciliates multiply by division. He thought, on the contrary, that they reproduced by minute round particles (1697, p. 36), which in fact were presumably food-vacuoles (see also 1681, p. 56).

FIG. 7. The earliest illustration of a protist in division. (Anon., 1704, plate opposite p. 1329, fig. G (*c*).)

The first figure of a ciliate in division was given by an anonymous contributor to the Philosophical Transactions of the Royal Society (Anon., 1704; see fig. 7 in the present paper). The author himself did not regard this as a stage in multiplication by division. On the contrary, he compared the appearance with that of flies in copulation (pp. 1368–9). From what he says, it is quite possible that he saw ciliates in stages of both conjugation and division.

Joblot seems also to have seen a stage in the division of an unidentifiable ciliate (1718, plate 2, fig. 5). Like the anonymous writer, he regarded it as representing two individuals 'accouplées' (1718, part 2, p. 14), and indeed he appears to have seen stages in conjugation (his plate 2, fig. 1, and plate 3, fig. 9).

The first person to witness the process of multiplication of a protist by division was Trembley. He saw it in 1744 in the colonial vorticellid *Epistylis anastatica* and in *Stentor* (Trembley, 1746), and later in *Carchesium* and *Zoothamnium* (1748). I have described these discoveries in detail elsewhere (Baker, 1952*b*, pp. 103–12). It must suffice to say that Trembley's studies of these organisms, carried out with extraordinary care and accuracy, established for the first time the method of multiplication of Protozoa and provided a

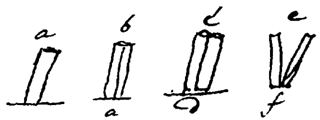


FIG. 8. The earliest illustration of cell-division. Trembley's sketch of the diatom *Synedra* dividing into two. (Trembley, 1766, folio 330.)

firm basis for disbelief in their spontaneous generation. The ciliates, however, can scarcely be considered as cells, in the sense in which that word is being used in this series of papers, on account of the highly polyploid nature of the macronucleus (see Baker, 1948*b*); and although this early work of Trembley's paved the way for the understanding of cell-division, yet it was not an investigation of cell-division itself. We shall therefore not pursue the subject of the reproduction of ciliates here, beyond remarking that Spallanzani, who corresponded with Trembley, also saw stages in their multiplication by division (Spallanzani, 1776, part 1, pp. 160 and 174–5, and his plate I, fig. VII, and plate II, figs. XIII and XIV).

Meanwhile Trembley himself had seen actual cell-division in the sessile, rod-shaped, fresh-water diatom, *Synedra*. I have described this discovery in detail elsewhere (Baker, 1951; 1952*b*, pp. 155–8). Trembley's sketch of the process is here reproduced in fig. 8. He noticed that a line appeared along the length of the organism, and became more conspicuous; then the whole object appeared to become a little wider, and the line was seen to be a groove; the parts on each side of the groove rounded themselves off from one another, and the previously single body was then seen to be double; finally the two halves of the originally single body diverged from one another at the unattached end. Trembley described this process first in a letter to a friend (1766, folio 330), and then, much later, in a book intended for the education of children (1775, vol. 1, pp. 293–7); in the interval another friend, Bonnet, had named the organism the *Tubiforme* and published the main facts of Trembley's discovery in his *Palingénésie philosophique* in 1769 (vol. 2, pp. 99–102). Trembley also observed cell-division in a stalked diatom, named by Bonnet the *Navette*;

this was almost certainly *Cymbella* (see Bonnet, 1769, vol. 2, pp. 104–5; Trembley, 1775, vol. 1, p. 297). Neither Trembley nor anyone else in his time realized that such organisms as *Synedra* and the component individuals of a *Cymbella* colony were cells.

Certain of Gleichen's figures suggest that he may have seen stages in the multiplication of the non-ciliate Protozoa of infusions, but the drawings are not clear enough to establish this (1778; see, e.g., his plate XVII, figs. C III and D III).

O. F. Müller described a dividing specimen of the desmid *Closterium*, which he called *Vibrio lunula* (1786, p. 57). His illustration is reproduced here in fig. 9. He also showed stages in the longitudinal division of a little organism found in stale sea-water, which may possibly have been a flagellate (his plate VIII, figs. 4–6).

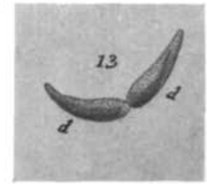


FIG. 9. O. F. Müller's figure of *Closterium* dividing into two. (Müller, 1786, plate VII, fig. 13).

The first person to describe the division of a protist with full realization that the process was one of cell-division, was Morren (1830). He describes *Crucigenia quadrata* as being ordinarily composed of *cellules* united in fours (see fig. 10). He describes the division of a single cell to form four, and of the four to form 16 (pp. 415–22). Later Morren saw stages in the multiplication of *Closterium*. He describes the extension inwards of a circular plate that makes a partition across the organism, which becomes jointed in this region; *déhiscence* then takes place (1836, p. 274).

Meanwhile Ehrenberg had started his celebrated researches. He described and figured an *Actinophrys* in the process of division (1830, p. 96); his illustration, here reproduced in fig. 11, A, suggests that the specimen was genuinely *Actinophrys*, not *Actinosphaerium*. Later (1832, p. 178) he saw a series of stages in the multiplication of *Euglena acus* by longitudinal fission (see fig. 11, B in the present paper). In his book on *Die Infusionsthierchen* (1838) he described and figured a number of examples of the multiplication of flagellates by division; for example, *Polytoma* (p. 25 and his plate I, fig. XXXII), *Pandorina* (p. 54 and plate II, fig. XXXIII), and *Glenodinium* (p. 257 and plate XXII, fig. XXII).

Nägeli described and figured the multiplication of certain diatoms by division (1844, plate I, figs. 1–6).

Cell-division in simple filamentous algae

The simplicity and immobility of most filamentous algae made them particularly suitable objects for the discovery of the way in which cells multiply.

In his careful researches on fresh-water algae, Vaucher at last succeeded in observing the germination of a zygote of *Spirogyra* (which he called *conferva jugalis*). He describes (1803, p. 47) how the cell-wall of the zygote (*grain*) opens at one end; a sack extends from it and begins to elongate into a tube.

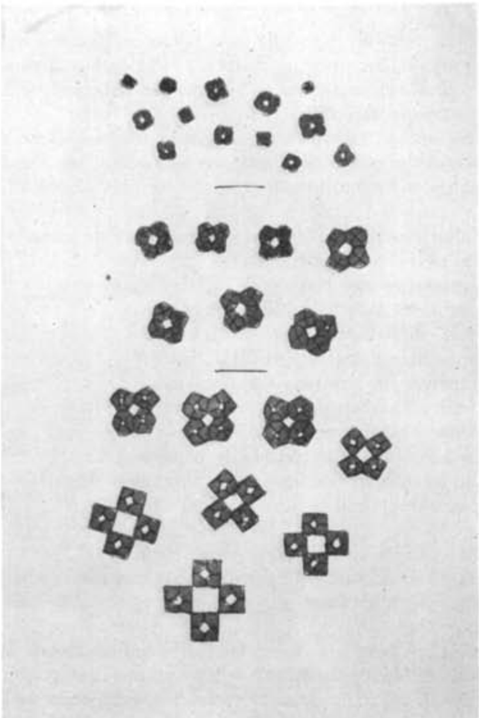


FIG. 10. Morren's figures of cell-division in *Crucigenia*. (Morren, 1830, plate 15, figs. 3–5.)

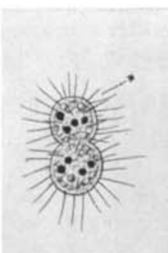


FIG. 11, A

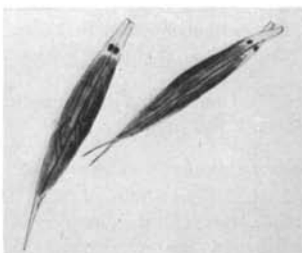


FIG. 11, B

FIG. 11. Ehrenberg's figures of unicellular organisms in division. A, *Actinophrys sol*. (Ehrenberg, 1830, plate II, fig. IV (6).) B, *Euglena acus*. (Ehrenberg, 1832, plate I, fig. III (*b*, *c*). The plate (not the text) is dated 1831.)

He notes how the partitions (*cloisons*) between the cells (*loges*) appear: first one, then two, then many, until finally the tube resembles the plant that gave birth to it. His illustration is reproduced here (fig. 12). In his plate X, fig. 3, Vaucher shows stages in the germination of another alga; the number of partitions is seen to increase. The book contains nothing about the *binary* fission of the cells of any alga.

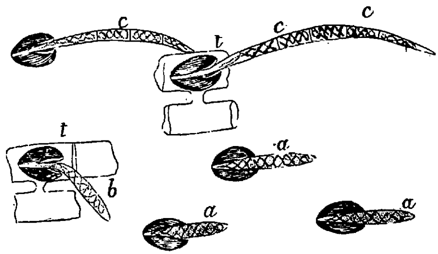


FIG. 12. Vaucher's figure showing new partitions between cells in a young *Spirogyra*. (Vaucher, 1803, plate IV, fig. 5.)

We have seen (p. 415) that Dumortier (1837) was mistaken about the way in which the cells of the embryo of *Limnaea* multiply. Five years previously, however, he had made an important contribution to the study of cell-multiplication in filamentous algae. He describes carefully (1832, pp. 226–7) how an extension inwards of the internal part of the cell-wall 'tends to divide the *cellule* into two parts'. He discusses whether the dividing wall or *cloison* is from the start double. He does not decide the question, but he says that in later stages it is certainly double in the conjugate filamentous algae. He supposed that cell-division was restricted to the cell at the extremity of a filament (see fig. 13 in the present paper). He remarks (p. 228) that new cells cannot originate from globules floating in the intercellular spaces, because some plants, such as the ones he was studying, have no such spaces.

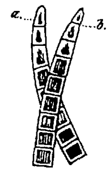


FIG. 13. Dumortier's figure of cell-division in *Conferva aurea*. '*a*, terminal cell that elongates more than the lower ones; *b*, the same divided into two parts by the formation of a median partition.' (Dumortier, 1832, plate X, fig. 15.)

Mohl's celebrated paper *On the multiplication of plant-cells by division* (1837) was first made public in the form of an inaugural lecture on his appointment as Professor of Botany at Tübingen in 1835. Like Dumortier, he studied filamentous algae (see fig. 14). His work on these organisms marks a turning-point in the history of the study of cell-multiplication, but he himself wrote with charming diffidence. 'Furthermore', he remarks, 'many appearances that I have observed in the various species of *Zygonema* [actually *Spirogyra*] make it seem to me more than likely that in

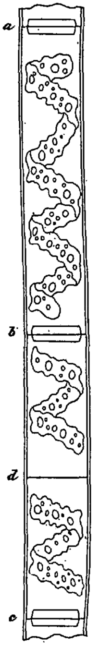


FIG. 14. Mohl's figure of cell-division in *Spirogyra*. The cell wall between the two newly formed cells is at *d*. (Mohl, 1837, plate I, fig. 8.)

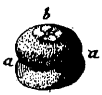


FIG. 15. Swammerdam's figure of a frog's egg, possibly at the 2-cell stage. (Swammerdam, 1737–8, vol. 2, plate XLVIII, fig. v.)

these plants also the individual cells possess the capacity to divide themselves in the middle by a partition-wall formed subsequently. . . . The observations cited above will suffice to prove that the increase of cells by division is not an altogether rare phenomenon among the Confervae' (pp. 29, 30).

Meyen (1838, p. 345) described the multiplication of the cells of certain filamentous algae by the process called in the present paper 'cell-division with constriction of the cell-wall'. He referred to this process, and also to cell-division by partitioning, by the name of *Theilung*.

Cleavage, and the recognition of blastomeres as cells

The study of the cleavage of the eggs of animals played an important part in convincing biologists that cells multiply by division. It was fairly easy to show that blastomeres did so; the difficulty was to discover that they were cells.

Swammerdam is thought by some to have seen a 2-cell stage in the cleavage of the frog's egg. One of his illustrations is reproduced here (fig. 15). He had placed the egg in a special fluid intended to dissolve the jelly, and this had so distorted it that one can neither affirm nor deny that he saw a stage in cleavage. He wrote, 'Next I observed the whole of the little frog divided, as it were, into two parts by a very obvious furrow or fold' (1737–8, vol. 2, p. 813). He never saw cleavage occurring in a living egg, nor did he see the 4-cell or later stages of the process. His observations on the embryology of frogs were perhaps made while he was studying these animals at Leiden in 1661–3. Dr. A. Schierbeck, however, who has made a careful study of the life of Swammerdam, thinks it probable that these observations were made in 1665. They were first published in the *Biblia naturae* long after his death.

It was stated by Bischoff (1842*a*, p. 46) that de Graaf (1672) saw a 2-blastomere stage in the rabbit. This is not true. De Graaf examined the Fallopian tubes and uteri of rabbits at various intervals after coition. He neither describes nor illustrates any stage in cleavage. From the third day onwards for several days he saw what must actually have been blastocysts (and perhaps late morulae), gradually increasing in size (pp. 313–14, and his plate XXVI, figs. 1–5). He saw no indication of the constituent cells.

Rösel von Rosenhof (1758) studied the development of several species of Anura. It is possible that he saw the 2-cell stage in the tree-frog, *Hyla arborea* (see his plate X, fig. 5, and p. 43). He also gives figures suggesting that he saw the first cleavage-furrow in *Rana temporaria* (plate II, figs. 9 and 10), but the accompanying text (p. 7) shows that the embryos were too old for this to be possible, and the drawings presumably represent neurulae.

Roffredi (1775) saw cleavage-stages in the free-living nematode *Rhabditis*. He figured the nuclei, but evidently did not understand what he was observing, for he did not notice the boundaries of the blastomeres (see Baker, 1949).

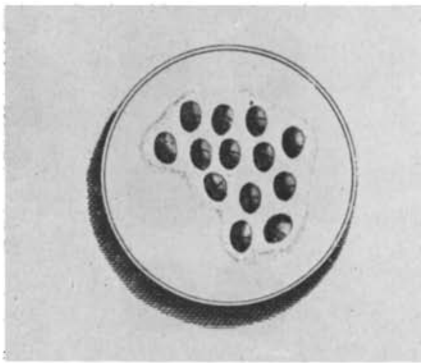


FIG. 16. Spallanzani's figure of the 4-cell stage in the development of the toad. (Spallanzani, 1780, plate II, fig. XI.)

It seems almost certain that Spallanzani (1780) saw the 4-cell stage in the toad (*Bufo*). His illustration is reproduced here in fig. 16. He calls the furrows *solchetti* (vol. 2, p. 25), and compares the appearance to that of the cupule of a chestnut when it has begun to split into its four lobes. He also gives what might be thought on casual reading to be a description of a 2-cell stage in the green frog (vol. 2, p. 13), but the *solco* was here actually the neural groove, not a cleavage-furrow. Spallanzani did not understand the process of cleavage. Indeed, he was so prejudiced by his belief in the actual pre-existence of later stages in the unfertilized egg, that he could not give any adequate account of the occurrences involved in development.

The process of cleavage, as it occurs in the living embryo, was first described by Prévost and Dumas in 1824. Their observations were made upon the eggs of what they called the *Grenouille commune*. This appears in fact to have been *Rana esculenta*, in which species the stages of cleavage are easier to observe than in *R. temporaria*. It is not clear whether they realized that the cleavage-furrows (*lignes* or *sillons*) went so deep as actually to divide the egg. They remark that the egg was soon *divisé* into two very pronounced *segmens* (p. 111), but from what they say farther on it is clear that at the stage to which they refer the furrow had not yet reached even the surface of the lower pole of the egg. In general, their observations were remarkably accurate. One of them observed and sketched what was occurring, while the other wrote down a short description. The later stages of cleavage occurred so rapidly that the authors could only compare them to the dissolving views (*changemens à vue*) seen at the theatre. Some of their drawings are here reproduced in fig. 17. They had no idea that the *segmens* were cells.

Prévost and Dumas noted the resemblance of the upper pole of the egg to

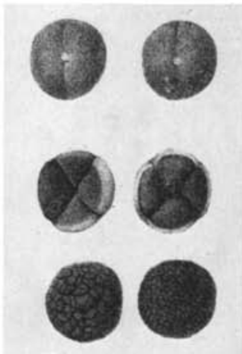


FIG. 17. Some of Prévost's and Dumas's figures of the cleavage of the frog's egg. (Prévost & Dumas, 1824, plate 6, figs. C, D, G′, G″, M, and N.)

a raspberry, at a late stage in cleavage (p. 112). As we shall see, later observers repeatedly noted the resemblance of such stages to raspberries, blackberries, or mulberries, in the development of various animals.

Cleavage stages in *Unio* were seen and figured by Carus (1832, pp. 44–45 and his plate 2, figs. I, III, X, XI), but he did not understand the origin or nature of the blastomeres.

It has already been mentioned (p. 415) that de Quatrefages (1834) saw the blastomeres or *globules* of various pulmonate gastropods of fresh water and thought that they multiplied by endogeny. He remarks (p. 109) that in the development of a species of *Limnaea*, the *globules* have formed a *tissu cellulaire* by the sixth day. The meaning of this is unfortunately not clear. We saw in Part I of this series of papers (1948, p. 112) that the expression *tissu cellulaire* was formerly used in a sense that seems very strange to us today, and de Quatrefages does not say distinctly that one globule represents one cell.

The cleavage of the eggs of frogs (*Rana temporaria* and *R. esculenta*) was re-investigated by von Baer (1834). The great embryologist thought that Prévost and Dumas had regarded the process as one of mere furrowing without actual division (von Baer, 1834, p. 481; 1835, p. 6). He made it perfectly clear that in fact the furrows actually divide the egg into discontinuous parts that are only pressed against one another (1834, p. 487). He used the word *Theilung* to describe the process. He compared the embryo at one stage to a blackberry and at a later stage to a raspberry (p. 493). He was thus the first to note the resemblance that was later perpetuated in the word *morula*. (The Romans used mōrum for both blackberry and mulberry. The diminutive form *morula* is a modern invention. The Latin word *mŏrula* meant a short delay.)

Rusconi gave excellent figures of cleavage in the *Wassersalamander* (1836*a*, his plate VIII, figs. 1–8) and of partial cleavage in the cyprinid fishes, *Tinca* and *Alburnus* (1836*b*, his plate XIII).

The cleavage of the egg by the formation of furrows had so far only been observed in vertebrates. Von Siebold now reported the same process in several genera of nematodes (1837). He called the blastomeres *Dottertheile* and remarked that when they had become small through repeated cleavage, the embryo resembled a blackberry. He saw the nuclei in the blastomeres from the 6-cell stage onwards; he did not use the word nuclei, but generally called them *helle Flecke* (p. 212). He called the nucleus of the egg the *Keimbläschen* or *Purkinjesche Bläschen*, and noticed the presence in it of a nucleolus or *Keimfleck* (p. 209). These observations constituted a considerable step towards the recognition of blastomeres as cells.

Schwann regarded *Dotterkugeln* as cells (1838*b*), but it is not clear from the context whether he here refers to blastomeres or yolk-globules. He recognized the protoplasts of the blastoderm of the hen's egg during the first day of incubation as nucleated cells, and gave a good figure of them, showing the nuclei and nucleoli (1839, pp. 63–66, and plate II, fig. 6).

It has been supposed that Cruikshank (1797) may have seen cleavage-stages in the rabbit, but neither his description nor his figures support this opinion. Jones may possibly have seen a morula-stage in the development of the same animal, but cells cannot be clearly seen in his illustration (1837, his plate XVI, fig. 1), nor does he describe them. The first person to describe the blastomeres of a mammal was the Scottish physician, Barry, who had worked with Schwann in Berlin (see Barry, 1838, p. 302). Barry (1839) gave admirable illustrations of cleavage-stages in the rabbit; two of them are here shown in fig. 18. As we have seen (p. 417), he was mistaken about the way in which blastomeres multiply, but credit is due to him for the first clear recognition that blastomeres are cells, or 'vesicles', to use his own word; he equates his vesicles with the cells of Schleiden and Schwann (p. 360). He remarks of the blastomeres of the 4-cell stage, 'Some of these vesicles presented in their interior a minute pellucid space, which may possibly have been a nucleus' (p. 323). In a footnote he adds, 'Later observations strengthen this supposition, and enable me to extend it to vesicles in the succeeding stages. The nucleus was very distinct in each of the two vesicles occupying the centre of the ovum in fig. 105½' (see fig. 18 in the present paper). He remarks, 'The nature of the alterations which the germ undergoes immediately after the termination of the primitive changes now referred to, I do not know, not having carried my investigations beyond that period. It is probable that they consist chiefly in the formation of new vesicles' (p. 365). In a later paper (1840, p. 542) he refers to the blastomeres of the 2-cell stage as 'cells'. Barry mentions the resemblance of the embryo at a certain stage to a mulberry (1838, p. 324).

The fact that blastomeres are cells was recognized by Reichert in 1840, independently of Barry. From his study of the frog's egg, Reichert concluded that the blastomeres gave rise to the cells of the adult, and he followed this out for various tissues (1840, pp. 13, 19, 58; 1841, p. 540). As we have seen,

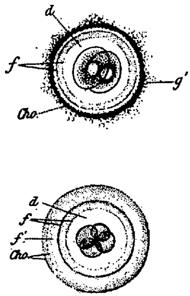


FIG. 18. Barry's figures of the 2- and 4-cell stages in the development of the rabbit. (Barry, 1839, plate VI, figs. 105½ and 106.)

however, he was entirely mistaken about the way in which bastomeres multiply (see above, p. 417).

The recognition by Barry and Reichert that blastomeres were cells constituted an important advance.

Bagge (1841) continued the work of Siebold by studying the early development of the eggs of nematodes. He followed cleavage in several species. In his figs. XI–XIX and XXI–XXIII (the latter wrongly labelled XXV–XXVII through the *Molestissima negligentia* of the engraver), he shows clearly, in the species he calls *Ascaris acuminata*, how the size of the cells is reduced by repeated division from the uncloven egg to the worm-shaped embryo. His great merit was his recognition (p. 10) that the large *vitelli partes* or blastomeres gave rise to the little *globuli* of the late embryo, by a process of repeated cleavage. It is unfortunate that when he used the word *cellulae*, he meant nuclei. He saw these in the blastomeres (e.g. in the 6-cell stage of *Strongylus*; see his fig. x). He noted the resemblance of the embryo at one stage to a blackberry or mulberry (one cannot say which, for he writes in Latin).

Bergmann of Göttingen, a student of the development of frogs and newts, was the first person who both understood the nature of cleavage and also recognized blastomeres as cells. He summed up his conclusions in words that show a restraint that is perhaps laudable. 'I may therefore state', he wrote, '*that the cleavage of the amphibian egg is an introduction to cell-formation in the yolk*. Indeed, I would even call it cell-formation, if the first, larger divisions of the yolk could unreservedly be called cells' (1841, p. 98). He compared his findings with those of Mohl in filamentous algae (see above, p. 425). He saw the *hellen Flecke* in the blastomeres, and thought that they might be nuclei.

Bergmann's slight hesitancy was caused by the absence of any resemblance between cleavage and the process of cell-formation as described by Schleiden. Although Bagge had not specifically homologized the *vitelli partes* and *globuli* with cells, yet Bergmann's hesitancy dissolved when he read the former's paper and found his own discoveries repeated in another group of animals. Bergmann now wrote of 'the identity of cleavage and cell-formation' (1842, p. 95). His two papers should form a landmark in the history of the cell-theory.

Vogt was one of the first to admit that Bergmann might be right, so far as frogs were concerned, but he denied that the latter's ideas were applicable to *Alytes* (1842, pp. 9, 25). Rathke (1842) recognized the blastomeres of *Limnaea* as cells: he saw within each its nucleus (*Kern*), and within the latter its nucleolus (*Kernkörper*). Bischoff (1842) gave excellent figures of cleavage in the rabbit (his plate III, figs. 21–26), but denied that the blastomeres of this animal were cells (p. 79). He was influenced mainly by the absence of cell-walls.

The truth now began gradually to be accepted. Reichert withdrew (rather half-heartedly) his idea that cleavage merely separated blastomeres that had already been formed endogenously, and allowed that it was the 'first act' of cell-formation (1846, pp. 274, 278). Kölliker was more explicit in his change of opinion. He made the important generalization that blastomeres always multiply by division, like infusoria, never by endogeny, as Reichert had supposed (Kölliker, 1847, pp. 12–13). Nearly a quarter of a century before, Prévost and Dumas had given a clear description of the cleavage of the frog's egg; but in the intervening years the theory of endogeny had taken root so firmly, that when blastomeres began to be regarded as cells, it was found hard to believe that they multiplied by division. Kölliker's generalization marked the end of the controversy on this subject. The credit, however, belongs to Barry, Reichert, Bagge, and especially Bergmann. Weldon (1898) was wrong in giving it to Kölliker.

The multiplication of other kinds of cells by division

Although the study of protists, filamentous algae, and blastomeres was of paramount importance for the discovery that cells multiply by division, yet quite a number of relevant observations were made from time to time on other objects. Grew may have had cell-division in mind when he remarked that some of the 'Pores' of the pith of plants were 'divided with cross Membranes' (1672; see above, p. 409); and Wolff, though he believed in exogeny as the usual method of cell-formation, yet allowed that partitions or *dissepimenta* were sometimes formed across the large cells of plants, with the production of smaller, included cells (1759, p. 21).

The division of the pollen mother-cells of *Cobaea scandens* (Polemoniaceae) into four young pollen-grains was observed by Brongniart (1827). His illustrations are here reproduced in fig. 19. The granules contained in the mother-cell, instead of forming a single mass, 'reunite in four perfectly distinct spherical masses, which float freely in the interior of the transparent utricle that contain them'. Each of these spherical masses 'continues to grow, and the membrane that covers it soon takes on a cellular aspect; the distended utricles that contain these globules in groups of four, split open' (p. 27). It is to be noticed that Brongniart did not describe binary cell-division.

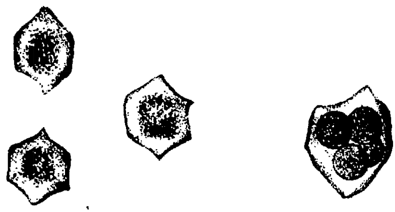


FIG. 19. Brongniart's figures of the division of the pollen mother-cells of *Cobaea scandens*. (Brongniart, 1827, plate 34, fig. 2 (E, F).)

Dumortier stated that all cells that are arranged in *rows* in the fronds of algae and in fungi, mosses, and Jungermanniales, multiply by partitioning in the same way as the cells of filamentous algae (1832, p. 229). Meyen, who was acquainted with Dumortier's findings, observed cell-division by partitioning in the developing lateral axes of *Chara*, and claimed to have observed it also in moulds (1838, pp. 339, 345). He would not use the name *Theilung* for those cases (e.g. endosperm-formation) in which new cell-walls are formed over the whole of the surface of the newly produced protoplasts; he referred to it instead as *Bildung der Zellen in Mutterzellen* (p. 346). Mirbel's *développement intra-utriculaire* (1835, p. 369) may perhaps have been cell-division. He seems to have recognized the varieties of the process that are called in the present paper 'partitioning' and 'cell-division with formation of entirely new cell-walls'.

Schwann himself allowed the possibility that in certain cases new cells might arise by partitioning of pre-existing cells (1839, pp. 5, 218), but he does not appear to have made any actual observations on this subject. Schleiden also equivocated slightly in a book (1842) published four years after his original communication. Though he still regarded endogeny as the standard method by which new cells arise in plants, and questioned the accuracy of Mohl's and Meyen's accounts of cell-division, yet he was clearly puzzled by observations he had made on the parenchyma of certain unspecified cacti. The cells were very regularly arranged, and he noticed here and there that one of them, though appearing single by its relation to the others, yet was clearly divided in two by a partition. This was very suggestive of multiplication by division; but Schleiden often noticed a *Cytoblast* on each side of the partition, and this allowed him to think it probable that even in this case, his own particular form of endogeny had been at work (pp. 267–9).

Remak (1841) would appear to have been the first person to observe a stage in cell-division in a many-celled animal, apart from cleavage. In the blood of a chick-embryo, in the third week of incubation, he observed pear-shaped cells, joined together in pairs by the stalks; each cell had a nucleus. He seems to have seen the remains of the spindle in the bridge between the two cells. He interpreted what he saw as a stage in cell-multiplication by division.

Vogt's observations on the notochord of the newt, *Triturus*, published the next year, were much more complete. He examined the cells at successive stages of larval development. 'The cell-wall bends inwards', he says, 'constricts, and thus at last divides into two halves, which are both exactly similar to one another and to the previously undivided cell, and they both continue their independent lives as cells' (1842, p. 128, and his plate 2, figs. 15 and 16; see also his pp. 46–47). It is strange that this clear description of the multiplication of cells by division should have been written by one who thought that cells ordinarily arise exogenously in a *Cytoblasteme* (see above, p. 412).

Valentin thought that blood-cells and other separate cells of multicellular animals in some cases multiplied by division (1842, p. 630). He instances the cells (*kernartigen Körperchen*) of the thymus gland of the embryo of the sheep; his figure (plate V, fig. 65) may indeed show actual stages of cell-division.

One of the most important contributors to our knowledge of cell-division was Nägeli (1844, 1846), but curiously enough, he himself would not allow that most of the processes he was studying constituted cell-division. He restricted the idea of division to *Abschnürung*, that is to say, to what is called in the present paper 'cell-division with constriction of the cell-wall'. In his earlier paper (1844, p. 97) he denied that this process was ever complete: a partition appeared before the constriction had become very deep. He writes of 'so-called' cell-division (p. 110). Later, however, he allowed the reality of complete *Abschnürung* in certain cases (1846, p. 60). By 'cell-formation' he meant the formation of cell-walls. For him, the cell-wall *was* the cell: if it did not constrict to nip the pre-existing cell in two, cell-division did not occur.

Although he concentrated so much attention on the wall of the cell, Nägeli by no means overlooked its *Inhalt* or protoplasm, and indeed he made some interesting observations on the multiplication of nuclei, to which it will be necessary to refer in the next paper in this series. He noticed that when cell-multiplication is about to occur, there is first of all an isolation or individualization of parts of the *Inhalt* (or, in modern terms, the protoplasm divides into two or more parts) (see fig. 20). A *Membran* or thin cell-wall then forms round each of the parts. In *wandständige Zellenbildung* this new cell-wall, from the moment of its appearance, is everywhere in contact with the wall of the original cell, except where the new *Inhaltspartien* are

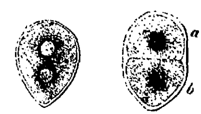


FIG. 20. Nägeli's figure of the division of a germinating spore of *Padina* (Phaeophyceae). (Nägeli, 1844, plate II, figs. 4 and 5.)

divided from one another; here a new partition is formed. This is a kind of cell-division by partitioning, in the terminology used in the present paper. In *freie Zellenbildung* the *Inhaltspartien* separate themselves entirely so that each is 'free'; a new wall is formed round each, and these walls are nowhere in contact with the original cell-wall (Nägeli, 1846, pp. 51, 60, 62; see p. 420 of the present paper).

The strangeness of Nägeli's papers is mainly verbal. When once one has grasped his use of words, it is clear that he made a massive contribution to our knowledge of the process by which cells multiply. He studied it in all the major groups of plants (other than bacteria). From his time onwards scarcely anyone could take seriously the contention that plant-cells multiply exogenously, and the foundation had been laid for a general understanding that the protoplast multiplies by division.

FIG. 21. Reichert's figures of the division of the primary spermatocyte of *Strongylus auricularis* into 4 spermatids. (Reichert, 1847, plate VI, figs. 5–7.)

It will be remembered that Reichert was mistaken about the nature of cleavage (see above, p. 417). He made important observations, however, on the multiplication of the male germ-cells of the nematode *Strongylus* (1847). He identified the cells at the blind upper end of the tubular testis as 'elementary nucleated cells', and understood that a series of stages in spermatogenesis was displayed along the tube, the pear-shaped ripe spermatozoa being found at the opposite end. Working along the tube from the blind end, he saw stages in the division of the spermatogonia (pp. 101–2), and further along again he saw and figured what were evidently the meiotic divisions (pp. 110–14); these he compared with the processes of pollen-formation (which, as we have seen, had been observed by Brongniart). Some of his figures are reproduced here in fig. 21. Like Nägeli, Reichert could not escape from the ideas of the nature of the cell that were current in his time, and he described cell-division as *Zellenbildung um Inhaltsportionen*. The process whereby the *Inhalt* (protoplasm) divided into its *Portionen* (daughter-protoplasts) was evidently of secondary interest to him, for he was always looking for the formation of a *Zelle* (cell-wall) round a newly formed protoplast. Like Nägeli again, however, he by no means overlooked the *Inhalt*, and it will be necessary to revert to his work on *Strongylus* in the next paper in this series, in which the multiplication of nuclei will be considered.

Omnis cellula e cellula

'The origin of cells', wrote de Candolle in 1827, 'like everything connected with the origin of organisms, is a problem that it is absolutely impossible to resolve in the present state of knowledge' (p. 27). Twenty years later the main facts had been discovered. Morren had recognized *Crucigenia* as a cell and followed its multiplication by division. Dumortier, Mohl, and Meyen had discovered how the cells of filamentous algae multiply. Dumortier and especially Nägeli (despite his misleading terminology) had established cell-division as the standard method of cell-multiplication in the main groups of plants. That the cleavage of eggs is cell-division had been revealed by the investigations of von Siebold, Barry, Reichert, Bagge, and Bergmann. Finally, cell-division had been demonstrated in notochordal and spermatogenetic tissues by Vogt and Reichert. It remained to realize that the process that had been studied and reported over and over again was the universal method by which cells multiply.

This realization, epitomized in the words *Omnis cellula e cellula* (surely one of the grandest inductions of biology), we owe almost entirely to two men, Remak and Virchow. The Latin phrase, however, does not exclude the origin of new cells by endogeny, and it must be remarked in passing that Raspail, Turpin, Schleiden, and Goodsir would perhaps have assented to it, if it had been put forward in their time. In fact, however, the phrase was introduced solely in reference to the origin of new cells by *division*.

Remak and Virchow had both been pupils of Johannes Müller, both were practical medical men as well as biologists, and both were in their thirties. In other respects they were very different. Remak was the typical research-worker. He carried out thorough investigations in the laboratory; he studied carefully the work of others, and made full acknowledgement of it; he wrote in a straightforward style and eschewed all fanciful ideas. Virchow, on the contrary, soared away in the manner of his predecessors in the school of *Naturphilosophie*, and left the reader guessing what the actual facts were that led him to his conclusion, and who discovered them.

Although both men published in 1852 and their papers cannot be exactly dated, yet the circumstantial evidence suggests that Remak was the first in the field. It will be remembered that he had observed a stage in the multiplication of blood-corpuscles by division in 1841 (see p. 433). In 1851, when writing on the cleavage of the frog's egg, he said that he must reserve to another paper his remarks on the transition from the cleavage-cells to the tissues, by repeated cell-division (p. 496). The promised article appeared in the following year.

By a careful review of the available evidence, but without adding new observations, Remak (1852) set out to explode Schwann's idea of the exogenous origin of cells and to set up in its stead a general theory of their multiplication by division. He remarks that the botanists no longer believe that cells arise outside pre-existing cells. To him, the extra-cellular origin of cells is as unlikely as the *Generatio aequivoca* of organisms (p. 49). Between the cleavage-cells there is no intercellular substance in which new cells could originate exogenously. Remak breaks loose at last from the domination of the vitelline membrane, which had so misled previous investigators. For them, the vitelline membrane *was* the cell; the protoplasm was its *Inhalt*. Thus, since the vitelline membrane did not change during cleavage, cell-division did not occur!

Remak plays down the *Dotterhaut*, remarking that it does not participate in the formation of the egg-cell. The protoplasm of the egg-cell passes over into that of the embryonic cells, and the nuclei of the latter are the derivatives of the nucleus of the first cell. Remak thinks it unlikely that new cells arise from extracellular substance even in diseased tissues. 'The statement that the cells of animals, like those of plants, have only an *intracellular* origin, seems to me to be a proposition established by a long series of reliable experiences' (p. 55).

Remak's elaborate study of the development of the chick and frog, recorded in his celebrated book (1855), convinced him of the correctness of the views he had expressed in 1852. Towards the end of the work, in a valuable general review of the cell-theory, he upheld division (*Theilung*) as the standard method of cell-formation. He is concerned once again by that bugbear of the cytologists of his time, the vitelline membrane, and points out that it is not always possible to distinguish with certainty between cell-membranes, thickenings of the outer parts of cells, and intercellular material (p. 174). He realizes that what is essential is the protoplasm, and this *divides*; 'all animal cells arise from the embryonic cells by progressive division' (p. 178). He is puzzled, however, by the fact that in certain rhabdocoels the germinal vesicles are formed in one organ, and the yolk in another; this makes him hesitate about saying unequivocally that the ordinary egg, with its yolk, is a cell. He understands clearly that the division of the egg by cleavage-furrows is not always complete.

It is impossible to tell whether Virchow had read Remak's paper of 1852 when he published his own in the same year. He makes no mention of Remak; but this is perhaps not very significant, for he mentions no one who had written on the multiplication of cells except Schleiden, Schwann, and Kölliker (and the latter only in connexion with the contractility of the vessels of the umbilical cord!). One does not know what were the chief facts that convinced him of the origin of cells from pre-existent cells by *Zertheilungen und Zerspaltungen* (1852, p. 377). Somewhat understating the case, he admits that his earlier definition of the cell as 'the indivisible living One' (see above, p. 419) was *nicht ganz richtig*; for *überall findet sich das Princip der Theilbarkeit, der Spaltbarkeit* (p. 378).

Like Remak, he returned to the theme in 1855. Like Remak, he pointed out that if cells did not arise from pre-existent cells, the state of affairs would resemble *Generatio aequivoca*. Unlike Remak, he uses strangely violent language in denouncing spontaneous generation as 'either pure heresy or the work of the devil'. He then proceeds to the great generalization. 'I formulate the doctrine of pathological generation, of neoplasia in the sense of cellular pathology, simply thus: *Omnis cellula a cellula*' (p. 23). It is noteworthy that in coining the aphorism, Virchow applies it to diseased tissues, and takes for granted that it applies to normal cells. It seems to have been Leydig who first put the phrase in its final form. Like Remak and Virchow, Leydig first of all denies the reality of *generatio aequivoca*. 'Observation knows only an *increase of cells from themselves*,' he proceeds, 'and the same validity might be ascribed to the proposition *omnis cellula e cellula* as to *omne vivum e vivo*.' This was the form of words adopted by Virchow in his statement on the subject in the *Cellularpathologie* (1859, p. 25). 'Just as we no longer allow', he wrote, 'that a roundworm originates from mucous slime, or that an infusorian or a fungus or an alga forms itself from the decomposing remains of an animal or plant, so also we do not admit in physiological or pathological histology that a new cell can build itself up from a non-cellular substance. Wherever a cell originates, in that place there must have been a cell before (*Omnis cellula e cellula*), just as an animal can only originate from an animal and a plant from a plant.'

If we deliberately overlook the strange style in which Virchow wrote his paper of 1852, we can see that he made a contribution towards the understanding that cells are derived from pre-existing cells by division. But if we compare his writings with Remak's, we cannot fail to recognize that the latter's must have had far more influence. Indeed, it does not seem likely that Virchow's writings by themselves would have had much effect upon opinion. Remak's paper of 1852 contains no catch-phrase, but it stands out as the first clear and solidly backed general statement of the way in which cells multiply.

It must be regretted that in later years Remak (1862) withdrew to some extent from the position he had adopted. No exception was definitely known to the rule that in normal tissues, cells multiplied by division: that he still allowed. But he now maintained that endogeny occurred in diseased tissues, and that in this process, pre-existing nuclei were not concerned. Further, he thought it probable that certain cells in normal tissues multiplied endogenously. He considered that spermatozoa originated within a mother-cell, and that merogony was a form of endogeny. The nuclei of certain cells, in his view, could not be traced back to the nuclei of the embryo. He instanced the star-shaped cells of connective tissue (presumably the fibroblasts), and the cells of the cutis and of the smaller branches of the blood-vessels of the frog.

These doubts must not be allowed to obscure the service that Remak had rendered to biology at the appropriate moment, ten years before. Nevertheless, we must guard against overestimating his contribution. Important though he was, Remak was not the discoverer of the way in which cells multiply. Trembley, Morren, Ehrenberg, Dumortier, Mohl, Meyen, Prévost, Dumas, von Siebold, Barry, Reichert, Bagge, Bergmann, Nägeli—these were the men whose discoveries had produced a situation in which a great generalization would be acceptable. Remak supplied it.

ACKNOWLEDGEMENTS

I am particularly grateful to Dr. Charles Singer for calling my attention to two important papers that I should otherwise have missed. I take the opportunity of adding Klein's *Histoire des origines de la théorie cellulaire* (1936) to the list of valuable works on the subject, given in the first part of this series of papers. My work on the cell-theory has continued to receive the support of Professor A. C. Hardy, F.R.S.

Correction. In part III of this series of papers (1952), I suggested that the word *coenocyte* appeared to be superfluous. Further consideration has led me to change this opinion. It seems desirable to have a special name for those syncytia that resemble single cells in shape (e.g. the binucleate components of mammalian liver). The word coenocyte will therefore be used in future parts of this series of papers when it is necessary to specify this particular category of syncytia.

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