THE CELL THEORY, PAST AND PRESENT.

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MR ROBERT HOOKE was one of the first men of science to employ the Microscope in the study of the structure of plants and animals. A chapter in his *Micrographia*[1] is entitled "Of the Schematisme or Texture of Cork and of the Cells and Pores of some other such frothy Bodies." This is probably the first use of the word CELL in histological description. In the course of this chapter he refers to the lightness of Cork, which he compares with froth, or an empty Honey Comb. Its substance, he says, is wholly filled with air, which "is perfectly enclosed in little Boxes or Cells distinct from one another." Further, he gives an idea of the dimensions of these cells by stating that about sixty could be placed endways in the $\frac{1}{18}$th part of an inch, and that 1,166,400 could be placed in a square inch. He thinks that they are the channels through which the juices of the plant are conveyed.

The term Cell was also employed to express a definite morphological unit by Dr Nehemiah Grew,[2] who shares with Malpighi the glory of being one of the fathers of vegetable physiology. When describing in his Anatomy of Plants the skin of the root (p. 62), he says the parenchymous material is

"frequently constructed of exceeding little *Cells* or *Bladders*, which, in some Roots, as of Asparagus, cut traverse, and, viewed through a Microscope, are plainly visible. These Bladders are of different sizes; in Buglos larger, in Asparagus less, and sometimes they coincide and disappear."

In his account of the parenchyma of the bark he again uses the word Cells (p. 64), and says that

[1] London, 1665.

[2] *The Anatomy of Plants*, London, 2nd ed., 1682. The several Books into which Grew divided his treatise were presented to the Royal Society of London at various dates between 1671 and 1675.

"each is bounded within itself, so that the *Parenchyma* of the *Barque* is much the same thing as to its Conformation, which the Froth of *Beer* or *Eggs* is as a fluid, or a piece of fine *Manchet* as a fixed body." These cells are so small as scarcely to be discerned without the microscope; more usually, however, Grew applies to them the term bladders or vesicles. In the chapter on the vegetation of roots he speaks of the sap swelling and dilating the bladders, and as being fermented therein, as transmitted from bladder to bladder, and leaving certain of its principles adhering to them. He thus recognised that the cells or bladders played an important part in the nutrition of the plant. Almost, indeed, he seemed to have grasped the idea that they exercised a selective or secreting influence; for, in describing the parenchyma of the fruit of the lemon, he speaks (p. 180) of "those little *Cells* which contain the essential Oyl of the fruit," whilst, he says, in other bladders, "lies the acid juyce of the limon."

Malpighi, whose work on the Anatomy of Plants[1] was almost cotemporaneous with the treatise of Grew, had also seen the structures which Grew named cells or bladders, and had designated them *utriculi*, and believed that they could be separated from each other. In a subsequent treatise[2] he described the lobules of fat in animals as consisting of adipose vesicles.

Leeuwenhoek, in the course of his microscopic inquiries into the structure of plants, gave the name of *globules* to many of the objects which we now term cells, though he expressly states that they were not perfect spheres.[3]

Clopton Havers, in his treatise on the skeleton, described[4] the vesicular structure of the marrow, and compared it, when seen under the microscope, to a heap of pearls.

Alex. Monro, *primus*, in his work on the bones,[5] when writing on the medullary structure, stated that it is sub-divided

[1] *Anatome Plantarum*, London, 1675.

[2] *Opera*, vol. ii. p. 41, 1686.

[3] Samuel Hoole, who translated many of Leeuwenhoek's writings (London, 1799, part 2, p. 178), when describing fig. 11, on pl. vi., says that the globules of meal are enclosed as it were in cells, and that some of those cells are represented at H. in the figure. Leeuwenhoek himself, however, in his description of the same figure (*Epistolæ physiologicæ*, Delphis, 1719, p. 25), does not use the word cellula.

[4] *Osteologia nova*, 1691, p. 167.

[5] *Anatomy of the Humane Bones*, Edinburgh, 1st ed., 1726; 2nd ed., 1732.

"into communicating vesicular Cells, in which the Marrow is contained. Hence it is that the Marrow, when hardned and viewed with a Microscope, appears like a Cluster of small Pearls. This Texture is much the same as what obtains in the other cellular parts of the Body where Fat is collected, only that the Cells containing the Marrow are smaller than those of the *Tunica adiposa* or *cellulosa* elsewhere."

Caspar F. Wolff[1] also recognised that fat was contained in small vesicles, surrounded by a fine membrane. He conceived also that the developing organs, both of plants and animals, consisted of a viscous substance which contained cavities, cells, or bladders which communicated with each other.

Fontana figured the fat vesicles, both free and surrounded by the fibres of the areolar tissue.[2]

Mirbel, in his botanical writings,[3] published at the beginning of the present century, stated that vegetables were composed largely of cells. He described *le tissu cellulaire* as composed of *les cellules*, which were contiguous with each other, so that the walls were in common. These walls were extremely thin and translucent, and sometimes riddled with pores. The term cells was also used both by his contemporaries and successors in their writings on the anatomy of plants.

But anatomists experienced much greater difficulty in distinguishing the presence of cells in the textures of animals. It is true that from the time of Malpighi and Leeuwenhoek, the globules or particles had been recognised in the blood, but it is only within a comparatively recent period that their cellular structure was determined. Both Bichat[4] and Béclard,[5] in their important treatises on General Anatomy, made no reference to cells as elements of the tissues. Both these authors had chapters *du tissu cellulaire* or *du système cellulaire*, a term which had

[1] *Theoria Generationis*, editio nova, 1774; Commentary "*Ueber die Nutritionskraft*," by Blumenbach and Born, St Petersburgh, 1789.

[2] See his Essay "*sur la structure primitive du corps animal*" in his "*Traité sur le vénin de la Vipere*," Florence, 1781 (Ph. viii. figs. 19, 20).

[3] *Traité d'Anatomie et de Physiologie végétales*, t. i., Paris, au x.; *Exposition de la Theorie de l'organisation végétale*, Paris, 1809. Ch. Robin, in the article "Cellule," *Dict. Encyclop. des Sciences médicales*, Paris, 1873, credits Mirbel with having introduced the term "cellules," but the extracts given in the text show that its English equivalent, cells, had been in use for upwards of a century before Mirbel wrote.

[4] *Anatomie générale*, Paris, 1812.

[5] *Élémens d'Anatomie générale*, Paris, 1823.

been in use from the early part of the last century. But by the tela cellulosa or cellular tissue, anatomists meant that form of tissue which we now more appropriately call areolar tissue; the so-called cells of which are not microscopic closed vesicles, but areolæ or spaces bounded by the fibres or laminæ of which the tissue is chiefly composed.[1] Béclard, in his description of the adipose tissue, stated that the lobules of fat consisted of microscopic vesicles $\frac{1}{100}$ to $\frac{1}{800}$ of an inch in diameter. The vesicles, he says, have walls, but they are so thin as to be indistinguishable. The presence of organised vesicles or globules in the tissues of animals had thus been recognised, but it needed further observations and facts in order to bring them into association with the cells of vegetable tissue.

This was supplied by the discovery in 1831 by the great English botanist, Robert Brown, of the "nucleus" or "areola" in the cells of the epidermis, and other tissues in Orchideæ and many other families of plants.[2] Following closely upon this discovery were the observations of Schleiden, published in 1838,[3] that the nucleus was a universal elementary organ in vegetables. Schleiden also came to the conclusion that the nucleus must hold some close relation to the development of the cell itself, and he consequently called the nucleus a "cytoblast." Schleiden further discovered that the cytoblasts contained one or more minute circumscribed "spots," or "rings," or "points," which he considered to be formed earlier than the cytoblasts, and which were regarded by him as hollow globules, and were subsequently named by Schwann "nucleoli."[4]

The cellular structure of some of the animal tissues had also begun to be recognised. Turpin had noticed the resemblance between the epithelium corpuscles found in vaginal discharges and the cells of plants. Johannes Müller had discovered that

[1] The term cellular tissue was originally applied to this texture from a fancied resemblance to the proper cell tissue of plants; the walls of the cells of which were believed to be formed of a framework of fine fibres.

[2] "Organs and Mode of Fecundation in Orchideæ and Asclepiadeæ," *Trans. Linn. Soc.*, vol. xvi., 1833; reprinted in *Miscellaneous Botanical Works*, vol. i. p. 511, Ray Society edition.

[3] "Beiträge zur Phytogenesis," *Müller's Archiv*, 1838, p. 137.

[4] Fontana (*op. cit.*) figured the "globules" or scales of the epidermis, in which he recognised the nucleus, but he neither gave it a special name, nor knew its importance (plate i. figs. 8, 9, 10).

the chorda dorsalis of fishes was composed of separate cells provided with distinct walls, though he did not detect a nucleus in them. Purkinje, Von Baer, Rudolph Wagner, Coste, and Wharton Jones had seen the germinal vesicle within the animal ovum. E. H. Schultz had observed the nucleus in the blood globules, and Valentin and Henle had seen it in the cells of the epidermis. The way was thus prepared for a fuller recognition of the essential correspondence between the elementary tissues of plants and animals and for a wider generalisation. Science had not long to wait for an observer who could take a comprehensive grasp of the whole subject; and in 1839 Theodore Schwann published[1] his famous researches into the structure of animals and plants, in which he announced the important generalisation that the tissues of the animal body are composed of cells, or of materials derived from cells:—

"That there is one universal principle of development for the elementary part of organisms, however different, and that this principle is the formation of cells."

Both Schleiden and Schwann entertained the idea, which had long before been present in the mind of Grew, that a cell was a microscopic bladder or vesicle. In its typical shape they regarded it as globular or ovoid, though capable of undergoing many changes of form. This vesicle possessed a cell-membrane or wall, which enclosed contents that were either fluid or somewhat more consistent. Either attached to the wall or embedded in it was the nucleus, which in its turn contained the nucleolus. Schwann, however, recognised[2] that many cells did not exhibit any appearance of a cell-membrane, but seemed to be solid, and had their external layer somewhat more compact. As showing, however, the importance which Schwann attached to the cell-wall, I should state that he regarded the chemical changes or metabolic phenomena as he termed them, as being chiefly produced by the cell-membrane, though the nucleus might participate. He explained the distinction between the character of the cell contents and the cyto-blastema external to the cell, to the power exercised by the cell-membrane of chemically altering

[1] "Mikroskopische Untersuchungen," 1839; and Preliminary Notices in Froriep's *Notizen*, 1838.

[2] P. 176 of Sydenham Society's translation of *Schwann's Memoir*.

the substances, which it is either in contact with or has imbibed, and also of separating them so that certain substances appear on the inner and others on the outer surface of that membrane. In this way, he accounted for the secretion of urea by the cells lining the uriniferous tubes, and for the changes which not unfrequently take place in the cell-membrane itself by thickening or deposition of layers on or within it.

Schwann described the nucleus as either solid or hollow and vesicular, in the latter case being surrounded by a smooth structureless membrane; whilst the contents of the nucleus, other than the nucleoli, were in his view either pellucid or very minutely granulous.

Both Schleiden and Schwann conceived that in the formation of a nucleus a nucleolus was first produced, that around it new molecules were deposited for a certain distance, and then a nucleus was formed. When the nucleus had reached a certain stage of development, new molecules were deposited upon its exterior so as to form a stratum, which when thin was developed into a cell-membrane, but when thick only its outer portion became consolidated into a cell-membrane. Immediately the membrane became consolidated its expansion proceeded by the progressive reception of new molecules; the cell-wall separated from the cell nucleus, and a vesicle was formed; the intermediate space at the same time became filled with fluid, which constituted the cell contents.

Schleiden contented himself with little more than a simple statement of what he conceived to be the process of cell formation in plants; but Schwann entered into an elaborate survey of cell-life both in animals and plants, and founded on it a theory of cells applicable to all organisms.

Schwann conceived that there existed in organised bodies a solid amorphous or fluid substance to which he gave the name *cytoblastema;* this substance might be contained either within cells already existing, or else be situated in the interspaces between cells; and he believed that the cytoblastema for the lymph and blood corpuscles is the fluid lymph-plasma and liquor sanguinis in which these corpuscles float. He held that in the cytoblastema new cells are formed in the manner just described. In animals he says it is rare for cells to arise within pre-existing cells; more usually they arise in a cytoblastema external to the cells already present. Schleiden, on the other hand, maintained that in plants new cells were never formed in the intercellular substance, but only within pre-existing cells. The idea obviously present in the mind of Schwann was that the process of cell formation in a cytoblastema had some affinity with that of crystallisation. He figuratively compares the cytoblastema to a mother liquid in which crystals are formed. He speaks of molecules being deposited around a nucleolus to form a nucleus; of a nucleus growing by a continuous deposition of new molecules between those already existing; and of the cell being formed around the nucleus by a progressive deposition of new molecules; and in more than one passage he indicated that this deposition is a precipitation. He obviously considered the principle of formation of the cell around the nucleus as the same as that of the nucleus around the nucleolus, a process which Valentin subsequently described as heterogeneous circum-position.

But Schwann at the same time showed that, with reference to the plastic phenomena, cells differed from crystals in form, structure, and mode of growth; for whilst a crystal increases only by the external apposition of new particles, a cell grows both by that method and by the intussusception of new matter between the particles already deposited. The difference, he says, is yet more marked in the metabolic phenomena, which he conceived to be quite peculiar to cells. Cells and crystals, however, he considered resembled each other in this point, that solid bodies of a definite and regular shape are formed in a fluid at the expense of a substance held in solution by that fluid, for both attract the substance dissolved in the fluid. Schwann concluded his memoir by advancing, as a possible hypothesis, the view that organisms are nothing but the form under which substances capable of imbibition crystallise; and although this hypothesis involves very much that is uncertain and paradoxical, yet he considered it to be compatible with the most important phenomena of organic life. Schwann inclined, therefore, to a physico-chemical explanation of cell-formation and cell-growth.

Shortly after the publication of Schwann's famous memoir, Henle, who had for some years been engaged in microscopic investigations on the tissues, published his well-known treatise on General Anatomy.[1] He attached great importance in cell formation to extremely minute particles, $\frac{1}{6000}$ to $\frac{1}{12000}$ of an inch in diameter, which he called *elementary granules.* He conceived that these appeared in a blastema, that several aggregated together to form a nucleus, in connection with which he thought it not improbable that a cell subsequently formed. He looked upon the elementary granules as the first and most general morphological elements of the animal-tissues, and he regarded them as vesicles consisting of excessively minute particles of oil coated with a film of albumen. It should be stated that Henle's observations on cell formation were conducted to a large extent on the products of inflammation, and on the lymph and chyle, in all of which fatty and granular particles abound.

As regards the part which the nucleus plays in the process of cell formation, both Schleiden and Schwann regarded it as of prime importance, though in the subsequent life of the cell they considered that its function terminated. Schleiden stated that, subject to certain exceptions which he enumerated, it is rare for the cytoblast to accompany the cell through its entire vital process—that it is often absorbed either in its original place, or cast off as a useless member, and dissolved in the cavity of the cell. Schwann, whilst contending for the exceedingly frequent, if not absolutely universal, presence of the nucleus, yet held that in the course of time it usually became absorbed and disappeared, so that it had no permanent influence either on the life of the cell or the reproduction of young cells, though he recognised that it remained in the blood corpuscles of some animals. Henle, again, maintained that, as there are nuclei without nucleoli, so also cells exist without nuclei, and that new cells may arise without the least trace of cytoblasts.

At about the same time, and immediately after the publication of the important investigations by these eminent German observers, a young graduate of medicine of the University of Edinburgh, Dr Martin Barry, stimulated, he says, by the researches and encouraged by the friendship of Johannes Müller, Ehrenberg,

[1] *Allgemeine Anatomie*, Leipsic, 1841; also French translation by Jourdan in *Encyclopédie Anatomique*, vols. vi., vii., Paris, 1843.

Rudolph Wagner, and Schwann, undertook elaborate researches into the structure of the ovum, more especially in mammals. His results were published in a series of memoirs printed in the *Transactions of the Royal Society of London* from 1838 to 1841.[1] In these embryological memoirs, Barry announced several important discoveries. In his first memoir (1838) he pointed out that the germinal vesicle which had been discovered in the mammalian ovum by M. Coste and Mr Wharton Jones, was the first part of the ovum to be formed both in mammals and birds, and he thought that this was probably the case throughout the animal kingdom. In his second memoir (1839) he described the formation within the rabbit's ovum of the body which he named, and which has been known since his time as the mulberry-like structure. This body arose at first as two vesicles, then as four, and so on in multiple progression, so that Barry was the first to recognise in the ovum of mammals the process which we now know as the segmentation of the yelk. He showed that the vesicles of the mulberry body were cells, and that each contained a pellucid nucleus, and that each nucleus presented a nucleolus. Further, these vesicles arranged themselves as a layer within the zona pellucida.

Barry's third memoir was published in 1840, and as he gave it the subsidiary title of "A Contribution to the Physiology of Cells," it is clear that he regarded his embryological inquiries as having an important bearing on the facts of cell-formation and function. He repeated his observations on the formation of the mulberry-like body, and now recognised that its component cells had been derived from the germinal vesicle, the contents of which entered at first into the formation of two cells, each of which presented a nucleus which resolved itself into other cells, and by a repetition of this process, the cells within the ovum became greatly augmented in number. Further, he stated that the whole embryo at a subsequent period is composed of cells, filled with the foundations of other cells. Although we may not agree with all the details given by Barry in his account of these observations, yet there can be no doubt that he had early recognised the important fact, that in animals new cells arose within pre-existing cells, as Schleiden

[1] *Phil. Trans.*, vols. cxxviii.–cxxxi.

had affirmed to be the case in plants, and that the nucleus acted as an important centre for the production of young cells. In recognising the endogenous reproduction of young cells in animals, Barry made an important advance on the view entertained by Schwann, who regarded the endogenous production of cells as quite exceptional amongst animals.

In this same memoir Barry incidentally mentioned that he saw in the ovum of the rabbit a cleft or orifice in the zona pellucida, and that on one occasion he observed what he believed to be the head of a spermatozoon within the orifice. Two years afterwards he read to the Royal Society[1] a short paper, in which he announced that he had seen a number of spermatozoa within the ova of the rabbit, and in October 1843 he published a figure of an ovum with spermatozoa in its interior.[2]

In a memoir on the Corpuscles of the Blood, published in 1841, Barry announced a still more definite conception of the function of the nucleus. He directly traversed the statement of Schleiden, that the nucleus, after having given origin to the cell membrane, has performed its chief office, and is usually cast off and absorbed; as well as that of Schwann, who had never, except in some instances in fat cells, observed anything to be produced by the nucleus of the cell. Barry stated that the nucleus is a centre for the origin, "not only of the transitory contents of its own cell, but also of the two or three principal and last formed cells destined to succeed that cell; and in fact, that by far the greater portion of the nucleus, instead of existing anterior to the formation of the cell, arises within the cavity." Further, he says, "young cells originate through division of the nucleus of the parent cell, instead of arising as a sort of product of crystallisation in the fluid cytoblastema of the parent cell." He regarded the division of the nucleus in pus corpuscles as not artificially produced by the agency of acetic acid, as was held by Henle and Schwann, but as a part of the process by which cells were produced, and apparently universal in its operation.

In a paper published in 1847, Dr Barry summarised his observations on the nucleus of animal and vegetable cells, and

[1] *Phil. Trans.*, vol. cxxxiii.; read Dec. 8, 1842.

[2] "On Fissiparous Generation," *Edin. New Phil. Jour.*, Oct. 1843.

whilst expressing certain opinions on the mode of formation of the nucleolus and nucleus and the growth of cells which cannot now be accepted, he continued to maintain that cells are descended from an original mother-cell by cleavage of the nucleus, and all subsequent nuclei are propagated in the same way by fissiparous generation. Every nucleus, therefore, was a sort of centre, inheriting more or less the properties of the original nucleus of the fecundated ovum, which he conceived to be the germinal spot, and exercising an assimilative power. Dr Barry's contributions, therefore, to a correct conception of the development of cells, are of the highest importance when viewed in the light of modern observations.

But another Edinburgh inquirer, Mr John Goodsir, afterwards as Professor Goodsir, the distinguished occupant of the chair of anatomy in the University of Edinburgh, was engaged between the years 1842 and 1845 in studying the processes of cell-life, both in healthy tissues and in certain pathological conditions.[1] In his important memoir on Secreting Structures, published in 1842, he demonstrated from a variety of examples that secretion is a function of the nucleated cell, and he gave, as one of his many illustrations, the cells of the testis containing spermatozoa which were derived from the nuclei of these cells. In the original memoir he was inclined to believe that the cell wall was the structure engaged in forming the secretion; but in a reprint of it in 1845, he modified that view, and gave as his opinion that the secretion would appear to be a product of the nucleus. Goodsir also stated in the memoir of 1842 "that the nucleus is the reproductive organ of the cell, that it is from it, as from a germinal spot, that new cells are formed," and he cited cases in which it became developed into young cells. He subsequently, in a short paper on Centres of Nutrition, extended this view to the tissues generally. He defined the nutritive centres as minute cellular parts, existing, for a certain period at least, in all the tissues and organs.

[1] "On Secreting Structures," *Trans. Roy. Soc. Edin.*, 1842; "On Peyer's Glands," *London and Edinburgh Monthly Journal*, April 1842; "On Structure of Human Kidney," *ibid.*, May 1842; *Anatomical and Pathological Observations*, Edinburgh, 1845; also, his collected papers in *Anatomical Memoirs*, Edinburgh, 1868, edited by W. Turner.

They drew from the capillary vessels or other sources nutritive material, which they distributed to the tissues and organs to which they belonged. He regarded a nutritive centre as a cell, the nucleus of which is the permanent source of successive broods of young cells, which from time to time fill the cavity of their parent. He called this central or capital cell the mother of all those within its own territory or department. Goodsir also showed that cells were important agents in absorption, ulceration, and inflammation. In inflammation of cartilage, for example, he described and figured the cells in the area affected as increased in size, modified in shape, and crowded with a mass of nucleated cells in their interior, through the agency of which the walls of the corpuscles and the hyaline matrix became absorbed. He also gave illustrations of the multiplication of nuclei within cells in the course of formation of cysts. Corroborative observations on endogenous formation within animal cells were also given by Mr H. D. S. Goodsir, as confirmatory of the doctrine propounded by his brother on the cell as a centre of nutrition, secretion, and production of young cells. In a research into the structure of the testis in Decapodous Crustacea, Henry Goodsir observed that the head of the spermatozoon corresponded with the nucleus.

As regards the physiological action of cells, Mr (now Sir William) Bowman had expressed the opinion[1] that there was a strong presumption that the epithelium of glands assimilated the secretion from the blood. That the secretion might be separated, either by the passage of its elements through the cells; or by the cells undergoing solution or deliquescence; or by the cells being cast off entire with their contents. Mr (now Sir John) Simon also expressed, in 1845, some important general conclusions on the physiological action of cells.[2] He looked upon the cell wall as of secondary importance and of inessential formation, and he regarded the nucleus with the material developed around it as constituting the sole physical evidence of activity in the part. He saw bile and other secretions within cells, and stated that when the products of

[1] Article "Mucous Membrane," in Todd's *Cyclopædia*, date probably 1842 or 1843.

[2] *Essay on the Thymus Gland*, London, 1845.

secretion can be seen within a cell, they are accumulated in the portion which corresponds to the nucleus as though it were the true centre of attraction. Simon also observed the development of spematozoa within cells, and had seen one end adhering to the relique of a cell, probably its nucleus.

The conception entertained both by Martin Barry and John Goodsir of the process of cell-formation and of the function of the nucleus was in the main very different from that propounded by Schleiden and Schwann. Whilst agreeing with Schleiden in holding that new cells were formed within parent cells, they did not look upon the process as one of deposition, in the first instance around a nucleolus and then around a nucleus, but they regarded the nucleus as the prime factor by the division of which new cells were formed.

With regard to the free formation of cells, as it was not unfrequently called, by deposition in a cytoblastema situated external to existing cells, to which Schwann and Henle attached so much importance in animals, they gave no concurrence. Both Barry and John Goodsir had grasped and advocated the fundamental principle, both of the endogenous development of cells from a parent centre and of an organic continuity between a mother cell and its descendants through the nucleus; and the brothers Goodsir had applied this principle in their anatomical, pathological, and zoological researches.

But histologists elsewhere had made isolated observations on the development in the animal body of young cells within parent cells. Even before the publication of Schwann's immortal treatise, Turpin had stated that the corpuscles which he found in vaginal discharges contained a new generation in their interior, and Dumortier had described secondary cells as formed in the ova of snails. These observations exercised, however, no influence on the progress of thought; and Schwann, though referring to them in the preface to his treatise, yet appeared to question their accuracy.

In 1841, Robert Remak published[1] an account of what he saw in the blood corpuscles of the chick, some of which were biscuit-shaped. At each end was a nucleus, and the two nuclei

[1] *Medicinische Zeitung*, p. 127, July 7, 1841.

were connected together by a thin stalk which traversed the intermediate part of the corpuscle. He thought it probable from these observations that a multiplication of blood corpuscles through division occurred. He obtained also similar evidence in the blood of the embryo pig, and saw both in the blood of the horse and of man red blood-cells formed in the interior of large mother cells. It is customary in Germany to credit Remak with being the first to recognise the division of the nucleus within the cell as a stage antecedent to, and associated with, the division of the cell itself; but from what has already been stated, it will be seen that Martin Barry had preceded him by some months[1] in the recognition of the importance of division of the nucleus in the production of young cells.

In 1843, Albert von Kölliker published[2] an interesting memoir on the changes which take place in the fertilised ova of various parasitic worms. He described and figured the production in regular progression of young cells within the ovum, and observed that in some cells the nucleus was elongated; in others constricted in the middle, as if about to divide; in others two nuclei were present, each smaller than the single nucleus of adjoining cells, as if they had arisen from the division of a larger nucleus. A legitimate inference from these observations was that in the formation of young cells, the nucleus of the parent cell divided into two, and that each of these gave origin to a new cell.

Observations on the endogenous multiplication of animal cells by division of the nucleus now began to be more widely recognised. It was described by Kölliker and by Mr (now Sir James) Paget in the embyro blood corpuscles, by Kölliker in

[1] Barry's later memoirs were read to the Royal Society of London, May 7, 1840; January 7, 1841; June 17 and 23, 1841. They are illustrated with numerous beautiful figures, in which the division of the nucleus and the endogenous production of young cells are shown. Further, it should be kept in mind that Remak's observation was on a single tissue, the embryonic blood corpuscle; whilst Barry's was a generalisation based on a large series of researches on the ovum, blood and mucous corpuscles, epithelium and other cells. John Goodsir, in a footnote to his important paper "On Centres of Nutrition," already referred to in text, p. 263, says—"For the first consistent account of the development of cells from a parent centre, and more especially of the appearance of new centres within the original sphere, we are indebted to the researches of Dr Martin Barry."

[2] *Müller's Archiv*, 1843.

cartilage and in the giant cells of the marrow of bones, and by various observers in the fertilised ovum. It acquired, therefore, much more importance as a mode of origin of animal cells than was accorded to it by Schwann.

At the time when I began the study of anatomy and physiology in 1850, the current teaching of the schools embraced two methods of cell formation,—the one through the intermediation of existing cells, which might be either by endogenous production within a mother cell through division of the nucleus, or by fissiparous division, or by budding off of a part of a cell; the other by a process of free cell-formation outside existing cells and within a blastema. When I came to Edinburgh in 1854 to act as demonstrator of anatomy, I found that the biologists were divided into two hostile forces,—the one was presided over by Professor John Goodsir, whose views on the intracellular origin of new cells I have already explained, and which he systematically expounded in his lectures; the other was led by the then Professor of the Institutes of Medicine, Dr Hughes Bennett. Dr Bennett, whose investigations into cell-formation and cell-life had been largely based, like those of Henle, on the study of pathological processes, was led to attach great importance to the granules or molecules which abound in the so-called inflammatory exudations and in purulent fluids. Bennett held that molecules arose in an organic fluid, and that an aggregation of molecules produced nuclei, upon which cell-walls may be formed; that the molecule was the primary, elementary and most simple form of organised matter, and that an aggregation of molecules might even form fibres and membranes without the agency of cells. His views were almost a reproduction of those of Henle, and he advocated them with great vigour and persistency, especially in regard to the production of pus and other products of inflammation.

Pathologists had indeed very generally supported the theory of the free formation of cells in exudations; but this view, however, was not universally entertained by them. Professor Goodsir[1] and Dr Redfern[2] had shown its inapplicability in

[1] *Opera citata.*

[2] "Abnormal Nutrition in Articular Cartilages," *Edinburgh Monthly Medical Journal*, August 1840; and separate *Memoir*, Edinburgh, 1850.

inflammation and ulceration of articular cartilages. Professor Virchow, in a series of papers in his *Archiv*, commencing with vol. i. in 1847, had described the endogenous formation of young cells in pathological structures. In his lectures on Cellular Pathology, published in 1858, Virchow, like Goodsir, announced his belief in the mapping out of the body into cell territories. Virchow's conception of the territory was the intercellular substance immediately surrounding a cell, and subject to its influence.[1] He maintained that in pathological structures there was no instance of development *de novo*, but that where a cell existed, there one must have been before. He called it the law of continuous development, which could be formulated in the expression *omnis cellula e cellula.* He adduced a great variety of specific instances to show the diffusion throughout the tissues and organs of nucleated cells, and he established, by a variety of proofs, the important part played by the cell elements, more especially those of the connective tissue, in the inflammatory process and in the production of new formations. He advanced, indeed, such a mass of evidence in support of this position, that the theory of free cell formation was shortly after abandoned in connection with pathological processes, as it had been some time previously by most observers in normal histiogenesis.[2]

The continued investigations into the structure of cells, both in plants and animals, led to modifications in the conception of their morphology. Hugo von Mohl announced that he had discovered[3] in the vegetable cell, after being acted on by alcohol and iodine, a thin nitrogenous membrane distinct from and applied to the inner surface of the cellulose wall of the cell, which he named the *primordial utricle.* He regarded it as forming a vesicle within the cell wall, and containing the contents and the nucleus. By subsequent observers it has been shown that the primordial utricle is nothing more than a thin

[1] He first used the term Zellen Territorien in his *Archiv*, Bd. iv., 1852, p. 383.

[2] In a Lecture which I delivered before the Royal College of Surgeons, Edinburgh, in 1863 (*Edinburgh Medical Journal*, April 1863), I summarised the evidence of the derivation of pathological cell formations from pre-existing cells, and adduced additional examples from my own observations.

[3] *Botanische Zeitung*, translated by A. Henfrey in Taylor's *Scientific Memoirs*, vol. iv., 1846.

layer of protoplasm lying close to the cellulose wall, and enclosing the sap cavity of the cell.

Professor Huxley, in an article on the Cell Theory,[1] criticised the views of Schleiden and Schwann, and introduced the terms *endoplast* and *periplast* into histological description. He regarded the primordial utricle as the essential part of the endoplast in the plant, and as homologous with the "nucleus" of the animal cell; whilst the protoplasm and nucleus were simply its subordinate modifications. The periplast, on the other hand, consisted in plants of the cellulose cell wall; whilst in animals the cell wall and matrix of cartilage, the cell walls and intercellular substance of connective tissue, the calcified matrix of bone, and the sarcous elements of muscular fibre were all examples of periplast which had passed through various forms of chemical and morphological differentiation. Huxley maintained that the periplast was the metamorphic element of the tissues, and by its differentiation every variety of tissue was produced, owing to intimate molecular changes in its own substance. The endoplast again might grow and divide, as in the process of cell multiplication; but it frequently disappeared and underwent neither chemical nor morphological metamorphosis; and so far from being a centre of vital activity, he held that it exercised no attractive, metamorphic, or metabolic force upon the periplast.

But about this time it began to be more distinctly recognised that many anatomical units which were to be regarded as cells, as Schwann had indeed admitted in a few exceptional cases, possessed no cell wall or investing membrane, and that the analogy with a bladder or vesicle could no longer be sustained. Thus in 1856,[2] Leydig gave as his idea of a cell a more or less soft substance, approaching in its original state to the globular in form, which enclosed a central body, the nucleus. Subsequently, the cell substance might harden into a more or less independent membrane, and the cell would then consist of membrane, contents, and nucleus. Leydig's conception therefore of what were the essential parts of a cell closely corresponded with the opinion expressed some years previously

[1] *British and Foreign Medico-Chirurgical Review*, Oct. 1853.

[2] *Lehrbuch der Histologie*, 1857. Preface dated October 1856.

by John Simon. Brücke again maintained[1] that the constancy of the presence of a nucleus was subject to certain limitations, especially in the cells of cryptogams, and that there was no positive information either respecting the origin or the function of the nucleus. He further showed that the soft contents of the cell were of a highly complicated nature, and that they frequently exhibited spontaneous movements and contractility. In 1861 and also in 1863, Max Schultze published[2] most important papers on the properties of cells. He adopted the term protoplasm which Von Mohl had employed to designate the contents in vegetable cells which surround the nucleus, and applied it to the substance which had the corresponding position in animal cells. He completely discarded the view that a membrane was essential to a cell, and defined a cell as a nucleated mass of protoplasm. He identified the protoplasm of the animal and vegetable cell as essentially the same substance as the contractile sarcode which forms the freely moving pseudopodia of the Rhizopoda, and he looked upon it as possessing great physiological activity. The conception of the functions and relative importance of the constituent parts of a cell had now undergone a material change. The suggestive ideas of Simon and Leydig had now been distinctly formulated by Max Schultze. Instead of the cell membrane being regarded as a necessary part of a cell, and the active element concerned in the formation of the cell contents, as Schwann believed, it now became universally recognised as only a secondary structure formed by a differentiation of the superficial part of the protoplasm. Schultze also maintained that the appearance of the membrane might be looked upon as a sign of commencing loss of activity, for a cell with a membrane can no longer divide as a whole, but the division is restricted to the protoplasm contained within it. A cell with a membrane is, he says, like an encysted Infusorian. Taking the embryonal cell as a type, he believed that both the nucleus and the protoplasm were derived from the corresponding constituents of another cell. The protoplasm was the substance especially endowed with living force; the nucleus, he thought, played an

[1] "Elementar Organismen," *Wien Sitzbericht*, 1861.

[2] *Müller's Archiv*, 1861, p. 1; *Das Protoplasma*, Leipzig, 1863.

important rôle, though its exact function could not be defined. The only structural character which Schultze recognised in the protoplasm, was a finely granular appearance throughout the somewhat jelly-like, contractile material in which the granules were embedded. Although the name of protoplasm was now given to this substance, yet it obviously corresponded morphologically with the blastema which both Schleiden and Schwann had recognised within the cell, between the nucleus and the cell wall; though it now assumed in the minds of observers a different physiological import.

The reign of protoplasm had now been inaugurated. Not only was the cell membrane believed to be a product of its differentiation, but the matrix of cartilage and of connective tissues, and the other intercellular substances, were thought to be produced not as a secretion, but by a conversion of the protoplasm of the cells into their respective forms. But, further, Max Schultze[1] described a non-nucleated Amœba; and Haeckel[2] and Cienkowski[3] other non-nucleated organisms, simple in their structure. These organisms were believed to consist solely of a clump of soft protoplasm, which might either be naked, when they were called *simple cytodes;* or encased in a wall or envelope, and then termed *encased cytodes.* Haeckel named these—the most simple of all organisms—Monera, and referred them to a group on the confines of both the animal and the vegetable kingdoms, which he termed Protistæ. Stricker[4] also excluded the nucleus as necessary to our conception of an elementary organism. He went so far as to say that the historic name of cell might be applied to the morphological elements of the higher animals, or to independent living organisms, even if they were only little masses of animal sarcode or protoplasm. He was not, however, disposed to extend the definition to isolated fragments of living protoplasm, unless the whole group of phenomena characteristic of an independent organism could be recognised. Stricker held that protoplasm may be fluid, solid, or gelatinous. It exhibited the phenomena of movement, of

[1] *Organis. de Polythal.*, 1854.

[2] *Zeitsch. f. wiss. Zool.*, 1865, Bd. xv.

[3] Max Schultze, *Archiv*, 1865.

[4] "Allgemeines über die Zelle," in *Handbuch der Lehre von den Geweben.* Leipzig, 1871.

nutrition, of growth, and the capability of reproducing its like, *i.e.*, the sum of the phenomena which are characteristic of living organisms.

The doctrine that a nucleated mass of protoplasm was the structural unit common to organisms generally, both plants and animals, though at the very bottom of the scale the phenomena of life could be manifested by a particle of protoplasm without a nucleus, received its most popular expression in this country at least, in a well-known Address by Professor Huxley.[1] In this address he stated that protoplasm, simple or nucleated, is the formal basis of all life, and that all living forms are fundamentally of one character. His views, therefore, had undergone some modification since the publication of his previous article on the Cell Theory.

But contemporaneous with these researches on the protoplasmic theory of cell structure and activity, an English physiologist, Dr Lionel Beale, was conducting investigations into the structure of the simple tissues from an independent and somewhat different point of view. He considered that the elementary tissues of every living being consisted of matter in two states,[2]—the one an active, living, growing substance, composed of spherical particles, capable of multiplying itself, and coloured red by carmine, which he named *germinal matter;* the other, named by him *formed material,* was situated peripherally to the germinal matter from which it was produced; it was passive, non-living or dead, incapable of multiplying itself, and not coloured red by carmine like the germinal matter. In adapting these terms to the ordinary nomenclature of the cell, Dr Beale states—

> In some cases the germinal matter corresponds to the "nucleus"; in others to the "nucleus and cell contents"; in others to the matter lying between the "cell wall," and certain of the "cell contents": while the formed material in some cases corresponds exactly to the "cell wall" only; in others to the "cell wall and part of the cell contents"; in others, to the "intercellular substance"; and in other instances to the fluid or viscid material which separate the several "cells, nuclei, or corpuscles" from each other.

[1] "On the Physical Basis of Life," a Lay Sermon delivered Nov. 8, 1868; *Fortnightly Review*, and Lay Sermons and Addresses, London, 1870.

[2] *Structure of the Simple Tissues*, London, 1861.

According to this theory of the tissues, all the elementary parts of the body consist of two substances—an active, living, germinal matter, and an inactive, non-living, formed material. Every living elementary part is derived from a pre-existing living elementary particle. The nuclei of the germinal matter, though remaining for a long time perhaps in a comparatively quiescent state, may become active and give rise to new nuclei. Dr Beale held that the cell wall was by no means constantly present in cells, and that when present, both it and the intercellular substance were formed or produced by, or a conversion of the germinal matter. In a subsequent work, Beale[1] substituted the term *bioplasm* for germinal matter, and included in it the nucleus, nucleolus, and some forms of protoplasm. It is from the bioplasm that the formed material is produced.

An important advance was made in the conception of the structure of the constituent parts of the cell when it was ascertained that protoplasm was not the structureless, granulated jelly, or slime, which it was originally supposed to be, but that it consisted of two parts, viz., a minute network of very delicate fibrils and an apparently homogeneous substance which occupied the interstices of the network. Stilling and Max Schultze recognised the fibrillated character of the protoplasm of nerve cells and axial cylinders, but Frommann, Heitzmann, Klein, and other histologists applied the observations to the structure of protoplasm generally.

The subject made a yet greater step forwards when it was ascertained by Strasburger and Flemming that the nucleus in its passive or resting stage consists, in addition to the nucleolus, of threads or fibres, some finer, others coarser, formed of *nuclein*, and arranged in a reticular network, so as to form little knots at the points of intersection of the fibres. In the interstices of the network an apparently structureless intermediate substance, nuclear fluid or *nucleoplasm*, is situated; and the nucleus is surrounded by a membrane.[2] By some observers the threads are regarded not as forming a network, but as a greatly coiled single thread. From the affinity which they have for colouring

[1] *Bioplasm*, London, 1872.

[2] This membrane is perhaps nothing more than a somewhat differentiated layer of the protoplasm of the cell arranged around the nucleus.

matter so that they easily stain with dye, Flemming has named them *chromatin fibres*.[1] But the whole question of the relation of the nucleus to the life of the cell, more especially in connection with the production of young cells, assumed a much more definite form when it was discovered that the chromatin nuclear fibres took a primary part in the division of the nucleus in the process of cell multiplication, and the nucleus was reinstated in its place as of primary importance in the structure of cells, and as an essential factor in the formation of new cells. The movements of the fibres within the nucleus, and their rearrangement so as to form definite figures, which changes precede the act of division, were named by Schleicher *karyokinesis*, or nuclear movement, a term which has now been generally adopted.[2]

Waldeyer states that Schneider of Breslau was the first to recognise these movements of the nuclear fibres, and to describe them in connection with the division of the ova, the sperm cells, and also the tissue cells of a flat worm, *Mesostomum;* but Bütschli and Fol made the process more generally known. The publication of their researches excited the greatest interest, and a host of observers, amongst whom I may especially name Strasburger, Flemming, E. van Beneden, Johow, Heuser, Pfitzner, J. M. Macfarlane, Hertwig, Balbiani, Carnoy, and Rabl, demonstrated the process in a number of plants and animals, and the literature of the subject is now very extensive. In order to express the appearances presented, and the changes which take place both in the nucleus and in the cell in the process of division, a new nomenclature has been introduced, and we now read of cytaster, monaster, dyaster, equatorial plate and crown, pithode or cask-shaped, spindles, ellipsoids, coils, skeins both compact and loose, pole radiations, spirem, and other terms. From the range of the literature it would be a work of considerable labour and time to make an analysis of the different observations so as to associate with the name of each observer

[1] The chromatin fibres appear to be composed of granules or spherules, named "microsome-discs" by Strasburger.

[2] Flemming proposed the term *Karyomitosis*, or nuclear threads, to express the thread-like figures formed in the process. M. Carnoy gives the name *enchylema* to the apparently structureless material which occupies the interstices of the network both of the nucleus and cell protoplasm.

the particular set of facts or opinions which he has made known. Fortunately, this is unnecessary on my part, as admirable resumés of the whole subject have recently been published both by Professor M'Kendrick of Glasgow[1] and Professor Waldeyer of Berlin.[2]

Without entering into a detailed description, it may suffice my present purpose to say that four stages may be recognised in connection with nuclear division.

The *first*, or *spirem stage*, exhibits several phases. At its commencement the finer threads, which connect the primary or coarser chromatin fibres of the resting nucleus together, and which give the network-like character, have disappeared along with the knots at their points of intersection and the nucleoli. The primary chromatin fibres, or *chromosome* as Waldeyer calls them, form a complex coil, the spirem or ball of thread, which divides into loops, about twenty in number, and forms a compact skein. The loops are placed with their apices around a clear space called by Rabl the "polar field," whilst their free ends reach the opposite surface of the nucleus or "antipole." The nucleus also increases in size cotemporaneously. The loops next become not so tightly coiled, and form the loose skein, though the individual fibres thicken and shorten. A most important change then occurs, which was discovered by Flemming, and which consists in a longitudinal splitting of each loop or primary chromatin fibre into two daughter threads. A spindle-shaped figure, first seen by Kowalevsky, next appears in the nucleus, which consists of threads that stain much more feebly than the chromatin fibres.[3] The spindle has two poles and an equator, and it finally occupies a position in the deeper part of the nucleus; its equator lies in the plane, through which division of the nucleus is about to occur. The loops of chromatin fibres group themselves in a ring-like manner around the equator (described by Fol and Schneider) of the spindle with their angles inwards, whilst from each pole of the spindle a radiated appearance (*cytaster*) extends into the protoplasm of the cell. The membrane of the nucleus has now disappeared,

[1] *Proc. Phil. Soc.*, vol. xix., Glasgow, 1888.

[2] *Archiv für Mikros. Anat.*, Bd. xxxii., 1888.

[3] Owing to the feeble staining of the spindle figure and of the nucleoplasm, the substances which compose them have been named *Achromatin*.

so that it is directly invested by the protoplasm of the cell; and it is possible, as Strasburger thinks, that there may be a direct flow of the protoplasm into the nucleus, and that the spindle may be produced by it. At the pole of the spindle, from the point at which the cytaster radiates, E. van Beneden has seen a small, shining, polar body, which Strasburger says is not found in vegetable cells.

The *second*, or *monaster stage*. When the chromatin loops have arranged themselves about the equatorial plane of the spindle with their limbs pointing outwards, and the angle of the loop towards the centre of the spindle, a single star-like figure (*monaster, equatorial plate* or *crown*) is produced. The two daughter threads into which each primary chromatin thread had previously split longitudinally, now separate from each other, and, according to Van Beneden and Heuser, pass to opposite poles of the nuclear spindle, where they form loops. These changes are known as the process of *metakinesis*.

In the *third*, or *dyaster stage*, the chromatin loops at each pole of the spindle arrange themselves so that the angles of the loops, though not touching each other, are close together at the pole, and the limbs of the loops are bent towards the equator of the spindle. Two stars are thus produced (*dyaster*), one at each pole, and each star is formed of one of the daughter threads into which each chromatin fibre of the monaster divides by its longitudinal splitting. Each star is sometimes called a daughter skein; around each daughter skein a membrane appears at this stage, and a daughter nucleus is then formed.

In the *fourth*, or *dispirem stage*, the chromatin threads thicken and shorten, and the loops arrange themselves with the angles towards the polar field of the nucleus, and the limbs to the anti-pole.

The division of the mother cell into two new daughter cells is now completed by the cell protoplasm gradually constricting in the equatorial plane until at last it is cleft in twain, and each daughter nucleus is invested by its own mass of protoplasm. The chromatin threads of the daughter skein then form a network of coarser and finer fibres, a nucleolus appears, and the resting nucleus of the daughter cell is completed. Two daughter cells have thus arisen, each of which possesses its own independent vitality. Owing to the very remarkable longitudinal splitting of the fibres of the chromosome, and the distribution of the daughter threads from each fibre to the opposite poles of the spindle, it follows that each daughter nucleus contains about one-half of each chromatin fibre, so that whatever be the properties of the chromosome of the mother cell, they are distributed almost equally between the nuclei of the two daughter cells. As regards the cleavage of the protoplasm, there is no evidence that such a rearrangement of its constituent parts takes place as to give to each daughter cell one-half of the protoplasm from each pole of the mother cell. It is probable that each daughter nucleus simply becomes invested by that portion of protoplasm which lies in proximity to it at the time when the constriction of the protoplasm begins. The young daughter cell, seeing that it is composed both in its nucleus and protoplasm of a portion of each of these constituent parts of the mother cell, possesses therefore properties derived from them both.[1]

Owing to the disappearance of the nuclear membrane at the end of the spirem stage of karyokinesis, at least in cells generally (though it is said to persist in the Protozoa during the whole process of karyokinesis), it follows that the nucleoplasma and the cell protoplasm cease for a time to be separated from each other, and an interchange of material may take place between them in opposite directions—both from the protoplasm to the nucleus, as Strasburger contends, and from the nucleus to the protoplasm, as has in addition been urged by M. Carnoy. In every case it should be remembered that the nucleus, being surrounded by protoplasm, can only obtain its nutrition through the intermediation of that substance, and thus there is always a possibility of the protoplasm acting on the nucleus, and in so far modifying it.

Having now sketched the progress of knowledge of the structure of cells and their mode of production, I may, in the next instance, state the present position of the subject. We have

[1] Dr J. M. Macfarlane has described as constantly present within the nucleolus of vegetable cells a minute body, which he terms *nucleolo-nucleus* or *endonucleolus*. He considers it as well as the nucleolus to become constricted and divided before the nucleus and the cell pass from the resting into the active phase of cell multiplication. See *Trans. Bot. Soc. Edin.*, 1880, vol. xiv., and *Trans. Roy. Soc. Edin.*, 1881–82, vol. xxx.

seen that the original conception of a cell was a minute, microscopic box, chamber, bladder, or vesicle, with a definite wall, and with more or less fluid contents. This conception was primarily based upon the study of the structure of vegetable tissue; and, as regards that tissue, it holds good to a large extent to the present day. For the cellulose walls of the cells of plants, with their various modifications in thickness, markings, and chemical composition, constitute the most obvious structures to be seen in the microscopic examination of vegetable tissue. Within these chambers is situated the active, moving protoplasm of the cell, and embedded in it is the nucleus; it also contains the sap, crystals, starch granules, or other secondary products. The cell wall is to all appearance produced by a conversion of or secretion from the protoplasm. But even in plants a cell wall is not of necessity always present; for, in the development of the daughter cells within a pollen mother cell, there is a stage in which the daughter cell consists only of a nucleated mass of protoplasm, prior to the formation of a cell wall around it by the differentiation of the peripheral part of its protoplasm. Again, the so-called non-cellular plants or Myxomycetes, before they develop their spores,[1] consist of masses of naked protoplasm, on the exterior of which, in the course of time, a membrane or cell wall is differentiated. In the substance of these masses of protoplasm numerous nuclei are situated.[2]

In animal tissues the fat cell possesses a characteristic vesicular form, with a definite cell wall, but neither in it nor in the vegetable cells does the cell wall exercise any influence on the secretion either of cell contents or of matters that are to be excreted. In animal cells a cell wall is frequently either nonexistent, or doubtful, and when present is a membrane of extreme thinness. Animal cells, therefore, do not have as a rule the chamber-like form or vesicular character of vegetable cells.

The other constituents of the cell, and the only essential constituents, are the nucleus and the material immediately surrounding it in which the nucleus is imbedded. It is of secondary

[1] *Lectures on the Physiology of Plants*, by Julius von Sachs. Translated by H. Marshall Ward, Oxford, 1887.

[2] The opinion for long entertained that the simpler algæ and fungi and cryptogams generally are destitute of nuclei has been shown by Schmidt and others to be incorrect.

importance whether this material be called protoplasm, or bioplasm, or germinal matter. The term protoplasm, however, is that which has received most acceptance. In adopting this term, it should be employed in a definite sense to express the translucent, viscid, or slimy material, dimly granular under the lower powers, minutely fibrillated under the highest powers of the microscope, which moves by contracting and expanding, and which possesses a highly complex chemical constitution. The term ought not to embrace either the cell wall of the vegetable or animal cell, or the intercellular substance of the animal tissues. For although these have in all probability been originally derived from the protoplasm, by a chemical and morphological differentiation of its substance, they have assumed formal and specific characters and have acquired distinct functions. Protoplasm, as above defined, is a living substance endowed with great functional activity. It possesses a power of assimilation, and can extract from the appropriate pabulum the material that is necessary for nutrition, secretion, and growth. Growth takes place not by mere accretion of particles on the surface, but by an interstitial appropriation of new matter. In cases, also, where the media in which the cell lives are suitable, as in the freely moving Amœba, or the white blood corpuscles, portions of the protoplasm may separate by budding from the general mass of the cell, and assume an independent existence; but the conditions under which the budding off of protoplasm can take place are exceptional in the higher organisms. Protoplasm, therefore, according to this definition, in addition to being a moving contractile substance, is the nutritive and secreting structural element of the tissues, and is always found relatively abundant where growth and the nutritive processes are most active.

In the fertilised ovum, after the process of segmentation has begun, and in the earlier stages of development of the embryo, the cells are nucleated masses of protoplasm, without cell walls, and with no intercellular material. In the course of time, in animals more especially, an intercellular substance arises apparently by a differentiation of, or secretion from the protoplasm. In many of the tissues this substance acquires such characters, magnitude, and importance as to overshadow the nucleated masses of protoplasm which it lies between and surrounds.

The intercellular substance is the principal representative of the "formed material" of Dr Beale. I cannot, however, agree with him in regarding it as passive and non-living or dead; for morphological and functional changes take place in it long after its original formation. Thus the hyaline matrix, or intercellular substance, of the young costal cartilages becomes converted into a fibrous matrix in the later period of life, and the striated substance of muscular fibre is one of the most physiologically active tissues in the animal body. In the general economy of the tissues, in the fitting of each to discharge the function for which it is specially intended, the intercellular substance plays an essential part. It gives strength to the bones, toughness and elasticity to ligaments and cartilage, motor power to muscles. It wastes by use and needs repair. But it is probably to the nucleated protoplasm within its substance that we are to look for the structural element which attracts to it the pabulum required for its nutrition, so that the interstitial waste which is consequent on its use may be made good.

The nucleus is also an active constituent of the cell. It is doubtful if it plays a part as a centre of attraction in secretion, or in the nutrition of the cell generally, an office which is most probably discharged by the protoplasm; but it undoubtedly acts as a centre for its own nutrition. Numerous observations, however, clearly prove the truth of the generalisation originally propounded by Martin Barry, and confirmed by Goodsir, that the nucleus is intimately associated with the production of young cells. The karyokinetic phenomena which have been observed during the last fifteen years have established this on a firm basis, beginning with the original segmentation within the ovum down to the latest period of cell formation.

But, along with the karyokinetic changes within the nucleus and its cleavage, there is also a cleavage of the protoplasm of the cell, so that the daughter cell consists of portions of both the nucleus and the protoplasm of the mother cell. The question therefore has been put whether the division of the protoplasm is a consequence or a coincidence of the division of the nucleus. I am inclined to think that the cleavage of the cell protoplasm is consequent on the nuclear changes; for it must be kept in mind that certain of the movements in and rearrangement of the chromatin fibres of the nucleus precede any rearrangement of particles in the cell protoplasm so far as yet observed, and, still more, the process of cleavage. Applying, therefore, to the cell the well-known economic principle of division of labour, and that differentiation of structure carries with it differentiation of function, I regard the protoplasm as the nutritive and secreting element of the cell, and the nucleus as its primary reproductive factor.

The present position of the CELL THEORY differs therefore in many important respects from the doctrine advocated by Schwann and his immediate successors. Cells are no longer regarded as of necessity bladders or vesicles. A cell wall is not constant but of secondary formation. A free formation of cells within an extracellular blastema by deposition around a nucleolus to form a nucleus, and then around the nucleus to form a cell, does not take place. Young cells arise from a parent cell by division of the nucleus, followed by cleavage of the cell protoplasm. Although in so many of its details, therefore, the theory of Schwann has been departed from, yet the great generalisation of the cellular structure of plants and animals holds good, and his work will continue to mark an epoch in the progress of biological science.

The study of the very remarkable series of karyokinetic phenomena described in an earlier part of this address has given an impulse to speculation and thought in connection with some of the most abstruse problems of Life and Organisation. The question of the hereditary transmission of properties, both as regards the constituent tissues of the organism and the individual as a whole, has been put on a more definite physical basis. The discovery by Martin Barry of the penetration of the ovum by the spermatozoon has been completed by the researches of Bütschli, Fol, E. van Beneden, and Hertwig. The conjugation of the male pronucleus or head of the spermatozoon with the female pronucleus derived from the germinal vesicle, and the consequent formation of the segmentation nucleus, has been demonstrated. The segmentation nucleus is built up of chromatin fibres and nucleoplasm, derived from both the nucleus of the male sperm cell or spermatozoon and the nucleus of the female germ cell. It is therefore a composite nucleus, and represents both parents. The cells derived from the segmentation nucleus in the early stage of segmentation contain chromatin nuclear particles which are in direct descent from the chromatin fibres of the segmentation nucleus, and through it from the corresponding fibres of both the sperm and germ cells. The segmentation cells then arrange themselves to form the blastoderm, which, in the more complex organisms, by the continuous subdivision of the cells, forms three layers ; from which, by a prolonged process of cell division and differentiation, all the tissues and organs of the adult body are ultimately derived. Karyokinetic changes mark the process of cell division throughout, and each daughter cell receives from the mother cell chromatin nuclear material derived from both parents, which, without doubt, convey properties as well as structure.

In the division of the segmentation nucleus within the ovum a cleavage of the protoplasm of the egg also takes place, and each daughter nucleus is enveloped by the protoplasm of the maternal egg. If during the period of nuclear division there is no interchange of matter between the nucleus and the protoplasm which incloses it, the cell protoplasm would then be derived solely from the ovum, and would represent maternal characters only, whilst the nucleus would possess characters derived from both parents. But if, as is most likely, during the process of karyokinesis, when the nuclear membrane has disappeared, an interchange of matter takes place between the nuclear substance and the cell protoplasm, the latter would then become, if I may say so, inoculated with some at least of the nuclear substance, and be no longer exclusively of maternal origin. Should this be so, the whole of the cells of the body and the tissues derived from them would, as regards both nucleus and cell protoplasm, be descended from material originally belonging to both parents.

Although ova in different organisms differ materially from each other in size, shape, the relative amount of food yolk which they contain, the mode of segmentation, and the presence or absence of a segmentation cavity, they all agree in this that the primordial cells of the egg are nucleated masses of protoplasm. Notwithstanding, the general resemblance of the morphological units which thus mark the first stage in the production of young organisms, each fertilised ovum gives rise to an organism resembling that in which the egg itself arose. Hence the offspring resemble the parents, and the species is perpetuated by hereditary transmission, so long as individuals remain to keep up the reproductive process. During sexual reproduction the substance of the segmentation nucleus undergoes karyokinetic changes during the act of segmentation, and the question arises if the process of karyokinesis is the same for all organisms, whether plants or animals, or if there are specific differences. As the fertilised ovum is potentially the organism which is to arise from it, specific differences not unlikely exist in the minute structure of the segmentation nucleus, which might be expressed by modifications in the arrangement of the chromatin fibres and in the number of their loops. The varieties which have been described in the forms of the karyokinetic figures and polar radiations in different plants and animals may perhaps mark these specific differences.

But there is another question which merits consideration. Are the karyokinetic phenomena which show themselves in the cells of a given tissue characteristic of that tissue; and, if so, would it be possible to distinguish one tissue from another in the same organism by differences in the process of cell division? On this point a commencement seems to have been made towards obtaining some positive knowledge. Strasburger and Heuser think that they have obtained evidence in certain plant cells that such is the case; Rabl concludes, from observations on the epidermic cells of Salamander, that the loops of chromatin fibres are constantly twenty-four in number in the same kind of cell in the same species of animal.

But in considering the different kinds of tissue, and the possibility of each kind possessing its characteristic karyokinetic process, it has to be kept in mind that more than one kind of tissue, each of which has its characteristic structure and function, arises from each layer of the blastoderm, so that there is a stage in development—a stage of indifferentism, if I may use the expression—when the blastoderm represents several tissues which have not yet differentiated. From the epiblast, for example, tissues so diverse in structure and function as cuticle and nerve tissue arise. Now, if there be a special karyokinetic process for the epidermal cells, and another for the nerve cells, does either of these correspond with the process of nuclear division in the cells of the epiblast in their stage of indifferentism, or do they both differ from it? When does the impulse reach the layers of the blastoderm, so as to produce in their constituent cells changes which so alter the characters of the cells as to lead to a differentiation into various forms of tissues, and to what is that impulse due? In the development of each species there seems to be a definite time within certain limits when the differentiation shall begin, and when the process of development of the tissues and organs shall be completed. This is a hereditary property, and is transmitted from parents to offspring. Is the impulse derived from the nucleus or from the cell protoplasm, or do both participate? As already stated, the nucleus is the element which is immediately descended from both parents, and which may therefore be supposed to be the primary, morphological unit through which hereditary qualities are transmitted. But, as is most probable, the nucleus reacts on the cell protoplasm—on the element of the cell through which the ordinary nutritive functions are discharged. As a consequence of this reaction when the appropriate time arrives in the development of each species, for the commencement of the differentiation of the protoplasm of a cell, or group of cells, into a particular kind of tissue, the necessary morphological, chemical, and physiological changes take place. When once the differentiation has been effected, it is continued in the same tissue throughout the life of the organism, unless through some disturbance in nutrition, the tissue atrophies or degenerates. Every multicellular organism, in which definite tissues and organs are to arise in the course of development, has therefore a period, varying in its duration in different species, in which certain of the properties of the cells are as it were dormant. But, under the influence of the potent factor of heredity, they are ready to assume an active shape as soon as the proper time arrives. When the process of differentiation and development is at an end, the organism has attained both its complete individuality as regards other organisms, and its specific characters.

Every organism, therefore, has to be viewed from both these points of view. Its specific position is determined by that of its parents, and is due to the hereditary transmission of specific characters through the segmentation nucleus. Its individuality is that which is characteristic of itself; and arises from the fact that in the course of development a measure of variability within the limits of a common species, from the organic form exhibited by its parents and their other offspring, is permitted. In all likelihood the variability, as Weismann has suggested,[1] is, to a large extent, occasioned by the bisexual mode of origin of so many organisms. Also to the possibility of the molecular particles of the segmentation nucleus and of the nuclei of the cells descended from it, having a method of arrangement and adjustment, and a molecular constitution characteristic of the individual as well as of the species. On this matter we have, however, no information. It is as yet a mere hypothesis. When we consider the extreme minuteness of the objects referred to, and recollect that it is only about fifteen years since karyokinetic phenomena were first recognised, it is astonishing what progress in knowledge has been made within this limited period. We owe this great advance to the much more complete magnifying and defining power of our microscopes, to the improved method of preparation of the objects, and to the acute vision and clear-thinking brains of those observers who have worked at the subject. By continuing the work, and extending it over a wider area, we may hope in time to be able to solve many questions to which we cannot now give an answer.

The nuclear material which makes up the substance of the male and female pronuclei, by the fusion of which the segmentation nucleus is formed, has been termed by Professor Weismann the *germ plasm*. In a series of elaborate papers he has developed a Theory of Heredity,[2] based upon the supposed continuity of the germ plasm. He believes that in each individual produced by sexual generation a portion of the germ plasm derived from both parents is not employed in the construction of the cells and tissues of the soma, or personal structure of that individual, but is set aside unchanged for the formation of the germ cells of the succeeding generation—that is, for reproduction

[1] See his Essay on the significance of sexual reproduction in the theory of Natural Selection; translated in *Essays on Heredity*, Oxford, 1889.

[2] Translations of these papers have been published by the Clarendon Press, Oxford, 1889.

and the perpetuation of the species. According to this theory, the germ plasm, more especially through the chromatin fibres, is the conveyer of hereditary structure and properties from generation to generation. Further, he holds that the cells, tissues, and organs, which make up the somatic or personal structure of the individual, exercise no modifying influence on the germ or reproductive cells situated in the body of that individual, which cells are also, he thinks, unaffected by the conditions, habits, and mode of life. In its fundamental idea Weismann's theory is in harmony with one propounded a few years earlier by Mr Francis Galton.[1]

In an address which I delivered at Newcastle in September last to the Anthropological Section of the British Association,[2] I reviewed this theory of heredity, and, whilst finding in it much with which I could coincide, I directed attention to points to which, I thought, objection might be taken. More especially I took exception to the idea that the germ plasm was so isolated from the cells of the body generally as to be uninfluenced by them, and to be unaffected by its surroundings.

On this occasion I propose to say a few words on the bearing of this theory on the development of the tissues and organs of the individual. If we examine the development of the embryo, say of one of the Vertebrata, we find that it makes a certain advance, varying in its time and extent according to the species, without any differentiation of a reproductive organ with its contained germ plasm being discoverable. I shall not enter into the much-disputed question of the layer or layers of the blastoderm from which the reproductive cells take their rise. But I may say that in the Chick, both in the third and fourth day of incubation, a layer of germinal epithelium may be seen in close relation to the Wolffian duct and the pleuro-peritoneal cavity. At the end of the fourth day or in the fifth day this epithelium becomes thickened, and the primordial ova appear in it as distinctly differentiated cells. In the Rabbit a corresponding differentiation does not appear to take place

[1] *Proc. Roy. Soc. London*, 1872 ; and *Jour. Anthrop. Inst.*, vol. v., 1876.

[2] This address was reported at considerable length in the *Times* newspaper, September 14th, and in full in *Nature*, September 26th. It will also appear in the reports of the Newcastle meeting published by the Association.

before the twelfth or thirteenth day. Up to the period of differentiation of the primordial ova, no isolation or separation of the reproductive cells and germ plasm has taken place; and so far as observation teaches there is nothing to enable one to say which cells of the blastoderm may give rise to primordial ova, or which may differentiate into cells for other histiogenetic purposes. But before the germ cells appear, the rudiments of the nervous, vascular, skeletal, muscular, tegumentary, and alimentary systems, and the Wolffian bodies or primordial kidneys have all been mapped out. Up to this time, therefore, in all probability, a more or less complete diffusion of the germ plasm throughout either one or more of the layers of the blastoderm has taken place. In this way one might account for the hereditary influence carried by the germ plasm being brought to bear upon the cells of the blastoderm generally, so as to impart to them the power of undergoing the morphological and chemical differentiation to form the several tissues, and to mould the entire organism so that it may acquire its specific and individual characters.

But with the diffusion of the germ plasm throughout either the whole of the blastoderm, or a part thereof, it is of necessity so intimately associated with the formative cells of the tissues generally, that it is difficult, if not impossible, to comprehend how it can be unaffected by them. Before, therefore, it again becomes stored up or isolated in an individual, in the form of ova or sperm cells, it has in its stage of diffusion been brought under precisely the same influences as those which in the embryo affect the formative cells of the whole body.

If the germ plasm, from the first stage of development of each organism, were completely isolated from the cells from which all the other cells of the body were produced, it would be possible to conceive its transmission from generation to generation unaffected by its surroundings. But as in each individual a stage of diffusion precedes that of differentiation into the special reproductive apparatus, it follows that the conditions which would secure the germ plasm and the soma cells from mutual interaction are not complied with.