The presence of electric charge and current requires: divergence $\mathbf{D} = \rho$; curl $\mathbf{H} = (1/c)(\mathbf{i} + \partial\mathbf{D}/\partial t)$. In addition, Maxwell included quantity-intensity relations for each field and relations for electrostatic and vector potentials, which he considered integral to the theory.

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CELL THEORY AND DEVELOPMENT

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Cell theory has passed through various stages of understanding during the three centuries since researchers first noticed the existence of cells. Likewise, the role of cells in development has also gone through different interpretations. Theories have included an elementary conception of basic microscopic units in the mid-seventeenth century, a more fully articulated cell theory in the early nineteenth century which held that cells are the basic building blocks of living organisms, a later nineteenth-century conviction that the actions of cellular material actually bring about organic development and differentiation, and the idea that cells hold a key to evolutionary development as well. Controversies and disagreements about detail have occurred, but some version of cell theory and the fundamental role of cells in development has persisted.

This essay will examine the intersection of studies of cells and studies of development, which necessarily leaves out much of both cytology and embryology. Yet the study of cells and their role in individual development has raised important questions and has shaped both the direction of cytology and the study of embryology. It is worth focusing on the intersection and on those few but valuable historical examinations of both cell theory and development.

1. CYTOLOGY AND CELLULAR STUFF

In 1665, Robert Hooke's *Micrographia* (1665) first brought cells to public attention.[1] Intended as a popularly accessible book rather than a specialised report, the *Micrographia* illustrated and described cells which Hooke had studied with his microscope. Taking a thin slice of cork, for example, he observed what looked like a honeycomb of pores, which he called cells since they were essentially spaces surrounded by walls and not unlike the monastic cells of the time. Then he observed similar textures in a number of other plant forms as well. Though convinced that these cells must have a proper purpose, this English observer was not quite certain what that purpose might be. He concluded that they might serve as channels to carry fluids through the plant material in just the way that arteries and veins move fluids through the animal body. Hooke thus established that structural units called cells exist in some organisms, but was not confident about further conclusions.

A few years later, other observers turned their microscopes to organic material as well. In particular, the Englishman Nehemiah Grew and the Italian Marcello Malpighi both began to observe more clearly the detailed structure of plant cells with their work which they called vegetable anatomy. Because the cellular structure of plant material is more obvious than that of most animals, they each clearly observed cells. Malpighi's *Anatomes plantarum* (London, 1675, and 1679) referred to the 'utricles' (or cells) and to the 'basic utrical structure' of the plants. At the same time, in work also communicated to the Royal Society of London, Nehemiah Grew addressed the question raised by Hooke as to whether plants have circulatory systems like animals. He did not find any valves or perfectly analogous vessels to answer that question, but he did provide more detailed and definitive descriptions of the cells in his work which culminated in *The Anatomy of Plants* (London, 1682). The contemporaneous work by Malpighi and Grew set the standard for discussion of cells as structural units for some time. It also demonstrates the close connection between microscopic exploration and cell study in the early years.

Since microscopic aid is valuable for seeing most cells, the increasing interest in microscopy in the seventeenth and eighteenth centuries brought with it an enthusiasm for describing the structure of materials, including the apparent cellular structure of living materials. Thus, some historians have cited the crucial directive role of technical advances, while others have argued that ideas preceded technical innovation. Whatever the technical contribution, questions arose among the microscopists. While Hooke, Grew and Malpighi located cells in plants, others questioned what those cells were: whether the basic units of life or parts of an interconnected fabric; whether accidental and occasional or ubiquitous structures; or whether perhaps only unimportant microscopic artifacts. Others asked whether cells exist in animals as well. The late eighteenth century brought discussion of 'globules', for example, as alternative fundamental material structures. Others saw 'fibrilles' as the more proper units of organic material, and some invested the latter with vital properties such as 'irritability'.

This proliferation of ideas creates problems for the historian who wants to examine cell theory, because it remains unclear what to count as cells. Do we include only those discussions that actually label their entities as 'cells', or do we also include references to 'globules' or 'fibrilles'? When examining cell theory *and* development, such work as Caspar Friedrich Wolff's seems important since he regarded embryos as made up from globules, which produced a sort of 'cellular tissue' analogous to plant cells. And yet the globules do not really correspond to visible cells or to basic organic structural units, as Shirley

Roe has clarified in *Matter, Life, and Generation* (Cambridge, 1981). It is reasonable, therefore, to exclude Wolff as belonging to a different tradition, with different concerns and commitments, and to remain with the microscopic-based study of what cells are and what their role is in development.

In order to begin addressing those developmental questions and to turn those structural spaces surrounded by walls into something more functional, it was useful, firstly, to fill them with something and, secondly, to determine how they arise. Felix Dujardin began to answer the first question in 1835. His 'sarcode' was the material which fills living cells: 'a glutinous, diaphanous substance, insoluble in water, contracting into spherical masses, sticking to the dissecting needles and letting itself be drawn out like slime, and, finally, being found in all the lower animals interposed between the other structural elements'.[2] Dujardin's work on infusoria, designed to examine the internal structure of that organic group, also raised the question of whether similar substances exist in other organisms. In 1839, the Bohemian researcher Jan Purkinje confirmed this and identified the fluid stuff inside the cell walls as 'protoplasm', a concept which Hugo von Mohl extended and developed into its modern form (Purkinje, *Übersicht über die arbeiten und Veränderung der schlesichen Gesellschaft für vaterländische Kultur im Jahre 1839* (Breslau, 1840); von Mohl, 'Über die Saftbewegung im Innern der Zellen', *Botanische Zeitung* 4 (1846), pp. 73–8 and pp. 89–94.)

Both Dujardin and Purkinje suggested that the internal fluid protoplasm might be the basic material of life, but it remained for the German cytologist Max Schultze to carry that suggestion into a fully developed theory – the protoplasm theory. In a paper of 1861 directed at clarifying the nature of a cell, Schultze acknowledged that a cell had been defined as a structure with 'membrane, nucleus, and contents', but that in fact only the nucleus and protoplasm appeared as universally basic. Thus 'A cell is a lump of protoplasm inside of which lies a nucleus'.[3] The membrane or cell wall separates the cell contents from the external environment but is not, in fact, really necessary since the unique protoplasmic substance is kept distinct from the surrounding material simply by the fact that it does not mix with water. He pointed out, in particular, that cells which are undergoing division have no membranes. For Schultze, the crucial internal contents do not consist of a simple watery fluid but rather of a thick viscous mucous substance, comparable to soft wax. This protoplasmic material is basic to life, while the nucleus plays an as yet unknown role. Though he worked with a variety of animals himself, Schultze also cited work on plants to demonstrate the uniform protoplasmic basis of all living material in protoplasm.

By 1861, the cell had acquired a very different consistency and role ascribed to it from the one Hooke had suggested nearly two centuries earlier. Thomas Henry Huxley's popular essay of 1868 suggesting that protoplasm was the 'physical basis of life' brought the protoplasmic view to wide attention ('On the

Physical Basis of Life', *The Fortnightly Review* 5, (1869), pp. 129–45) and stimulated further discussion. What was the relative importance of nucleus and protoplasm, and in what sense were the cells the *units* of life if protoplasm was the *stuff* of life? The different lines of research, with respective emphases on plants or animals, or on adult or dividing embryonic cells, for example, gave rise to different views of the cells and their importance. Generally, those stressing the central importance of protoplasm de-emphasised the significance of cellular units and of what has historically been called 'the cell theory' which an alternative tradition stressed. It is the latter tradition which provided the strongest basis for progress in interpreting the cellular role in development and which must remain central for historians concerned with both cells and development.

2. CELL THEORY AND CELLULAR DEVELOPMENT

At the same time as the theory of cell substance was evolving, in the mid-nineteenth century, a very different theory of how cells come into existence was also emerging. The German botanist Jakob Mathias Schleiden and the zoologist Theodor Schwann collaborated to present what has come to be labelled as *the* cell theory. Their theory depended very directly on their definition of how cells come into existence as part of their life cycle and it differed from the protoplasm theory in emphasising the essential role of the cell wall for defining this basic unit of life.

Schleiden was one of those young biologists of the early nineteenth century who could not accept the then traditional preformationist interpretation of the origin of organic form.[4] Preformationists of the previous century had answered the age-old question: 'how does an individual come to have his particular differentiated form?' with the answer: 'from pre-existing form'. An individual organism inherits its form from its parent. Logically, therefore, an individual cell would also inherit its form from earlier cells. But Schleiden and others, such as the German embryologist Karl Ernst von Baer, had begun to reject such a preformationist interpretation and to turn instead to epigenesis. (See art. 33.) An epigenetic position holds that form emerges anew, shaped by the interaction of living internal material and its external environment. As an epigenesist, then, Schleiden wanted cells to emerge anew in each generation. He maintained that those newly-arising material cells serve as the fundamental units of both organic structure and organic function for all of organic nature.[5] Cells are the basic units of life. Schleiden and his collaborator Schwann further insisted that all cells in both plants and animals originate according to the same general set of procedures; all cells must therefore be fundamentally the same sorts of things. Unity of nature reigned, as it did for most early-nineteenth-century German naturalists.

Schleiden's theory of free cell formation held that the following process occurs for plants: inside the contents of a cell a granular substance arises; by accumulating surrounding material, this gives rise to a nucleus; as the nucleus grows a cell forms and a surrounding membrane appears to set it off as a new cell. Schleiden maintained that this process occurs as an 'altogether absolute law'. The resulting cell consists almost incidentally of those internal contents labelled by others as protoplasm, but also necessarily includes a nucleus and cell wall.

Stimulated by his discussions in Berlin with Schleiden, Schwann further developed the 'Schleiden-Schwann cell theory' with his animal investigations.[6] He suggested that, beginning with a structureless substance or 'cytoblastema', a dark granule arises, which in turn gives rise to a nucleus. Then layers of substance accumulate around this core to produce a full cell. For Schwann, this process takes place in material surrounding, rather than inside, the old cells, so that in this respect, he differed from Schleiden. For both, nonetheless, the new cells are really new and not simply inherited or pre-existent in any sense. They both maintained that cell formation strictly follows the inorganic and hence materialistic process of crystallisation. Then once formed, the cells serve as structural and functional units for living organisms.

Published together and translated in 1847, the claims of Schleiden and Schwann became the basis for a 'cell theory', which held cells to be the fundamental organic units common to all living beings and as developed by 'free formation' out of formless cytoblastemic substance in the same basic way. Some challenged the exact definition of the cell – whether it requires an enclosing membrane or wall to define it, for example. Others questioned the mode of cell origin – whether always *de novo* rather than from pre-existing cellular material in particular. Work on plants and animals also diverged as researchers questioned the respective natures of plant and animal tissues. Yet most researchers had nonetheless begun to accept some version of cell theory by the mid-nineteenth century. The problem remained of sorting out the details and of elaborating the extent to which cells function as *the* fundamental units of life and living processes. In particular, Jacob Henle and Albert von Kölliker adapted the theory into classic full discussion within anatomy and histology, but cell theory as a basis for development took longer to elaborate. Maintaining a focus on cells, the German zoologist Robert Remak and the pathologist Rudolf Virchow moved towards a different and eventually more widely acceptable interpretation of cell theory, which proved more useful for embryology.

In 1855 Remak published the results of his extended study of freshly laid frogs' eggs and concluded that the cells in his embryos developed in a different manner from the one that Schleiden had described for adult plant cells. In citing the substantiating support of other researchers' results as well as his own earlier work, Remak endorsed an endogenous theory of cell formation, whereby cells form only from material internal to other cells. Indeed, all cellular development begins with the fertilisation of the egg cell, while subsequent cell cleavages result from a series of divisions directed by the nucleus (*Untersuchungen über die Entwicklung der Wirbelthiere* (1850–55)).

Also in an essay of 1855 and with much more detail in his classic work *Die Cellularpathologie* (1858), Virchow agreed with Remak and other cytologists who had begun to question free formation, asserting that all cells arise only from other cells: 'Omnis cellula a cellula'. Cells do not crystallise in any intercellular cytoblastema, and since cells require both a nucleus and membrane, they must begin as more than tiny material nucleus-producing granules. Life is continuous as one cell gives rise to another, one generation to another. The complex and responsive cellular material is not only the basic *structural* unit of living material, it can also be the basic unit of *life*.

Virchow and others had come to the conclusion that cells somehow divide. Rather than new cells crystallising in a strictly materialistic manner around a granular core, Virchow saw the existing cellular material accumulate new material and grow larger, eventually reaching a point at which it divides. According to this vitalistic interpretation, living material does not emerge from non-living material. In fact, the history of the cell theory in the nineteenth century became closely tied with arguments about materialism vs. vitalism. According to Ackerknecht's (1953) interpretation, Virchow's particular interpretation of cell theory reflected his political vision of the role of individuals within the state.

Not everyone who accepted the doctrine that cells arise only from other cells also agreed with Virchow's politics or his form of vitalism. But continuity of cellular, living material made the epigenesist's task easier. If cells provide continuity from one generation to the next, then the epigenesist need not explain the production of form from completely homogeneous matter. Instead, he may assume the existence from the beginning of something which is already living, inherited from the past. As John Farley has pointed out, 'the re-emergence of sex' and sexual reproduction as a driving biological problem in the 1870s, accompanied by improvements in microscopic and cytological techniques and hardware, served to refocus attention on the cells – notably on the egg and sperm or ovule and pollen cells – and their roles in development.

What resulted, as researchers embraced Virchow's view of cell formation and substantiated it with observations resulting from improved microscopic techniques, was a move towards emphasis on cell division. As it stood at mid-century, the cell theory depended on an interpretation of how cells develop, but did not provide significant clarification of how individual organisms develop and become differentiated. If each cell grows by accretion of material, then the question remains of how cells mutate, and in such a way that a whole organism is created. What guides development?

Pursuing epigenetic interpretations of development, researchers began to accept that cell division may be the key to development of individual organisms and hence the key to what differentiates life from non-life, namely, the ability to reproduce successive generations of individuals. By the 1870s, enthusiasm for the materialistic Schleiden/Schwann interpretation of cellular development and for protoplasm ideas had faded. Research had begun to enter a new stage, exploring the importance of cell division for development. This change in problems and approaches, with attendant shifts in meanings of words and in emphases, creates pitfalls for unwary historians who cast backwards for the roots of today's ideas. Unfortunately, biologists who have written casually about the history of cell theory have also fallen into that trap and have made the picture seem rather clearer than it was. It is important to recall that 'cells' do not even refer to the same thing as we move from the seventeenth to the nineteenth century, for example.

Out of the proliferation of studies in the 1870s, two very different lines of research emerged which need to be examined as separate traditions. One, growing out of the cytological tradition, carefully examined the structure of the cell. Using histological techniques for fixing, staining, preserving and cutting cells, the cytologists began to be able to look more deeply and to discern fine differences between cells. The nucleus attracted the first and most concentrated attention, but gradually other cellular parts also attracted interest. And with their discovery, researchers began to ask also what the cellular parts were for.

A second line of research took a wider look. Instead of focusing down into smaller and smaller parts, this group asked how the cells fit within the whole organism. Of particular interest for our purposes, embryologists began to see that distinctions between different cells might begin to explain established facts of heredity and evolution, since an individual organism begins as a single egg cell which is the product of an evolutionary past and of inheritance from its parent. That individual egg cell is also the beginning of a new individual and hence must contain whatever is needed to pattern that individual. This second group of researchers began to examine more closely what happens in the course of cell division: what, in fact, happens as the one original egg cell divides? Different groups focused respectively on the nucleus or on the whole cell.

3. CELL THEORY AND DEVELOPMENT: INTO THE NUCLEUS

The cell nucleus seems first to have attracted the serious attention of British botanist Robert Brown. In 1831 he determined that the nucleus is, in fact, an important part of at least living cells and not just an artifact of microscopic observation ('Observations on the Organs and Mode of Fecundation in Orchideae and Asclepiadaea', *Transactions of the Linnaean Society* 16 (1833), pp. 685–742). Brown was the first to label this body the nucleus and to observe systematically that it occurs in a range of types of organisms. Yet he did not develop his observations into a more general theory, nor did he speculate about the significance of that nucleus. In time, others did, as they also extended his sketchy suggestions concerning fertilisation as a result of kinetic interaction of ovule and pollen in plants.

In fact, work on fertilisation highlighted the first line of research into cell theory and development.[7] Advances in microscopic techniques such as improved sectioning, fixing, and staining as well as the advent of the oil immersion lens, allowed a closer look at cell contents. Observers could now distinguish more than just a general nucleus, protoplasm and membrane. Thus, the 1870s and 1880s brought a flurry of new studies, of which those by the Belgian Edouard van Beneden, the Germans Walther Flemming and Oscar Hertwig, the Polish/German Eduard Strasburger and the Frenchman Hermann Fol were particularly important. Their technical disagreements, aggravated by imperfect microscopic evidence, make it more difficult – and also particularly valuable – for historians to clarify the threads of thought during this time.

Each of these men declared that the egg and sperm cell – for by then fertilisation was generally agreed to involve the union of those two cells – contain a distinct nucleus. Therefore, the nucleus does not come into being simply for the purposes of cell division and then disappear, as some believed, but maintains its individuality across generations. And yet, Fol, at least, denied that the structure of the nucleus has any purity or continuity and that the nucleus could play any significant role in heredity. However, as he continued work through the 1880s, Fol began to see the centrosomes as permanent structures, with each parent cell contributing two centrosomes or one which divided soon after fertilisation. Centrosomes might play a role in heredity. Hertwig disagreed, maintaining that the nucleus itself and its components have continuity but that centrosomes do not. Furthermore, for both Hertwig and Strasburger, the nucleus served as the bearer of heredity while for Fol it did not. When Hertwig, Strasburger and others actually saw the nucleus divide during cell division, that evidence considerably strengthened their case for a nuclear role in heredity and subsequent development.[8]

If the cell, and particularly the nuclear part of the cell, really exists as an identifiable and continuous entity, and if fertilisation actually involves the joining of a nucleus from each of two parents, then the nuclei must play a basic role in heredity. But how? And how does the stability between generations, assumed to be brought by heredity then translate itself into the differentiation of individual development? For this group of researchers, inquiry began to focus on details of the process of nuclear division.

The occurrence of mitotic nuclear division (or mitosis) had been recognised as early as 1873. Many researchers immediately attacked the subject and determined that nuclear division is basic to cell division. Strasburger insisted that nuclear division occurs transversely, that is, across the chromosome, dividing it into two separate pieces of different materials. In contrast, van Beneden and Flemming insisted on longitudinal division. Van Beneden observed the movement of chromosomes as they moved during cell division. Then Flemming provided a striking set of studies demonstrating the stages of mitotic division, which he presented in three papers published from 1879 to 1881. He believed that this indirect division of what he called chromatin (the stainable nuclear material, which Wilhelm Waldeyer labelled as chromosomes in 1888) provided the basis for the process of cell division in all forms of cells. By the 1880s a group of researchers had decided that the nucleus plays a role, if not *the* critical role, in cell division generally and thus in the development of individuals. Flemming's *Zellsubstanz, Kern und Zelltheilung* (1882) provides an excellent review of work prior to that time.

Furthermore, by the late 1880s it began to seem as though the nucleus also plays a – or the – critical role in moving from one generation to the next. Van Beneden and Theodor Boveri from 1887–8 and Hertwig in 1890 had each clearly observed that something unique happens during the production of germ cells.[9] During this process of maturation division when one cell gives rise to the ripe germ cells, each chromosone divides once while each cell divides twice. Thus, each ripe germ has only half the original full complement of chromosomes. The chromosomes must play some important role in heredity to result in this complex process, but what? Earlier, equally careful cytologists such as Strasburger had insisted on transverse division of chromosomes and did not see an important difference between germ cell and adult cell production (or mitosis and what was later called meiosis). Only gradually during the 1880s and 1890s did researchers work out details of the structural and chemical constitution of the chromosomes and of the nucleus. And only after 1900 did theories begin to emerge, explaining the chromosomal role in heredity. (See art. 33, sect. 6.) The work of the British researchers John Bretland Farmer and John E. S. Moore first explicitly stated what happens in reduction division and the workings of the 'maiotic phase'. Their classic paper 'On the Maiotic Phase (Reduction Division) in Animals and Plants' (*Quarterly Journal of Microscopical Science* 48 (1904), pp. 487–569) also provides a useful survey of material to date.

Yet such detailed researches into the nucleus and nuclear division focused more and more narrowly on the fine structure and parts of the cell. This concentration drew attention away from development, partly because no one saw how nuclear change translated into epigenetic developmental change. By the 1890s, it was the second line of research, looking at whole cells, that still concentrated on cell theory and on development.

4. CELLS AND DEVELOPMENT: THE CELL'S ROLE IN DEVELOPMENT

Cell theory, as American cytologist Edmund Beecher Wilson wrote in his classic *The Cell in Development and Inheritance* (New York, 1896), was the second great generalisation of biology in addition to evolution theory. He realised that only recently had the two ideas begun to converge in a way that promised major progress for biology. In addition to those researchers concentrating on applying new microscopic techniques to observe more clearly the fine structure of intracellular material, others such as Wilson focused on the cell as a whole or on the organism as a whole. A tradition emerged, directed at showing how the different cells resulting from division of the egg give rise to different parts of the body. The researchers participating in this tradition were concerned with embryology (and evolution) rather than with the earlier stage of fertilisation or with nuclear change. They included especially a group of Germans and a group of Americans.

In the 1870s, embryologists had concentrated on the collections of cells making up germ layers rather than on particular cells. For one thing, it was simply too hard to see individual cells and what they did during development. Furthermore, evolutionary theory and Ernst Haeckel's particular interpretations of what happens suggested that the broader-reaching germ layers rather than individual localised cells held significance for understanding evolution and genealogical relationships. How could the peculiarities of one individual cell be the product of evolution, selectionists would have wondered?

Stimulated by improved research techniques, embryologists began to ask what happens to individual cells. Given that the egg and sperm and their union are all cells, perhaps careful detailing of what happens to cells in development could be worthwhile. A group of German physiologists and zoologists began to study *Entwickelungsmechanik* or *Entwickelungsphysiologie*. Alongside the work of researchers including Wilhelm His, Eduard Pflüger, Gustav Born and Hans Driesch, Wilhelm Roux devised an elaborate theory of the action of blastomeres, cleavage and then of cells and cellular parts and their roles in development.

Roux and other developmental researchers studied the factors which cause the egg cell to divide and how this division occurs. They investigated the effects on development of conditions such as experimentally-altered gravitational field, artificial light source, altered nutrients and chemical manipulations. With manipulative experimental studies, the researchers could begin to establish that not only does the individual organism respond to external conditions but it also exhibits a great deal of internal control over its development and differentiation. Eventually, Roux constructed a theory of mosaic development, according to which each cell division separates off cellular material which then, because of its constituent material, develops in a unique and appropriate way.

In particular, Roux performed a famous experiment in which he used a hot needle to kill one of the two cells resulting from the first cell division of a frog's egg, as discussed in his summary work *Die Entwickelungsmechanik der Organismen* (1890). He left the dead material but it did not grow, so he considered that the cell had been functionally eliminated. The other cell developed into precisely the half embryo that it would have done under perfectly normal conditions. Therefore, Roux concluded, it must have been something inside the cell itself, part of its own material which directed it, in this case, to develop as a half embryo. He presumed that the same constituent would also direct a normal cell product to develop in its appropriate manner. Thus, cells are parts of organisms but develop largely independently, according to their own internal instructions. Those instructions, he decided, came from the nucleus and specifically from the chromosomes.

For Roux, the chromosome is a complex mixture of different chromatin granules, which represent different qualities. These align themselves in preparation for cell division and then divide. Division may occur quantitatively, so that the original granules reproduce and then separate, with all qualities represented in each of the two daughter cells. Division may also occur qualitatively, so that the two daughter cells end up with sub-sets of the original materials and are thereby differentiated. The latter process occurs during embryonic development. By this process, each nucleus receives its own unique set of chromatin, and the course of development involves a successive separating-out of original pieces into the various cells. Because it contains its own chromatin qualities, each cell is capable of self-differentiation and experiences some autonomy even while it is part of the whole, complex organism.

In *Das Keimplasm* (1892), August Weismann developed a similar theory, carrying much further the idea that separate bits of chromatin represent different qualities. He constructed an elaborate hierarchy of cellular parts with biophores as the basic units. These are then aggregated progressively into determinants, ids, and idants, the latter of which finally represent the visible chromosomes. The complex chromosome structure is inherited from one generation to the next because the cells of the germ plasm retain the full complement of sub-units, while body cells receive only part and become differentiated accordingly. Mitosis serves to distribute the smallest differentiated bits of chromatin to the different cells and thus becomes the mechanism for effecting individual development as well as intergenerational heredity. Eventually, each cell will have only one kind of determinant in it, which will give it its specific character.

For both Roux and Weismann, whose ideas came to be labelled the Roux-Weismann theory in the mid-1890s, the cell remained basic. Chromatin carries the material of heredity, but it is the division into separate cells that brings development. Cell theory was once again a basic assumption for these biologists, but with a very different emphasis. Roux and Weismann had explained a mechanism by which individual cells become differentiated and hence by which complex organisms grow, but many others did not find this explanation satisfactory. The resulting discussions provide valuable material for historians examining cells and development.

Hertwig and others in Germany rejected the Roux-Weismann interpretation of development, saying that it really explained nothing. For Hertwig, Weismannism represented a hopeless sort of preformationism which throws everything back on to the nucleus and chromatin rather than on to preformed little beings, but which is preformationism nonetheless (*The Biological Problem of Today* (1894)). Questions of cells and development therefore became tangled with traditional debates about whether epigenesis or preformation better explains development. A further question arose as to whether perhaps cell theory itself had been overtaken. Perhaps the cell is not the smallest basic unit of life after all. Roux and Weismann expanded discussion about the role of cells in development and about their status as the smallest basic functional, structural and even developmental units of life, but others disagreed.

Reactions became particularly lively among American biologists around the turn of this century, especially among researchers who gathered at the Marine Biological Laboratory (MBL) in Woods Hole, Massachusetts, each summer. The first MBL director, Charles Otis Whitman, directly questioned the dominance of the 'cell standpoint' in his paper 'The Inadequacy of the Cell Theory of Development', (*Biological Lectures* 1893 (1894), pp. 105–24). In particular, he regarded the cell theory of development as inadequate. The whole individual organism directs development, he insisted, for the individual has an organisation that the study of cells alone cannot explain. Whitman endorsed Huxley's view that cells are like seashells. They are left behind by the tide and map the tide's effects, but the seashells themselves do not represent or record the tidal process of change, which is ultimately the interesting phenomenon. Organisation of an individual, then, does not result simply from cell division but instead precedes and directs cell division. Whitman rejected the full implications of the Roux-Weismann theory of independent development of individual cells.

And yet he certainly did not claim that cells have no importance. In fact, Whitman inaugurated a series of cell lineage studies during the 1890s by his students and colleagues at the MBL and at the University of Chicago. These studies were designed precisely to illustrate the patterns of cellular development and the way in which the original egg takes on differentiation. Cell lineage studies consisted of using exacting histological and microscopic techniques to trace what happens to the cell and its nuclear and cytoplasmic parts as the cell

divides. What happens inside, and what is the result as the cell products each begin to assume their own individualities as well? Researchers including Whitman, Wilson, Edwin Grant Conklin and a host of others carried out these detailed studies on a variety of organisms in order to assess similarities and differences which might reveal ancestral evolutionary relationships.[10] They also sought to evaluate the extent to which the original egg cell is already differentiated by determining how regular or 'determinate' the cleavage process and products are from one individual to another. If every organism of the same type divides in the same way, and if each cell product gives rise to the same differentiated adult parts as that same cell product in other organisms, then individual development must somehow be strongly determined by the structure or content of the egg cell. If, however, there is considerable variation and flexibility, then the egg is not strictly determined, and environmental factors must direct development. Cell lineage study, in fact, focuses on cells and cell fates and reveals a complex interaction of external and internal directive factors operating on development.

Whitman insisted that it was the whole functioning organism which ultimately directs differentiation. Cell boundaries simply do not follow predetermined and invisible lines in the egg. Nor does cell division respond blindly to internal nuclear directions. Instead, cells respond, following the laws of a sort of organic physics and chemistry, to the needs of the whole, which in turn result from the long-term action of evolutionary selection. Conklin agreed, priding himself on his being 'a friend of the egg' as a whole. While some emphasised the role of either nucleus or cytoplasm in development, Conklin and others joined Whitman in stressing the significant role of both and of the integrated organism. For example, Charles Manning Child stressed that 'It is the organism – the individual, which is the unit and not the cell'.[11]

Yet other American researchers, including E. B. Wilson who also worked closely with Whitman at the MBL, did regard the cell as basic. One could study the cell and its role in directing development and inheritance to productive effect because each cell does have significant individuality, even if co-ordinated with other cells within a more complex organism. As Wilson interpreted the revised cell theory of 1896, it held that higher life forms, whether animal or plant, consist of structural units known as cells. Out of these cells arise tissues and the other body parts. Cells are not hollow, as Hooke's choice of words would suggest, but are filled with protoplasm. The cell and its protoplasm serve as the 'physical basis of life'. Cells are all the basic, elementary units of both organic structure and function, even though they appear very diverse. In higher organisms, according to Wilson, as cells become more specialised, they enter a 'physiological division of labor'. Study of the cells and their actions must provide a basis for all study of life, Wilson felt, for:

> Each bodily function, and even the life of the organism as a whole, may thus in one sense be regarded as a resultant arising through the integration of a vast number of cell-activities; and it cannot be adequately investigated without the study of the individual cell-activities that lie at its root.[12]

The result of the co-existence of these alternative interpretations and emphases on the cell's importance even at the same summer laboratory resulted in heated discussion. This discussion, as it found expression in published lectures and papers, stimulated further attention to the cell.

By 1900, the cell was generally accepted as a legitimate subject of study in its own right. And yet at least for this group of researchers, understanding of cell theory had changed. The cell could still be the most common, fundamental unit of life, but researchers did not have to take the cell as the proper unit for *all* analysis. Cells are not completely independent and do not either develop or live alone – at least most cells from multicellular organisms do not. Cell theory and its role in interpreting development had gained considerable complexity by 1900, but this complexity complemented and refined rather than undercut the value of older cell theory. It is the historian's task to sort out the different traditions, and to assess the influence of new techniques and questions in modifying early observations, in order to explain the move from early observations of cellular structures to the cell theory and on into the developmental examinations of the late nineteenth century. So far, only parts of the story have been told, and too often from a retrospective perspective, unquestioningly seeking past equivalents of modern cells and missing such important questions as how cell theory influenced theories of development.

5. CELL THEORY IN THE TWENTIETH CENTURY

In this century, researchers have recognised that the most serious weakness of the cell theory is its inability in itself to explain cell-to-cell interaction or that organisation of many cells which became Whitman's stumbling-block. By mid-century, Hans Spemann and others did, however, begin to attack such interactions in various ways. Considerable recent work, especially since the Second World War, has been directed at dealing with this weakness. Studies of exchanges at cell junctions and across cell membranes have begun to show the ways in which cells join together into functional multi-cellular units. Advances in biochemistry and molecular biology, as well as the advent of observation techniques and equipment such as electron microscopes which allow ever more detailed resolution, have led the way in this work.[13]

Since the Swiss physiological chemist Johann Friedrich Miescher theorised in 1869 that nuclei of cells may all consist of a characteristic substance (which he went on to identify as 'nuclein', later called nucleoprotein), biochemists have provided increasingly detailed information about the cell. While the researchers discussed above concentrated on the structural elements: on the nucleus or the cytoplasm or the whole cell and its relation to other cells, a few other researchers analysed what substance is *in* the cell. In the twentieth century, it has gradually become clear that cells of different types exhibit remarkable consistency in their cell substances. (See art. 32, sect. 5.) DNA material is remarkably uniform throughout all living cells, and so is much of the rest of the cellular material. This discovery has reinforced the view of the cell as the basis of all life. It has also returned biologists to the sorts of questions about evolution and the relationships among cells that earlier cell lineage researchers were asking.

If all cells contain much the same substance, as well as exhibiting similar structural elements, then perhaps the cell is the ancestral unit of life. Perhaps a simple cell actually came first, rather than a complex multicellular and even multilayered ancestral organism such as Ernst Haeckel and most other nineteenth-century naturalists had envisioned. Such a hypothesis certainly satisfies the often-repeated call for simplicity in science.

Unicellular organisms presumably preceded multicellular organisms, perhaps (as it seems recently) with the boundary having been crossed several times. Studying cells and their similarities and subtle differences among different types of cells or between eukaryotes and prokaryotes, can provide a key to evolutionary or phylogenetic development, as Margulis's recent investigation into *The Origin of Eukaryotic Cells* has shown (1970). The twentieth century has thus added a new layer of significance to the original cell theory. Evolutionary study has not replaced embryology or the study of cell division or the biochemistry of cells certainly, but has complemented it. The cell theory – as the statement that all life consists of basic cellular units, which arise only from other cells – has gained new dimensions and new confirmation.

NOTES

1. Selections of this and a number of the other works mentioned in this article are translated in Thomas S. Hall (ed.), *A source book in animal biology* (Cambridge, 1951).
2. Felix Dujardin, 'Sur les prétendus estomacs des animalcules infusoires et sur une substance appelée Sarcode', *Annales des sciences naturelles; zoologie*, 4 (1835), 343–77; quotation from Hall, p. 438.
3. Max Schultze, 'Über Muskelkörperchen und das, was man eine Zelle zu nennen habe', *Müller's Archiv für Anatomie, Physiologie und wissenschaftliche Medicin* (1861), 1–27; Hall excerpts, pp. 449–55, quotation Hall, p. 451.
4. Ernst Mayr, *The growth of biological thought* (Cambridge, Mass., 1982), p. 655. On Schleiden, see Marcel Florkin, *Naissance et déviation de la théorie cellulaire dans l'œuvre de Theodore Schwann* (Paris, 1960).
5. Matthias Jakob Schleiden, 'Beiträge zur Phytogenesis', *Müller's Archiv* (1838), 137–76; translated as 'Contributions to Phytogenesis', with Theodor Schwann's *Microscopical researches into the accordance in the structure and growth of animals and plants* by Henry Smith (London, 1847), pp. 231–68; Schleiden, *Grundzüge der wissenschaftliche Botanik* (Leipzig, 1842, 1843), translated

by Edwin Lankester as *Principles of scientific botany* (London, 1849), and reissued with introduction by Jacob Lorch (New York, 1969), pp. ix–xxxiv.

6. Theodore Schwann, *Mikroscopische Untersuchungen über die Übereinstimmung in der Struktur und dem Wachstum der Tiere und Pflanzen* (Berlin, 1839), translated by Henry Smith. As Frederick Churchill has pointed out, 'Rudolf Virchow and the pathologist's criteria for the inheritance of acquired characteristics', *Journal of the history of medicine and allied sciences*, 31 (1976), 117–48, p. 124, Schwann's ideas about cells first appeared in a series of letters.
7. For an early summary discussion of such work see John Gray McKendrick, 'On the modern cell theory and the phenomena of fecundation', *Proceedings of the Royal Philosophical Society of Glasgow*, 19 (1887–8), 71–125.
8. Hermann Fol, 'Le Quadrille des Centres. Un épisode nouveau dans l'histoire de la fécondation', *Archives des sciences physiques et naturelles*, 25 (1891), 393–420; Oscar Hertwig, *Ältere und neuere Entwicklungs-theorieen* (Berlin, 1892); Eduard Strasburger, *Zellbildung und Zellteilung* (Jena: 1875, 3rd edition, 1880); Strasburger, 'Die Controversen der indirekten Zelltheilung', *Archiv für mikroscopische Anatomie*, 23 (1884), 246–304. The details of chromosomal and related division were explored by many researchers in the late nineteenth century, as discussed by Gloria Robinson, *A Prelude to genetics: theories of a material substance of heredity* (Lawrence, Kansas, 1979).
9. Eduard van Beneden, 'Recherches sur la maturation de l'œuf et la fécondation', *Archives de biologie*, 4 (1883), 265–640; Hall excerpts, pp. 456–58; van Beneden, 'Nouvelles recherches sur la fécondation et la division mitosique chez l'Ascaride mégélocéphale', *Bulletin de l'Academie Royale des Sciences, des Letters et des Beaux-Arts de Belgique*, 14 (1887), 215–95; Theodor Boveri, *Zellenstudien* (Jena, vol. 1 1887, vol. 2 1888, vol. 3 1890, vol. 4 1900); Oscar Hertwig, 'Experimentelle Studien am tierischen Ei vor, während und nach der Befruchtung', *Jenaische Zeitschrift*, 24 (1890), 268–313. Other related studies proliferated as well, including especially important contributions to the study of cell division and heredity by Richard Hertwig and Theodor Boveri and work on reduction division by August Weismann.
10. Reports of the cell lineage work appeared in a numbr of articles in the *Journal of morphology* which Whitman edited and in the MBL's *Biological lectures* through the 1890s. Jane Maienschein, 'Cell lineage, ancestral reminiscence, and the biogenetic law', *Journal of the history of biology*, 11 (1978), 129–58 discusses the work.
11. Charles Manning Child, 'The significance of the spiral type of cleavage and its relation to the process of differentiation', MBL's *Biological lectures* 1899 (1900), 231–66, quotation p. 265.
12. Wilson, *The cell*, pp. 4–6, quotation p. 6.
13. For introductions to some of this work: C. H. Waddington, *Biological organisation. Cellular and sub-cellular* (New York, 1959) presents results of a working discussion-oriented symposium of 1957. Jean Brachet and Alfred E. Mirsky's *The cell* (New York, 1959) presents six impressive volumes of papers summarising the conclusions about methods and problems (vol. I), cell components (vol. II), meiosis and mitosis (vol. III), specialised cells (vol. IV and V), and a supplement (vol. VI). Since then there has been an explosion of books, journals, textbooks and even popular books devoted to study of the cell and cell theory.

FURTHER READING

Erwin Ackerknecht, *Rudolf Virchow. Doctor, statesman, anthropologist* (Madison, 1953).

John R. Baker, 'The cell-theory: A restatement, history, and critique', *Quarterly review of microscopical science*, 89 (1948), 103–25; 90 (1949), 87–108; 93 (1952), 157–90; 94 (1953), 407–40; 96 (1955), 449–81.

Jean Brachet and Alfred E. Mirsky (eds.), *The cell* (New York, 1959), 6 vols.

William Coleman, *Biology in the nineteenth century* (Cambridge, 1977), chaps. 2 and 3.

—— 'Cell, nucleus, and inheritance: an historical study', *Proceedings of the American philosophical society*, 109 (1965), 124–58.

John Farley, *Gametes and spores* (Baltimore, 1982), especially Chap. 6.

Gerald L. Geison, 'The protoplasmic theory of life and the vitalist-mechanist debate', *Isis*, 60 (1969), 273–92.

Thomas S. Hall, *Ideas of life and matter* (Chicago, 1969), vol. II, pp. 121–304 on 'Tissue, cell and molecule, 1800–1860'.

Arthur Hughes, *A history of cytology* (London, 1959).

Julius Sachs, *History of botany* (Oxford, 1890).

Edmund Beecher Wilson, *The cell in development and inheritance* (New York, 1896, 2nd ed. 1900).