

The great ideas of biology

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The Harveian Oration is given annually at the Royal College of Physicians of London under an indenture of William Harvey in 1656. This article is based on the 2003 Oration given on 16 October 2003 by **Sir Paul Nurse** FRS Hon FRCP, Nobel Laureate; Head of the Cell Cycle Laboratory, Cancer Research UK

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ABSTRACT – Four of the great ideas of biology are discussed: the cell as the basic structural and functional unit of life, the gene as the mechanism of heredity, evolution by natural selection, and life as chemistry. A fifth idea is explored whereby biological organisation is explained in terms of logical and informational processes and structures.

KEY WORDS: biochemistry, cell, evolution, fermentation, gene, history, hybridisation, information, organisation

William Harvey was not only an eminent physician, but also a distinguished biologist. He was one of the first experimental scientists, working some years before Galileo who is the scientist usually credited with this distinction. So with Harvey's example as encouragement, I have decided to use this Oration to discuss the history and significance of four of the great ideas of biology, finishing with discussion of a fifth idea which has yet to be properly developed. Generally biology is rather bereft of great ideas and grand theories. Biologists prefer to deal in particulars and details; they like catalogues and descriptions, such as lists of species in particular habitats, the number of hairs on a beetle leg, or determining the sequences of genes. But there are some great ideas, and the four I have chosen are core to biology and are also of relevance to medicine, so I hope they will be of interest to members of the College.

The cell

Scientists are always interested in identifying fundamental units of structure, the archetypal example being the discovery of the atom as the basic unit of

matter. Biology's atom is the cell, which is not only the basic structural unit of all living organisms but is also the basic functional unit of life. The cell theory can be summarised as follows: all life is composed of cells, and the cell is the simplest unit exhibiting the characteristics of life. Given the importance of this idea for understanding biology, it is perhaps surprising that it has not caught the public imagination more than it has. This might be because the idea was a long time in development, taking nearly 200 years to become properly formulated, and also because the theory ultimately required the efforts of many scientists rather than a few dominating personalities, so may lack human interest. The history of this idea is excellently reviewed in Harris.¹

The story of the cell begins in 1665 with Robert Hooke (1635–1703), experimentalist to the newly formed Royal Society. As is often the case in science, it was technology that begat discovery, and for the discovery of cells it was the invention of the microscope based on improvements in lenses during the seventeenth century. Hooke turned his microscope on a thin slice of cork and observed walled cavities, illustrations of which can be found in his book, *Micrographia* (Fig 1). These he termed cells after the Latin *cella*, meaning small room or cubicle. Within a few years, Nehemiah Grew (1641–1711) and Marcello Malpighi (1628–1694) had comprehensively described and beautifully illustrated plant cells, and their observations had led to the view that plants are composed of aggregates of cells (Fig 2). Towards the end of that century Malpighi, Anton van Leeuwenhoek and Jan Swammerdam had also described cells in animals, observing corpuscles in blood. But the difficulties in fixing and microscopically observing solid animal tissues meant that it was over a century before it was fully recognised that animals were also aggregates of cells. Animal cells also presented a more fibrous appearance and lacked the well-defined geometry of plant cells which meant that interpretation of the microscopic images was more difficult. Leeuwenhoek (1632–1723) was also the first to describe single-celled organisms or 'animalcules' which he found growing in the extracts of plants. Leeuwenhoek is an appealing character, not a gentleman scientist like most Fellows of the Royal Society at that time, but a Delft spectacle-maker with insatiable curiosity. As he was the friend and trustee of the painter Johannes Vermeer, I like to imagine that the

Key Points

The cell is the basic structural and functional unit of life

The gene is the basis of heredity

Evolution by natural selection is a characteristic of life

Life is based on chemistry

Biological organisation is based on logical and informational processes and structures

Vermeer portraits of apparently the same man in *The geographer* and *The astronomer*, both to be found in the Louvre, might be based upon the spectacle-maker scientist.

During the eighteenth century and into the beginning of the nineteenth century, fixation and microscopic techniques improved, allowing the identification of more cells in animal tissues. There was also an increasing interest in fundamental units of structure, particularly of matter. The idea that matter consisted of indivisible units or atoms had its origins in Ancient Greece, but experimental support for the idea emerged from research workers in chemistry only towards the end of the eighteenth century. Given this increasing interest in fundamental units of matter, it was natural for biologists to begin thinking about the fundamental units of life. An important speculation was made by Lorenz Oken in 1805 who argued that plants and animals are assemblages of the animalcules or 'infusoria' such as protozoa that grew in animal and plant extracts,² and this speculation set the stage for the cell theory to be formulated.

After this long gestation the cell theory was born during the first half of the nineteenth century. It was popularised by two Germans, the botanist Matthias Schleiden and the zoologist Theodore Schwann, who in 1839 wrote 'we have seen that all organisms are composed of essentially like parts, namely of cells'. Over the next two decades this idea was further developed, with cells being recognised not only as the basic structural unit but also as the basic functional unit of all living organisms.³ The

pioneer pathologist, Rudolf Virchow (1821–1902), wrote in his 1858 book, *Cellularpathologie*, 'that every animal appears as a sum of vital units, each of which bears in itself the complete characteristics of life'. This discovery was a major landmark in the history of biology.

Schleiden and Schwann did not understand how cells were formed. They thought cells arose by a process related to precipitation of crystallisation which occurred in part of a pre-existing cell. In fact, already in the previous century Abraham Trembley had described the protozoan *Synhedra* reproducing, and his illustrations clearly demonstrate the binary fission of cells. Others, like Barthelemy Dumortier working with plants cells and Robert Remak with animal cells, clearly recognised that cells arose by binary fission of pre-existing cells. This view was further championed by Virchow who popularised the phrase '*Omnis cellula e cellula*', that is, all cells come from cells.

Once cell division was understood, it could be seen to be the basis of the growth and development of all living organisms. Rudolf Kolliker in the 1860s observed that cleavage of early embryos was the consequence of cell division.⁴ It became clear that embryogenesis was based on repeated rounds of cell division followed by the differentiation of cells into more specialised tissues and organs (Fig 3). By the 1880s it was accepted that all living organisms, regardless of their complexity, emerged from a single cell (Fig 4). We should all respect cells a little more when we recognise that everyone of us was once a single cell!

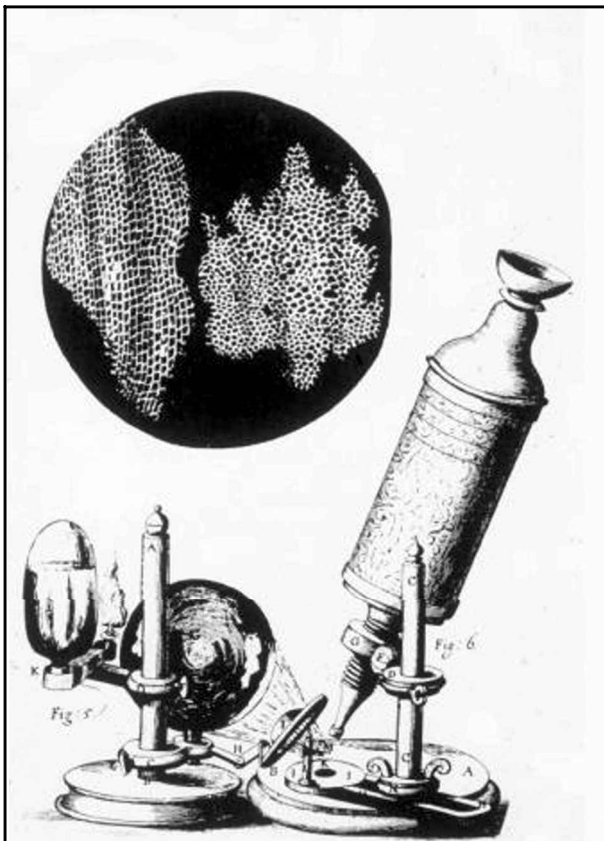


Fig 1. Robert Hooke's microscope and an illustration of cork cells from his book, *Micrographia*. Reproduced from Ref 1.

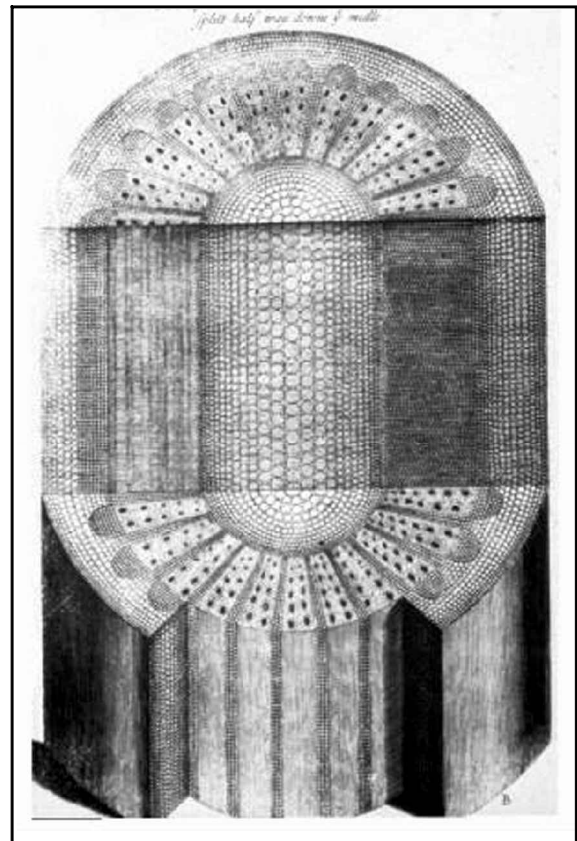


Fig 2. Nehemiah Grew's section of a vine stem illustrating plant cells. Reproduced from Ref 1.

The gene

A universal characteristic of all living organisms is their ability to reproduce, generating offspring which resemble their parents. The similarities between parents and offspring were recognised in classical times and this led to speculations from the time of the Greeks onwards about issues like how much was contributed from each sexual partner during reproduction, did the different sexual partners determine different parts of the offspring, and how much did characteristics like the heat of the womb or the quality of the testes influence the outcome. It took the discovery and characterisation of genes to provide the foundation for understanding heredity, and this is the second great idea of biology that I want to discuss.

As is well known, it was Gregor Mendel (1822–1884), Abbot of Brno Monastery now in the Czech Republic, who first postulated the existence of genes. It was his careful crosses with plants and incisive analysis of the outcomes carried out in the Monastery garden during the 1860s that led him to become the father of genetics. It is perhaps less well known that other researchers had also experimented with plant hybridisation before him, and had made important discoveries relevant to Mendel's subsequent theories.⁵ In particular, the German Joseph Kolreuter (1733–1806), working in the mid-eighteenth century, carried out crosses with tobacco, pinks, and carnation varieties, and concluded that the first hybrids (F1) from differing parents often exhibited rather uniform phenotypes which were intermediate in character between the parents. In contrast, the second generation (F2) were much more varied and more like one or

other of the originating parents. Another important precursor of Mendel was Carl Friedrich von Gaertner (1786–1833) who worked with both peas and maize during the first part of the nineteenth century. He reported the dominance of certain characters in the F1 hybrids and their subsequent reappearance or segregation in the F2 hybrids. Both of these observations were important for Mendel's subsequent work.

These observations set the stage for Mendel's famous pea hybridisation experiments which he started in Brno in 1856. Probably because of his training as a physical scientist and his meteorological studies, he employed a quantitative approach, counting the different phenotypes produced in the F1 and F2 hybrids. This revealed the famous simple ratios which led Mendel to propose an elegant particulate theory for heredity, with phenotypic attributes determined by the action of pairs of factors passed on as unchanging discrete entities or particles, one from each parent to the hybrid offspring. His experiments were very careful and the results impressive; in fact, too much so for the statistical geneticist Ronald Fisher who thought they were too good to be true. Of course Mendel's gardener was blamed, to leave the great man's reputation intact! Mendel's analysis and subsequent abstract reasoning were brilliant and awesome. However, his work remained unrecognised for over 30 years, until the beginning of the twentieth century when it was rediscovered by three geneticists, the most important of whom was the Dutch plant hybridist Hugo de Vries, whose own work also revealed Mendel's simple ratios.⁶

This delay between discovery and recognition is interesting, and I think reflects the general resistance of biologists to abstract thinking because of their greater reliance upon more empirical approaches. During the intervening period there were extensive cytological studies of dividing cells, the simplest example of reproduction in biology. From their microscopic observations of cell division, Walter Flemming and Eduard Strasburger



Fig 3. Early mammalian embryo showing cells. Reproduced from Ref 15.

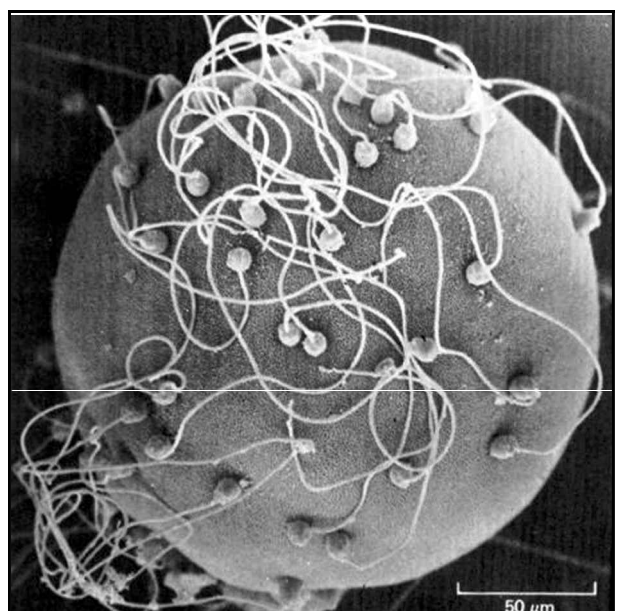


Fig 4. A mammalian egg with sperm. Reproduced from Ref 15.

described the appearance of elongated chromosomal threads which were seen to split lengthways before shortening and thickening as mitosis proceeds. Strikingly, Edouard van Beneden (1846–1910) showed in a fertilised nematode egg that these chromosomes are derived in equal numbers from the egg and sperm. Finally, August Weismann (1834–1914) focused attention on chromosomes by proposing that they formed the basis of heredity. So when Mendel's abstract laws were rediscovered they could be immediately linked with these concrete observations of chromosome behaviour. Chromosomes were discrete entities which split in two during cell reproduction and during the formation of a hybrid, pairs of chromosomes were inherited one from each parent. Mendel's laws could be seen to be no longer abstract but based on the observed behaviour of chromosomes.

Arguably the development of the idea of the gene was the most outstanding contribution to biology during the last century. It is a story that has been well told, particularly by Judson⁷ and so I shall discuss it only briefly here. The first part of the century saw the gradual accumulation of data from classic genetic crosses that confirmed the idea of the gene. Then in 1944 the genetic material was shown to be deoxyribonucleic acid (DNA) when it was demonstrated that DNA could transfer phenotypic characteristics into *Pneumococcus* bacteria.⁸ This was the birth of molecular genetics, although it was the unravelling of the crystal structure of DNA which truly ushered in the new era.⁹

The intellectual beauty of the DNA double helix structure is its ability to explain both the ability of DNA to encode information and to be able to replicate itself. These explanations emerge from the facts that DNA is a linear sequence composed of different nucleotide bases, and that pairing rules for base pairs generate complementary sequences for the two paired strands making up the double helix. Seldom is such insight so immediately obtained from experimental observations as was the case for the structure of DNA. Almost as impressive were the series of subsequent experiments and reasonings which laid the foundations of molecular biology and genetics.⁷ These include the demonstration of semi-conservative replication of DNA, the breaking of the genetic code, and the description of how information flowed from the DNA sequence to protein sequence. This last discovery finally confirmed that the properties of proteins play a major role in determining phenotypic characteristics, and that the properties of the proteins are ultimately determined by the DNA sequence of the relevant gene.

Evolution by natural selection

Evolution by natural selection is the idea proposed by Charles Darwin which he explained in his 1859 book, *The origin of species*.¹⁰ It is the best known idea of biology and has led to the whole publishing industry of Darwinia. The suggestion that life evolved over time was not original to Darwin. As he himself notes in *The origin of species*, Aristotle had argued that body parts of animals might appear or disappear over time. Charles' own rather colourful grandfather, Erasmus Darwin (1731–1802), was an enthusiastic supporter of evolution, and even had a motto

inscribed on his coach which said '*E conchis omnia*', that is 'everything is from shells', advertising his belief that all life developed from microscopic ancestors. Erasmus was a member of the Lunar Society and a successful doctor in Lichfield and Derby around 1800.¹¹ He had to remove the motto from his coach after pressure from the Dean of Lichfield Cathedral, otherwise he would have been in danger of losing his more respectable, and therefore more wealthy, patients. He was an early proponent of female education and set up two of his daughters as teachers to run one of the first schools for girls. During his lifetime he was also considered a distinguished poet, expounding his views on evolution in verses from a poem, *The temple of nature*:

*First forms minute, unseen by spheric glass
Move on the mud, or pierce the watery mass;
These, as successive generations bloom,
New Powers acquire and larger limbs assume;
Whence countless groups of vegetation spring
And breathing realms of fin, and feet, and wing.*

His grandson Charles was more scientific and systematic in his approach to evolution. He amassed huge amounts of observational data from the fossil record which strongly supported the view that living organisms evolve. But he did much more than that by proposing natural selection as a mechanism for evolution,¹⁰ a mechanism also proposed independently by the naturalist collector Alfred Wallace. This idea is based on the fact that in a population of breeding living organisms there are usually a range of phenotypic variants to be found. These variants are frequently genetically determined, and so will be inherited from generation to generation. Some of these variants will be more successful in producing offspring, and this greater success means that the offspring from these variants will make up a greater proportion of the population in the next generation. This process is known as natural selection because selection occurs as a consequence of natural factors. Natural selection leads to survival of the fittest and in the elimination of individuals less well adapted to their environment. As a consequence, genetic changes accumulate in the population which bring about evolutionary change. This is a very profound idea which has significance beyond biology, in disciplines like economics and computing.

For evolution by natural selection to take place, living organisms must have a number of characteristics. Firstly, they must be able to reproduce. Secondly, they must have a hereditary system whereby information defining the characteristics of the living organism is copied and inherited during their reproduction. Thirdly, the hereditary system must exhibit variability, and this variability must be inherited during the reproductive process. It is this variability upon which natural selection operates. Interestingly, these characteristics are linked closely with the two ideas already discussed, the cell and the gene. All cells reproduce during cell division. Cells have a hereditary system made up of genes which are copied and inherited on the chromosomes during cell division. The genes are copied by replicating complementary strands of the double helix, and during the course of replication mistakes can occur leading to changes in the

nucleotide sequence. This variability persists during subsequent reproduction and generates the phenotypic variability upon which natural selection can operate. In short, the ideas behind cells and genes provide the conditions which allow natural selection and evolution to take place.

Hermann Muller took these ideas one step further and proposed that evolution by natural selection could provide a good definition of life.¹² He argued that all living organisms have properties which allow them to undergo natural selection and so to evolve, the important properties being the three characteristics discussed above. The strength of this definition is that it can be used to define life forms that are not based upon carbon, which might be encountered on other planets or solar systems. The limitation of Muller's definition is that it is essentially historical, that is it describes how different life forms can come about but does not give much insight into understanding how living organisms actually work. For that we have to move to the fourth idea, life as chemistry.

Life as chemistry

Until the middle of the nineteenth century many biologists believed that the vital phenomena exhibited by living organisms were due to special forces distinct from those of physics and chemistry. These were termed vital forces and were thought to be found only in living organisms. The beliefs of the vitalists seem strange to us today, but the early biologists would have found it very difficult to explain the rich and extraordinary activities which living organisms exhibit purely in terms of physical and chemical forces.

The idea that many of life's activities can be understood in terms of chemistry has its origins in studies of fermentation and is well reviewed in Dressler and Potter.¹³ Antoine Lavoisier (1743–1794) was one of the founders of modern chemistry whose part-time, and probably dubious, activities as a tax collector meant he lost his head during the French Revolution. He became interested in fermentation, the practice used since ancient times whereby crushed fruits were fermented to produce alcohol. Noting that a major component of grape juice was sugar and that the primary product of fermentation was ethanol, he proposed that 'fermentation was a chemical reaction in which the sugar of the starting grape juice was converted into the ethanol of the finished wine'. Investigating this further, he showed that it was the 'ferment' (now known to be yeast) present during fermentation that played a key role in the chemical reaction. If he replaced the grape juice by pure glucose and then added a small amount of ferment, ethanol was produced just like during a normal fermentation. Exactly what the ferment was, however, was not clear at the time, although a little later Theodor Schwann of cell fame and other workers speculated that the ferment was yeast.¹⁴ This speculation, that the chemical reaction was dependent upon a living organism, was unpopular with the chemists of the time who perhaps resented this intrusion of biologists into their areas of interest.

Clarity emerged a quarter of a century later with the work of the great French polymath, Louis Pasteur (Fig 5). Asked by the

ethanol-producing industry to investigate why fermentations sometimes went wrong, he showed that certain fermentation batches produced lactic acid instead of ethanol. Microscopic examination of sediments in the fermentation vats revealed that the alcohol-generating vats contained yeast cells, some of which had buds suggesting that they were actively growing. In contrast, these yeast cells were absent in the vats producing lactic acid. From these simple observations, Pasteur proposed that the microbial life form yeast was responsible for generating ethanol whilst another microbe generated the lactic acid. The important point here was that the growth of a living cell resulted in the accumulation of a specific chemical substance. This led Pasteur to conclude that chemical reactions were an expression of the life of the cell. To confirm this view, Pasteur inoculated the sediments from the two vats into fresh flasks containing sugars, and showed that the yeast produced alcohol and the other microbe, a bacterium, produced lactic acid. These experiments and study of further fermentations producing different chemical products led him to argue that the chemical reactions were 'physiological acts giving rise to multiple products, all of which are necessary for the cell'.

The next advance in establishing that the phenomena exhibited by living organisms were due to chemical activities was the demonstration that living cells contained substances which could promote chemical reactions similar to the ones which occurred during fermentation. Marcelin Berthelot (1827–1907) broke up yeast cells and obtained a soluble activity which could be purified away from the cells but was still able to break down the sugar, sucrose, into its constituent components, glucose and fructose. The substance responsible for this activity he called invertase, and he concluded that living cells themselves were not necessary for the chemical reactions to take place, but rather the cells gave rise to substances which were still active when the



Fig 5. Louis Pasteur (1822–1895), whose studies of fermentation provided early evidence of life as chemistry. Reproduced from Ref 13.

living cells were no longer present. About 30 years later, at the turn of the twentieth century, these observations were extended by two German brothers, Hans and Eduard Buchner. They extracted an enzyme from yeast cells and showed it was responsible for the chemical reactions. The Buchner brothers broke open yeast cells by grinding them up with sand, and then filtered out the cell debris to generate a cell extract. This extract could ferment sugars and produce alcohol, demonstrating that this chemical reaction could occur *in vitro*. They concluded that yeast cells contained a substance, *zymase*, now known to be an enzyme, and that this intracellular substance was responsible for the chemical reaction converting sugar to alcohol.

This body of results formed the cornerstone of biochemistry.⁶ They showed that fermentation, a phenomenon associated with life, could be reduced to chemical reactions catalysed by intracellular substances called enzymes. Generalising from these results, it could be argued that most activities of living cells were based on chemical reactions catalysed by enzymes. Modern biochemistry has frequently confirmed this view. We are now aware that thousands of chemical reactions are taking place simultaneously within cells all the time, and that these are responsible for the vital phenomena exhibited by living organisms. These multitudes of reactions are carried out by an extensive range of enzymes each of which require a specific chemical micro-environment in order to function effectively. The different micro-environments are characterised by a particular pH level, ionic conditions, substrate availabilities and so on. Therefore, to work properly, these micro-environments need to be separated from each other. Cells exploit a range of mechanisms to achieve this. At the simplest level, the surfaces of the enzymes themselves provide spaces which are isolated from the local environment. If enzymes are combined together, complexes are generated which have greater opportunities for isolation of appropriate chemical micro-environments, leading to the channelling of substrates and products from one enzyme to the next through an ordered series of chemical reactions which make up metabolic pathways. Complexes can also form molecular machines isolated from the local environment like ribosomes responsible for protein synthesis. At a higher level, membrane-bound organelles provide a more extended level of compartmentation. Finally, the whole cell has a plasma membrane separating the entire cellular contents from the outside world. This spatially organised variety of chemical micro-environments gives rise to the highly complex structure of the cell (Fig 6).¹⁵

Another less obvious mechanism that can be used by the cell to separate chemical micro-environments is to exploit changes of the cell in time. Different micro-environments can be established in the same spatial region of the cell if they are separated in time. One situation when this occurs is seen during the cell cycle when changes occur in the local environment of the chromosomes. Chromosomes are condensed and free in the cytoplasm during mitosis to allow their proper segregation to take place, and are decondensed and confined to the nucleus during S-phase to allow the enzymes of DNA synthesis to operate. As a consequence, during S-phase and mitosis, DNA can be associated with different chemical micro-environments.

So modern biologists are very comfortable with the idea that the phenomena of life can be explained in terms of chemistry. But it is important to understand that this is a rather special form of highly organised chemistry. As Jacques Loeb argued in 1912, the living cell should be considered as a chemical machine. Two characteristics of machines which are very important for organising the chemistry of cells, are how the chemical reactions are regulated and how they communicate with each other. The many thousands of different intracellular chemical reactions have to be properly ordered and regulated to bring about the purposeful behaviours that make up the higher order functioning of a cell. A machine analogy which is often used to explain this type of regulation is the 'governor' found on a steam engine. Comprised of two balls spinning on an axis, as the engine goes faster the balls are forced out by centrifugal forces and automatically reduce the flow of steam into the engine, thus reducing its speed. Such feedback regulation is central to regulating flux through metabolic pathways. Products of an enzyme sequence can feed back on earlier steps in the pathway, down-regulating enzyme activities and so reducing overall flux through the pathway. Another more complex example of regulation is seen with the proof-reading controls operative during both protein translation¹⁶ and DNA replication. In these cases, control mechanisms exist which measure the strength of chemical interactions. For example, during translation the stability of the interaction between the mRNA codon site and the tRNA anticodon site is monitored and if the interaction is weak because the wrong tRNA is in place, then that tRNA is rejected. Such regulation makes the chemistry of the cell work together as a whole, helping it to generate purposeful behaviours.

The examples of regulation discussed so far act locally within the immediate vicinity of the chemical reactions taking place. However, in addition to local regulation there needs to be longer range communication between the different spatially isolated chemical micro-environments. The different, often incompatible, chemical micro-environments have to be kept distinct, and

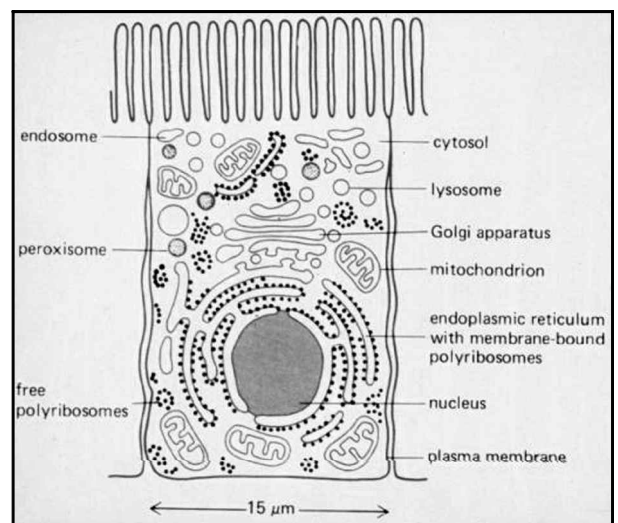


Fig 6. Schematic representation of cell structure. Reproduced from Ref 5.

special signalling mechanisms need to be in place to ensure communication between the micro-environments whilst maintaining their separation from each other. Signalling occurs between different parts of the cell and there are also specialised transport mechanisms which move chemicals and components from one place to the other. We are very familiar with the signal transduction pathways which are part of the inter-cellular communication processes, but generally less attention is paid to the intra-cellular signalling which is necessary for activities of the cell to be properly regulated and coordinated. As well as a need for signalling through space for proper functioning of a cell, there is a requirement for signalling between different time periods in the life history of a cell. This is obvious during the cell cycle when the status of events that occur early in the cycle have to be 'remembered' and signalled forward to later events in the cycle. For example, if DNA replication is incomplete this needs to be registered and relayed to the mechanisms which bring about mitosis so the cell does not attempt to divide until DNA replication is completed. Similar examples are found on a longer time-scale during the differentiation of cells or the development of an organism.

Relevance to medicine

These four ideas have been crucial for biology, but how relevant are they for medicine? I shall start with the cell theory because this idea finally came to fruition about the same time as medicine was becoming more scientific in its practice. As already discussed, Virchow played a crucial role in developing the cell theory. But because he was also one of the first pathologists, he also thought about the relevance of the cell to the origin of disease. He argued that diseased tissues are generated from normal tissues because the former contain malfunctioning cells, so when normal tissue cells start behaving aberrantly the tissue can become diseased. This was an important proposal because it focused the attention of physicians on changes in cellular behaviour as critical factors for understanding disease. This shift in thinking was further enhanced by the third idea, life as chemistry. If the behaviours of cells are determined by the chemical reactions going on within them, then the explanations for the malfunctioning cells found in diseased tissues are likely to be found by looking for alterations in the chemical reactions taking place within and between those cells. This is really the impetus for molecular medicine, which considers disease in terms of alterations of molecules in the diseased cells and tissues, an approach which has become the dominant way medicine is viewed today.

The idea of the gene is also relevant to this way of thinking because the transfer of information from DNA through RNA to protein provides the conceptual base for understanding molecular behaviour within diseased cells. Many medically oriented laboratories today focus on the analysis of DNA, RNA and protein molecules in their research. As well as this, the gene theory helps understanding of the inheritance of disease, which prior to Mendelian analysis could barely be investigated at all. Following the rediscovery of Mendel during the first half of the twentieth century, major genes predisposing to disease began to be identi-

fied, but it was the subsequent boom in molecular genetics which led to the recent great advances in human and disease related genetics. Although sometimes over-stated, and nearly always over-reported in the press, this approach will ultimately be very important for understanding human disease. Many of the major single gene effect diseases have now been associated with the relevant genes, already allowing useful genetic counselling and diagnosis, with the promise of new treatments being developed based on this knowledge. Geneticists are beginning to turn their attention to more complex genetic situations where a number of genes influence disease predisposition. The jury is still out on many of these studies, but in the coming years it will be possible to judge better the relative contributions of both inherited genes and the effects of the environment on particular diseases, which will help in working out the complex effects of environment. With both genes and environment influencing final disease outcome, analysis is very complex, but if the effects of genes can be simplified by understanding the genetics, then the effects of the environment can be more readily unravelled.

This leaves the final idea of evolution by natural selection. Because this is essentially a historical theory, at first sight it looks as if it contributes less than the other three ideas. It can help explain why certain disease traits may be present, sickle cell anaemia and malaria being the obvious example, but does not generally help much in understanding and managing disease. However, there is one major exception to this generalisation, and this is with the disease of cancer. Cancer comes about when genes important for controlling the growth and division of cells become damaged or rearranged leading to uncontrolled cell proliferation. This is an example of evolution by natural selection happening at the level of the cell within the human body. The genes and chromosomes in a cell can become damaged or re-arranged during the cell cycle or as a consequence of external damage, and if genes important for cell proliferation are damaged then cells containing these genes will proliferate, whilst the surrounding normal cells in the tissue do not. Just like evolution within a population of organisms, these pre-cancerous or cancerous cells will gradually overtake the population of cells making up the tissue. Because the sub-population of damaged cells increases, there is a greater chance of further changes taking place within the cells having this altered genotype, leading to an accumulation of genetic damage and the generation of more aggressive cancerous cells. This system has the three characteristics necessary for evolution by natural selection to take place: reproduction, a hereditary system, and the ability of the hereditary system to exhibit variability. It is paradoxical that the very circumstances which allowed human life to evolve are also responsible for one of the most deadly human diseases. More practically, it also means that population and evolutionary biologists should be able to contribute significantly to our understanding of cancer.

Biological organisation

The fifth idea is an emerging view of the research community concerned with understanding biological organisation and how

it is brought about. Biological organisation operates at a range of levels, from cells through organisms to populations and ecosystems. Here I will focus discussion at the level of the cell which is the simplest unit to exhibit the characteristics of life.¹ A cell is highly organised, acting as a coordinated whole to bring about higher levels of cellular structure and function. This leads to cells being both spatially organised, containing defined yet often dynamic structures, and also temporally organised, persisting and yet changing with time, for example during the cell cycle and differentiation. Cells also exhibit a wide range of purposeful behaviours, a characteristic of life which Jacques Monod has termed 'teleonomy'.¹⁷ These functions include the ability to communicate, to bring about homeostasis, to adapt to external stimuli, to undergo reproduction, and so on. So a useful way to view biological organisation is to consider it as organisation with purposeful behaviour.

This approach looks for explanations of biological organisation in terms of the logical and informational processes that operate in living cells.¹⁸ Two good examples are the significance of DNA structure for heredity, and of gene regulation for cellular homeostasis. The double helix is made up of two linear complementary strands of nucleotide sequence with the association of the strands being dependent upon the pairing rules between bases. This double helical structure is interesting because of its significance for the coding and replicative capacities of DNA. Knowing that genes are made of DNA and that genes encode information, focuses our attention on the ability of the nucleotide sequence to store information. This is encoded in the order and type of nucleotides that make up the linear sequence, much like the letters making up words and sentences. The DNA sequence of a gene is then transcribed into an RNA which is subsequently translated into the amino acid sequence of the gene encoded protein. Attempts to explain the replicative capacity of DNA have focused on the ability of the complementary nucleotide sequences to become precisely copied. Replication occurs by separating the strands and using the base pairing rules to build new complementary strands. Thus the biological significance of the biochemistry underlying both the coding and replicative capacities of DNA can be best understood in terms of information encoded in the DNA structure, and the flow of that information from the gene sequence to protein function. The point is that understanding the biological organisation that results in heredity comes about by transforming the molecular and biochemical descriptions of these processes into logical representations explaining how information is communicated and processed. The second example is gene regulation. Biochemical descriptions of gene regulation have led to the identification and characterisation of repressor and activator proteins which bind specific DNA regions upstream of the gene being regulated, and lead to changes in the level of gene expression. However, to generate biological understanding of the process, these descriptions need to be transformed into the logical structures underlying how genes are regulated. Once this logic is understood, information processing concepts emerge, such as the existence of negative and positive feedback loops which regulate gene transcription. As with DNA structure, biological organisation that

leads to gene regulation can be best understood in terms of the logical and informational processes generated by the molecular and biochemical mechanisms involved.

Such an approach played an important role during the early stages of molecular biology, when great emphasis was placed on understanding how information flowed from gene to protein, and how that flow was regulated.⁷ The argument being made here is that a similar approach will be very useful for understanding all aspects of biological organisation that underlie the structure and function of a cell. With this view the cell should be considered as a logical and computational machine, processing and managing information. Our objective should be to identify what logical and computational modules operate in cells and how they are derived from the underlying molecular, biochemical and biophysical mechanisms. I shall briefly discuss two examples of higher level cellular function which should profit from this approach: signalling networks and spatial organisation.

The potential complexity of signalling networks is very considerable. The connections between different parts of a network can include both positive and negative loops feeding both forwards and backwards within the signalling sequence. Certain steps can also have different thresholds for input signals leading to different output signals and outcomes. The dynamics of the signalling pathway may also be exploited to convey information, for example if different periods of an oscillating signal are used. A good analogy for thinking about such dynamical effects on signalling is the Morse code, where information is conveyed in the duration and order of signal pulses. These behaviours are much richer than a signalling sequence conveying a simple on or off message. It is also important to appreciate that biological systems including signalling networks have evolved by gradual 'add-ons' assimilated during natural selection. This means that the networks are likely to exhibit redundancy and will be less

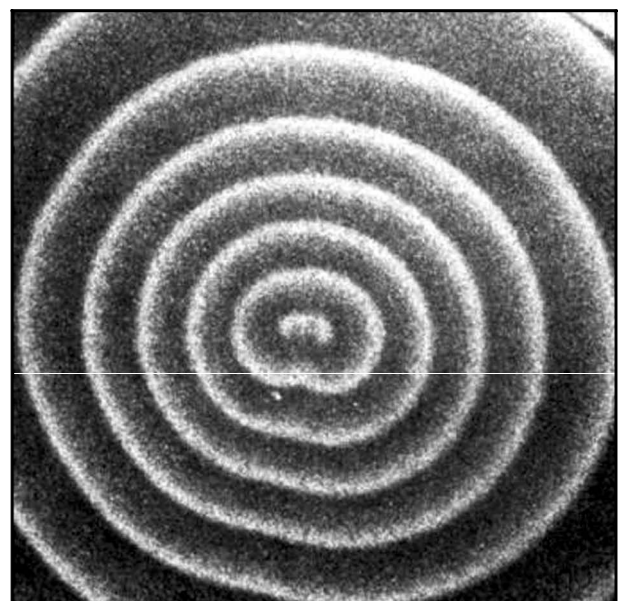


Fig 7. A reaction diffusion chemical reaction generating spatial order.

economic in function than human-designed control circuits. Such richness and redundancy makes the analysis of biological signalling networks difficult, and their analysis may require new methods and ways of thinking. It is also possible that the outcomes and solutions obtained may not always be obvious and may even be very unexpected.

A second higher level cellular function is how spatial organisation within a cell is achieved. Spatial organisation is important for separating the different chemical micro-environments within a cell and for making cellular structures. The generation of structure is only well understood for small biological objects which are direct assemblies of molecules, examples being phage heads and ribosomes. The shapes of these small scale objects are determined by the chemical bonds responsible for the direct interactions between their molecular constituents. More interesting, but more difficult to understand, is the generation of form at a more extended level beyond the scale of direct molecular interaction. This level includes objects such as vesicles, organelles, cells and whole organisms. A common characteristic of spatial organisation at these higher levels is their ability to regulate, that is to generate the correct form despite variations in the size of the domain being organised. This cannot be achieved by mechanisms based on direct molecular interaction which cannot adjust to differences in domain size. The molecules involved in these mechanisms must be able to generate spatial maps of cells which can still be made if the size of the cell changes. Reaction diffusion type models are often discussed in this context (Fig 7), although in their simplest form these models cannot regulate in response to changes in the size of the domain being organised. As with signalling networks, the objective should be to seek satisfactory explanations in terms of the logical structures and information processing which emerge from the molecular mechanisms that are responsible for bringing about cell form.

So the basis of this emerging idea is to look for ways that can transform molecular interactions, biochemical activities and biophysical mechanisms into logical and informational structures and processes.¹⁹ This will lead to an understanding of biological organisation by considering the cell as a logical and computational machine. It is possible that this approach will shift biology away from the rather common sense and familiar world that it has generally occupied in the past to one that is more abstract. The complex situations operative may lead to strange and non-intuitive behaviours,²⁰ and to work these out biologists will need assistance from scientists in other disciplines, such as mathematicians and physicists, who are more used to thinking about explanations not easily encompassed by the common sense world of our everyday experience.

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The full text of the Harveian Oration on which this paper is based is available from the Publications Department of the Royal College of Physicians. This lecture is also published in the Lancet.