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Death

Rupert Sheldrake

Death is out of fashion, rarely discussed, forgotten as much as it can be. It is too close to us all. But however much or little we may choose to think about our own inevitable mortality, death is a fact of life which must be considered by any science of life. But even within biology death has been more or less ignored. I think that this has imposed a great limitation on our understanding of life itself.

Life is change. Multicellular organisms grow, senesce and die. This is very obvious, one of the most immediate facts of our experience. But if we turn to biology and ask why do organisms grow, develop, senesce and die we hardly find even the beginnings of an answer. The picture that has emerged as the greatest triumph of molecular biology and biochemistry is an essentially static one. At the core of modern biology are a number of conceptions which are rather like Platonic ideal forms, changeless and universal. These are, firstly, the idea of DNA as the universal chemical of heredity, with a universal structure and a universal code; it can be copied more or less exactly, but is itself essentially static. Then there is the biochemical picture of metabolism, summed up in the Metabolic Charts which one often sees pinned up on laboratory walls; a universal biochemistry which is more or less the same in microbes, plants and men; an interlocked network of biochemical pathways and cycles. This whole system, although dynamic, is thought of as being in a steady state. Deviations from the steady state are corrected by negative feedback mechanisms so that, although oscillations are possible within the system, they are oscillations around a steady state. The third essentially static element in biology is a structural one, derived from the study of dead and fixed tissue by light and electron microscopy. This is represented in biology textbooks by means of a picture of an Idealized Cell, with nucleus, mitochrondria, membranes, ribosomes and so on. There is another static structural element in biology, of older vintage, produced by the study of anatomy and morphology; the ideal forms of the different species of organism; the visual image is one of plants preserved on herbarium sheets or animals in bottles of formalin; these are further formalized in drawings and diagrams.

Of course biologists are not unaware of the fact that life is change. Sciences such as embryology and the now fashionable

subject of developmental biology are avowedly and explicitly concerned with development. But the tendency of practically all modern biology is essentially mechanistic; it is not simply the description of change which is aimed at, but the analysis of the mechanisms of change. Here lies one of the greatest difficulties in the whole of biology; this difficulty stems from the attempt to explain the change and development of organisms in terms of the essentially changeless and universal concepts derived from molecular biology, biochemistry and electron microscopy. If a cell is thought of as being in a more or less steady state from a structural and biochemical point of view, then the only way in which change can be brought about is by the imposition of some external stimulus. And indeed changes of this type have been analysed in considerable detail. If one adds the sugar lactose to the medium in which the prototypic bacterium *E. coli* is growing, changes occur such that new enzymes are manufactured which enable lactose to be used as a source of food. If one supplies yeast cells with oxygen they produce energy by respiration; but if one changes the environment to one without oxygen they produce energy by fermentation; a new steady state is established in response to external change. The same sort of analysis is applied to the differentiation and development of cells in higher organisms, but here the external agents of change are chemical messengers, i.e. hormones, formed within the organism itself. But if hormones regulate the cellular changes, how are hormonal changes themselves regulated? This problem seems relatively easy to answer for certain hormones studied by animal physiologists, such as insulin; but this relative simplicity is misleading. The hormones whose formation and control are understood are all hormones concerned with regulating the steady state; they are a very special and limited class of hormone. Any attempt to understand developmental changes in terms of chemical messengers thought of by analogy with this small class of steady-state hormones leads straight back to the problem of trying to understand change and development in terms of static concepts.

I have tried to summarize briefly and perhaps in an oversimplified way what I think are the central patterns of thought within modern biology. The cell and the organism tend to be seen as being in a steady state unless change is imposed from without. Within this framework of thinking, ageing and death are very difficult to explain. Indeed they are not explained. They are ignored as much as possible; they are hardly mentioned in most biology textbooks. The study of ageing is relegated to the special science of gerontology, or within medicine to the specialists in geriatrics. Ageing tends to be thought of in terms of the stiffening of collagen fibres in the connective tissues or the accumulation of unpleasant

fatty substances in the arteries. A number of more sophisticated theories of ageing have been advanced within the last few years which involve accidental internal changes within the cells, but these theories are in general limited to the only form of internal, accidental change which is readily admitted by most biologists, namely genetic mutation. Ageing is supposed to result from the accumulation of defects in the DNA. This may indeed be part of the explanation, but the danger is that now some sort of molecular biological mechanism has been proposed, the problem of ageing will be regarded by many as more or less solved, at least to the extent that no serious thought need be given to it by most biologists.

I want to propose that the processes leading to ageing and death are intrinsic to all cells all the time; only by postulating such internal changes can we make any sense not only of ageing and death but also of growth and development. These changes must be ones which occur progressively with time and be changes which are irreversible. Life is change; living organisms exist within duration; they have time within them; in Bergson's phrase, they are gnawed on by the tooth of time. These internal changes *are* ageing and lead inexorably towards death. Cells have the seeds of death within them; death is not a footnote to life; death and life are intertwined and interdependent.

Unicellular organisms such as amoebae and bacteria are often considered to be immortal. The cells grow, divide, and the daughter cells grow and in turn divide. Some of the daughter cells die; indeed most of them die but the ones that survive go on growing and dividing. An individual unicellular organism is not immortal, but the cell can escape death by growth and division. Multicellular organisms are constituted differently. They depend on a specialization of cells, on a division of labour between the cells, tissues and organs of which they are composed. They contain differentiated cells. And the differentiation of cells is not compatible with their continued growth. In general cells can either divide or they can become differentiated; they cannot do both. So in multicellular organisms most of the cells lose the potential for unlimited growth and division; the organisms could not exist otherwise; they would not be organisms at all but mere aggregations of cells.

I am now going to propose in general terms a mechanism for the sort of process I have been describing in a very abstract way. This mechanism is not the only one conceivable, but it makes it easier to understand the sort of approach I am trying to propose.

I suggest that in all cells there is a progressive accumulation of toxic substances, whose accummulation leads inexorably towards the

death of the cell. These substances could, for example, be breakdown products of proteins or of lipids from cell membranes; but speculation on their chemical identity is not necessary for the purposes of the present argument. From its otherwise inevitable death, the cell has one route of escape: to grow and divide. The toxic products will then be diluted and the daughter cells will have a new lease of life. But again time will lead to a further accumulation of these substances and again the only escape will be further growth and division. Even so there will be a progressive build-up of these compounds in the cells (since each cell inherits some from its mother cell, forms more itself and thus passes on more to its daughter cells than it itself received) and death will finally overtake the cells after a given number of divisions. Such a situation does indeed seem to be the case. Cells taken from the lungs of human embryos can be grown in the laboratory and go on dividing quite happily for about 50 cell generations. Then they die. Similar cells taken from the lungs of adult humans grow and divide for about 20 generations and then die. Death can be evaded by continued growth, but the ancestral debt gradually builds up and finally overwhelms the cells at a time which depends on the number of generations through which the cells have passed.

But the type of cell division I have been referring to here is a symmetrical cell division, where both the daughter cells receive half of the accumulated toxic products of the mother cell. Another type of division is possible, an asymmetric division. Here one of the daughter cells may receive all or most of the accumulated toxic products and the other be truly rejuvenated, having almost none. The slate would be wiped clean; one cell would for a while have escaped from the progressive effects of time while the other would be condemned to differentiation and death, a death which might occur sooner or later but which it cannot escape unless (as occurs in some forms of regeneration) it divides again unequally, producing a rejuvenated cell and a cell even more mortal than itself. In all multicellular organisms, visibly asymmetric cell divisions are quite common; it is possible that these involve an asymmetric distribution of toxic products in the manner described above.

In the light of this hypothesis I now want to consider the growth, development and death of higher animals and plants. Firstly plants. If we look at a large tree we find that it is always growing (except when it is dormant in the winter). Year after year the shoots form the same sorts of leaves; year after year the roots grow in the soil. The tree grows old not because its shoots senesce; the tree dies not because of an inbuilt senescence but because it gets so big that it eventually falls over, or succumbs to disease, or is struck by lightning. But the shoots are perpetually young; cuttings taken from

an old tree will give rise to healthy young trees and this process can be repeated indefinitely. So the growing points of the tree, the meristems, do not age; they can elude senescence and death. If we look at the way the cells within the meristem divide, we find that they divide asymmetrically. Each division gives one cell that remains young, that grows and divides again; but the other cell enlarges, differentiates and sooner or later dies. Some of the cells, for example the wood cells, die as they differentiate; as they die they release substances which control the pattern of further growth and differentiation. So the price payed for the continued growth of the meristematic cells is the death of half the daughter cells, which differentiate and eventually die. The differentiated cells of the leaves die; the leaves drop off. The differentiated cells of the stem die, forming the wood and the bark. But the shoots go on growing. In a tree we see layers and layers of dead tree formed in the previous years; the living tissues are superimposed on the dead whose accretion proceeds as long as the tree is growing.

The tree represents the fundamental pattern of indefinite growth which is characteristic of plants. There are of course plants which do not grow indefinitely, such as the annuals, which die after they have flowered. But even annuals are capable of growing for much longer than their normal life span if they are prevented from flowering, showing that death is caused by flowering and is not due to an innate inability to go on growing.

Animals are different. They do not go on growing. They reach a fixed size; their growth is determinate, and they inevitably die. The initial rate of growth of an animal embryo is very high; but this growth rate slows down until the organism reaches its final size. The progressive decline in the rate of growth led Minot to say in 1890 that the younger the organism is, the more rapidly it ages. This sort of statement is very unfashionable in modern biology; but it focuses our attention on the process of embryology in a far more interesting way than any amount of molecular biology. At first the cells of the fertilized egg divide rapidly, more or less symmetrically. But then the rate of cell division slows down; tissues begin to differentiate; and throughout the development of the embryo tissues and groups of cells die in the midst of other tissues which continue to grow. This striking phenomenon, although commented on by embryologists, has received very little attention. The death of these cells may not only be the price that is payed for the growth of other cells, but also provide a major source of the elusive chemical messengers which are supposed to influence the patterns and types of differentiation which occur in the embryo. In the adult organism, some tissues continue to grow: the skin, the intestinal wall, the liver; and blood cells continue to be formed.

But in all these cases continued growth is offset by cell death. The skin, for example, is constantly being replaced; the skin cells die as they differentiate. It is probable that the living cells at the base of the skin divide unequally, like the cells of a plant meristem, one cell remaining young and capable of dividing again, the other differentiating and dying. Tissues such as the skin which retain the ability to grow are the least mortal parts of the body. On the other hand there are some tissues whose differentiation is completed relatively early in life and which possess little or no capacity for regeneration; muscle is to a large extent like this but the supreme example is found in the nervous tissue. The cells of the central nervous system are all differentiated; they cannot divide and they inevitably die. And when they die they are not replaced.

But while the individual animal is made up of mortal tissues, there is one type of cell which escapes from death, when the slate is wiped clean and which is rejuvenated to the highest degree. This is the egg cell. The freeing of a cell from the accumulated products of ageing can, I have suggested, occur only by asymmetrical cell divisions; the renewed vitality of one cell is bought at the price of the death of its sister cell. It is a remarkable and well-known fact, but one to which little or no significance has been attached, that in both animals and plants the formation of the egg cell involves two asymmetric divisions of the egg mother cell such that four cells are produced, three of which die. The similarity of animals and plants in this respect is particularly significant because sexuality has evolved independently in the animal and plant kingdoms; in both only one of the four potential egg cells actually becomes an egg. The contrast with the formation of the male germ cells is also very striking. In both animals and plants all four of the potential sperm cells or pollen grains remain alive. But pollen and sperm cells are mortal; they have a limited life span; the lucky ones reach the egg cell, fertilize it by passing their nucleus into the egg, but the pollen tubes or sperm cells themselves remain outside the egg, and die.

Death at the cellular level is therefore significant in two major ways: the death of cells resulting from asymmetric cell division may pay the debt of mortality which enables their sister cells to be rejuvenated and to escape for a while from ageing, in a sense to conquer time. Secondly, cell death may play a role as a source of chemical messengers that are released as by-products of the breakdown of protoplasm. At least in plants, there is considerable evidence that this is in fact the case. But there is a third way in which cell death may be of importance. In the most differentiated of all tissues, the brain, the nerve cells develop and differentiate quite early, mostly during the period of embryonic growth. Some

new nerve cells are formed after birth, but in man the maximum number has been reached by about the age of two. These cells are differentiated, they are mortal; and they die. Nerve cells are dying all the time; on average there are about 10% fewer at the age of 80 than there are at age of 20.

The conventional view of this process is to ignore it as much as possible, but otherwise to assume that all it can mean is a progressive deterioration of function in the brain which only becomes of importance during senile decay. This view derives from a static conception of physiology. In the naive models of the brain based on analogies with telephone switchboards or computers, the structure has to be taken for granted as a perfectly functioning whole. These models see the brain as both genetically programmed and self-programming; information is processed according to these complex programmes by permutating it and recombining it in all sorts of ways. Since computers are not creative in any very interesting way, a computer model of the brain implies a lack of creativity. But the most striking difference between the human mind and a computer is that human beings are creative and computers are not. It is precisely this creativity which the computer models cannot account for and which leads at least the less sophisticated adherents of this type of thinking to deny that creativity exists at all. It can be explained, they argue, by permutations and recombinations of information in a complex but potentially predictable way.

But creativity is not a mere reshuffling; it is the production of the new and unforeseeable, which cannot, by definition, be predicted. The creativity that is expressed in biological evolution is explained in neo-Darwinian theory by chance mutations. Monod refers to mutations as chance caught on the wing and also speaks of the inexhaustible resources of the well of chance as being the only source of absolute newness; random inner change lies at the heart of evolutionary creativity.

If the brain were an essentially changeless structure, a super computer working smoothly, it would have no source of inner change which could account for creativity. But the brain is not like this; its inner structure is undergoing constant change precisely because it is mortal; cells are dying and they are not replaced. The death of these cells must be regarded as taking place at random, by chance. The inner changes brought about in the brain are thus unforeseeable; they are thus potentially a source of absolute novelty by exact analogy with chance genetic mutations.

Unless we adopt the very unlikely hypothesis that the numerous cells within the brain that die are doing nothing and that their disappearance makes no difference, it seems necessary to conclude

that cell death might have profound consequences for the nervous connections in the brain. Some pathways of conduction might be broken, others be formed and new combinations produced in a completely unforseeable manner. In conscious life, a new connection, a new idea, may just appear—we are unable to explain where it comes from. And in dreams the most amazing variety of impressions, recollections and images are combined with unfailing novelty. These processes might be going on in all our brains all the time; the vast majority may be dismissed and forgotten, as we forget most dreams; and many may never reach consciousness. An immense wealth of novelty may lie within everyone all the time; but only in some people some of the time are new ideas or images selected, developed and used. Again we can think of the analogy with genetic mutation and natural selection: most mutations are harmful and are removed by natural selection. In some very conservative species, the living fossils, nearly all mutations are filtered out. But in others some of the mutations are preserved, developed and contribute to the creation of new species and forms of life. But too many mutations are lethal; the organism breaks down. Similarly, if cell death within the brain is to act as a source of useful novelty, the mechanisms which filter out harmful changes and which preserve and develop others must themselves continue to function. We do not grow more and more creative as we approach senility: too many cells have died; the balance between change and conservatism breaks down. Cell death can only play a positive roll when it is relatively rare. Although it may be precisely because the brain is mortal and because cells die within it that creativity is possible, this process must lead towards senility and death.

These hypotheses are speculative. They may be wrong. But unless we think about the mortality of cells we cannot begin to understand the mortality of organisms. And unless we think about the mortality of organisms we cannot make sense of evolution, which depends on the cycles of growth, reproduction and death. In Goethe's phrase, death is Nature's device for having life in abundance. Without death there could have been no evolution, no creation of new forms of life. Without human death there could have been no evolution of culture. And our own mortality is a necessary condition for the growth and development of consciousness itself.