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Conclusion

The Integron

That heredity can today be interpreted in molecular terms does not constitute an end in itself; nor is it a proof that all biology must in future become molecular. It signifies primarily that the two major currents of biology, natural history and physiology, that went their separate ways for so long almost unaware of each other, have finally joined forces. The old quarrel between integrationists and reductionists has thus been resolved in the distinction established long ago by physics between the microscopic and the macroscopic. On the one hand, the variety of the living world, the wonderful diversity of forms, structures and properties at the macroscopic level are based on the combinative system of a few molecular species, that is, on very simple devices at the microscopic level. On the other hand, the processes that take place at the microscopic level in the molecules of living beings are completely indistinguishable from those investigated in inert systems by physics and chemistry. Only at the macroscopic level of organisms do special properties appear, imposed by the necessity of self-reproduction and of adaptation to certain conditions. The problem, then, is to interpret the processes common to beings and things in terms of the special status assigned to living organisms by their origin and purpose.

Recognition of the unity of physical and chemical processes at the molecular level has deprived vitalism of its *raison d'être*. In fact, since the appearance of thermodynamics, the operational value of the concept of life has continually dwindled and its power of abstraction declined. Biologists no longer study life today. They no longer attempt to define it. Instead, they investigate the structure of living systems, their functions, their history. Yet at the same time, recognition of the purpose of living systems means that biology can no longer be studied without constant reference to the 'plan' of organisms, to the 'sense' which their very existence gives to structures and functions, an attitude obviously very different from the reductionism that was long dominant. In the era of reductionism, to be really scientific, analysis had to exclude any considerations beyond the system immediately under study and its specific role. The rigour imposed on description required elimination of that element of finality which the biologist refused to admit. Today, in contrast, one can no longer separate a structure from its significance, not only in the organism, but in all the chain of events that have led the organism to become what it is. Every living system is the result of a certain equilibrium between the parts of an organization. The interdependence of these parts means that modification at any point affects the whole of relationships and sooner or later produces a new organization. By isolating systems of different kinds and complexity, it is possible to recognize their constituents and justify their relationships. Yet whatever the level studied – molecules, cells, organisms or populations – the perspective is necessarily historical and the principle of explanation necessarily that of succession. Each living system has to be analysed on two planes, two cross-sections, one horizontal and the other vertical, which can be separated only for the sake of explanatory convenience. On the one hand, one has to distinguish the principles governing the integration of organisms, their construction, their functioning; and on the other, the principles that directed their transformations and their succession. The description of a living system requires reference to the logic of its organization, as well as to the logic of its evolution. Today biology is concerned with the algorithms of the living world.

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The organization of living systems obeys a series of principles, as much physical as biological: natural selection, minimum energy, self-regulation, construction in 'stages' through successive integration of sub-sets. Natural selection imposes finality, not only on the whole organism, but on each of its components. In a living organism, every structure has been selected because it fulfils a certain function in a dynamic self-reproducing whole. It is therefore by their history and continuity that the molecules composing living systems differ from all others. Some have not varied for millions of years: in a certain sense, they remain copies of the molecules formed in ancient times. Others, on the contrary, have been transformed under some selective pressure. Numerous were those lost on the way; perhaps more numerous still those which appeared in new species, in man, for instance. But over and above the demands of selection, living systems, just like inanimate systems, remain subject to the law of minimum energy. Whether or not they involve true chemical bonds, whether they entail syntheses or mere associations of molecules, the reactions in the living organisms always proceed in the same direction, towards a decrease of free energy. The rate of these reactions is always determined by the activation energies required by the transitions involved.

Regulatory circuits give living systems both their unity and the means of conforming to the laws of thermodynamics. These laws state that a chemical reaction can be modified only in terms of its equilibrium or rate. In a simple reaction, the equilibrium constant is a function of the molecules taking part. Catalysis simply increases the rate by decreasing the required activation energy. In an enzymic reaction involving such a complex structure as a protein, it is the shape of the protein that determines both its affinity for the substrate and the rate of the reaction. Affinity and rate can be changed only by changing the shape of the protein. All the coordination of the cell is thus dependent on the geometrical deformation of a few proteins by interactions with certain metabolites acting as specific signals. In multicellular organisms, there are additional regulatory circuits for harmonizing and integrating the activities of the cells. Here direct contacts between cells, as well as hormones and the nervous system, play their part. It is not yet known how these circuits function. It seems likely, however, that hormones and chemical mediators of the nervous system also act by deforming certain proteins in the membrane or the cytoplasm of sensitive cells. In themselves, these compounds have no significance. They acquire value as signals for certain cells only because of the presence of proteins that serve as receptors, i.e. ultimately because of the genetic programme in these cells. But in all cases the regulation of biological systems affects the equilibrium and rate of reactions. In all cases, it simply expresses the interaction of components, that is, the properties inherent in their arrangement, and therefore in their structure.

Construction in successive stages is the principle governing the formation of all living systems, whatever their degree of organization. Even the simplest organism is so complex that it could probably never have taken shape, reproduced and evolved if the whole had had to be built piece by piece, molecule by molecule, like a mosaic. Instead, organisms are built by a series of integrations. Similar elements are assembled to form a set of the level just above, and so on. It is thus by combining more and more elaborate elements, by fitting subordinate structures into one another, that complexity is born in living systems. These systems can be reproduced from their elements at each generation, because at each level the intermediate structures are thermodynamically stable. Living beings thus construct themselves in series of successive 'parcels'. They are arranged according to a hierarchy of discontinuous units. At each level, units of relatively well defined size and almost identical structure associate to form a unit of the level above. Each of these units formed by the integration of sub-units may be given the general name 'integron'. An integron is formed by assembling integrons of the level below it; it takes part in the construction of the integron of the level above.

This hierarchy of integrons, this principle of a box made up of boxes is already illustrated at the microscopic level in the way protein structures are produced inside the cell. Three stages, in fact, can be seen in the building of these structures. In the first stage, inorganic elements are converted into small specific molecules, the protein sub-units, or amino acids, by a series of enzymic reactions. The specificity of the reactions depends on the associations between enzymes and substrates and on their equilibria. Their rates are coordinated through the interaction of enzymes with certain metabolites. In a second stage, the polymers are arranged along nucleic-acid templates where protein sub-units are lined up in precise order. This arrangement depends on specific associations that do not involve any chemical bond. Only when they are properly in place are the sub-units connected to each other by enzyme action. In a third and final stage the protein chains fold up and form superstructures.

The simplest superstructures are assembled only as a result of the capacity of association that their structure affords to the components: the affinity of the elements for each other is sufficient for the system to form spontaneously. For more complex superstructures, kinds of 'centres' are perhaps involved in the organization of some components; centres acting either as structural agents to modify the conformation of the other components, as kinds of enzymes to accelerate their association, or even as templates favouring one particular arrangement among all those that are thermodynamically permissible. But invariably, the possible arrangements of an organized structure depend on the bond energies between elements. Invariably, they are an equilibrium property of the system. Even if such centres exist, their formation is still determined by the interactions of the components. In the end, the most complicated structures are built up in a series of stages in which intermediates may be used, not only as material, but also, should the occasion arise, as agents in constructing the next structure. Until further notice, only the components incorporated into the structure are required for its formation. Living organisms are formed by spontaneous assembly of their components.

In many ways the properties of these structures recall those of crystals. This is an old analogy, already invoked more than two centuries ago to explain the shape, growth and reproduction of organized beings. It had been necessary to abandon this comparison, however, once the structure of a perfect crystalline solid was brought to light. Such a crystal requires the same pattern to be repeated in three dimensions. It is a regular arrangement of atoms from the centre to the surface. Being inaccessible, the interior of the structure has no function. The crystal can develop only by the addition of components to its surface. It does not reproduce. But subsequently, the concept of a crystal has been generalized: it applies to any organization of matter that is repetitive in two, or even in one dimension. From particles that have no dimension, so to speak, fibres and surfaces like membranes or three-dimensional bodies can form spontaneously. From this point on, the analogy between crystals and living structures regains an operational value. What gives a collection of objects the property of assembling is their sameness.

Not only can they form geometrical structures; they can do so spontaneously. But there is no way of telling how far the sameness must go and what differences in structure can be tolerated. Although constraints on the formation of three-dimensional crystals appear strict, they seem less stringent in other cases, so that nucleic-acid or protein sub-units are sufficiently similar objects to be placed in geometrical arrangements. A whole series of biological structures – polymers, membranes and intracellular organelles – thus have their own internal logic, a logic which is not exactly that of the three-dimensional crystals, but very little different. All these structures can exercise a chemical function only through their surface.

Yet, although the principles involved in the organization, construction and logic of living systems can now be perceived, although their origin can be glimpsed by extrapolation, it is still hard to grasp the series of events that led from the organic to the living. For the biologist, the living begins only with what was able to constitute a genetic programme. For him, an object deserves the name of organism only when it offers a foothold for natural selection. He sees the mark of the living in the ability to reproduce, even if a primitive organism may have required several years to form its like. For the chemist, in contrast, it is somewhat arbitrary to make a demarcation where there can only be continuity. Every organism contains a panoply of structures, functions, enzymes, membranes, metabolic cycles, energy-rich compounds and so on. Whatever the beginning assigned to what is called a living system, it is possible to envisage its organization only in an environment already prepared well in advance. Biological evolution is necessarily the unbroken continuation of a long process of chemical evolution. It is possible to try to reconstitute in the laboratory the conditions that apparently prevailed on earth before the appearance of living organisms. Whole series of organic compounds are then seen to form spontaneously. Even polymers can arise by chance associations between the sub-units. Although inefficient, the reactions required for producing the macromolecules characteristic of living organisms really seem to occur without biological catalysts. Yet it is difficult to imagine the appearance of an integrated system, however primitive; the origin of an organization able to reproduce even badly, even slowly. For the humblest organism, the simplest bacterium, is already a coalition of enormous numbers of molecules. It is out of the question for all the pieces to have been formed independently in the primeval ocean, to meet by chance one fine day, and suddenly arrange themselves in such a complex system. The first ancestor could only have been some kind of nucleus, an association of several molecules helping each other to re-form after a fashion. But then how did it all begin? And with what? The genetic message can be translated only by the products of its own proper translation. Without nucleic acids, proteins have no future. Without proteins, nucleic acids remain inert. Which is the hen, which the egg? And where can traces be found of this precursor, or of some precursor of the precursor? In some still unexplored corner of the globe? On a meteorite? On another planet of the solar system? Without any doubt, the discovery somewhere or other, if not of a new form of life, at least of somewhat complex organic vestiges, would be priceless. It would transform our way of envisaging the origin of genetic programmes. But as time passes, the hope of this diminishes.

For want of vestiges to examine, biology is reduced to making conjectures. It tries to arrange the problems in series, to individualize the objects and formulate questions that can be answered by experiments. Which of the polymers, nucleic acid or protein, came first? What is the origin of the genetic code? The first question leads one to speculate whether anything vaguely like a living organism would be conceivable without both types of polymer. The second raises problems both of evolution and of logic. Of evolution, because univocal correspondence between each group of three nucleic-acid sub-units and each protein sub-unit cannot have arisen at a single stroke. Of logic, because it is difficult to perceive why this particular correspondence was adopted rather than another; why one nucleic-acid triplet 'means' a certain protein sub-unit and not another. Perhaps primitive organizations had some constraints of structure we know nothing about: it would then be the adjustment of molecular conformations that would have imposed, if not the whole system, at least some of its equivalences. But again perhaps there was no constraint at all: then it would have been purely by chance that the equivalences were produced and persisted afterwards. For once a system of relations has been established, the relations cannot be changed without the risk of the whole meaning of the system being lost and all its value as a message destroyed. A genetic code is like a language: even if they are only due to chance, once the relations between 'sign' and 'meaning' are established, they cannot be changed. These, then, are the questions molecular biology is trying to answer. But nothing indicates that the transition between the organic and the living can ever be really investigated. It may perhaps never become possible to estimate what the probability was of a living system appearing on earth. If the genetic code is universal, it is probably because every organism that has succeeded in living up till now is descended from one single ancestor. But, it is impossible to measure the probability of an event that occurred only once. It is to be feared that the subject may become bogged down in a slough of theories that can never be verified. The origin of life might well become a new centre of abstract quarrels, with schools and theories concerned, not with scientific predictions, but with metaphysics.

And yet biology has demonstrated that there is no metaphysical entity hidden behind the word 'life'. The power of assembling, of producing increasingly complex structures, even of reproducing, belongs to the elements that constitute matter. From particles to man, there is a whole series of integration, of levels, of discontinuities. But there is no breach either in the composition of the objects or in the reactions that take place in them; no change in 'essence'. So much so, that investigation of molecules and cellular organelles has now become the concern of physicists. Details of structure are now defined by crystallography, ultracentrifugation, nuclear magnetic resonance, fluorescence and other physical techniques. This does not at all mean that biology has become an annex of physics, that it represents, as it were, a junior branch concerned with complex systems. At each level of organization, novelties appear in both properties and logic. To reproduce is not within the power of any single molecule by itself. This faculty appears only with the simplest integron deserving to be called a living organism, that is, the cell.

But thereafter the rules of the game change. At the higher-level integron, the cell population, natural selection imposes new constraints and offers new possibilities. In this way, and without ceasing to obey the principles that govern inanimate systems, living systems become subject to phenomena that have no meaning at the lower level. Biology can neither be reduced to physics, nor do without it.

Every object that biology studies is a system of systems. Being part of a higher-order system itself, it sometimes obeys rules that cannot be deduced simply by analysing it. This means that each level of organization must be considered with reference to the adjacent levels. It is impossible to understand how a television set works without first knowing how transistors work and then something about the relations between transmitters and receivers. At every level of integration, some new characteristics come to light. As physicists already observed at the beginning of the twentieth century, discontinuity not only requires different means of observation; it also modifies the nature of phenomena and even their underlying laws. Very often, concepts and techniques that apply at one level do not function either above or below it. The various levels of biological organization are united by the logic proper to reproduction. They are distinguished by the means of communication, the regulatory circuits and the internal logic proper to each system.

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Everyone agrees that there is a direction in evolution. In spite of errors, of dead ends, of false starts, a certain road has been covered during more than two thousand million years. Yet it is difficult to describe the course that natural selection has imposed on chance. The words 'progress', 'progression' and 'improvement' are not suitable. They suggest too much regularity, purpose and anthropomorphism. Their criteria remain ill defined. If one criterion is adaptation to survive, then the bacterium *Escherichia coli* appears just as well adapted to its environment as man to his. The words complication or complexity are hardly better. There are gratuitous complications, and others that, because of over-specialization, prohibit any possibility of further evolution. What is perhaps most characteristic of evolution is the tendency to flexibility in the execution of the genetic programme; it is an 'openness' that allows the organism constantly to extend its relations with its environment and thus to extend its range of action. In so simple an organism as a bacterium, the programme is carried out with great rigidity. It is 'closed' in the sense that the organism can only receive very limited information from its environment and can only react in a strictly determined way to this information. All that a bacterium perceives is the presence or absence of certain compounds in the culture medium. The sole response that it makes is to produce or not to produce the corresponding proteins. Its perceptions and reactions are reduced to one alternative, yes or no. 'Success' in evolution leads to increases in both the ability to perceive and the ability to react. For an organism to differentiate, for it to become more independent and to extend its exchanges with the outside world, there must be a development not only of the structures which link the organism to its environment, but also of the interactions which coordinate its constituents. At the macroscopic level, therefore, evolution depends on setting up new systems of communication, just as much within the organism as between the organism and its surroundings. At the microscopic level, this is expressed by changes in genetic programme, both qualitative and quantitative.

The notion that evolution results exclusively from a succession of micro-events, from mutations, each occurring at random, is denied both by time and by arithmetic. For the wheel of chance to come up step by step, sub-unit after sub-unit, with each of the several ten thousand protein chains needed to compose the body of a mammal would require far more time than the span generally attributed to the solar system. Only in very simple organisms can variation occur entirely in small independent stages. Only in bacteria can speed of growth and size of populations allow the organisms to await for the appearance of a mutation in order to adapt. Evolution has become possible, only because genetic systems have themselves evolved. As organisms become more complicated, their reproduction also becomes more complicated. A whole series of mechanisms appears, always based on chance, which help to reassort the programmes and compel them to change: the scattering of the genetic programme over several chromosomes; the presence of not one but two copies of each chromosome in each cell; the alternating phases of one set or two sets of chromosomes during the life cycle; the independent segregation of chromosomes; the recombination by breakage and reunion of homologous chromosomes, and so on. But the most important inventions are sex and death.

Sexuality seems to have arisen early in evolution. At first it was a kind of auxiliary of reproduction, a superfluous gadget, so to speak: nothing obliges a bacterium to make use of sexuality in order to multiply. It is the necessity of resorting to sex as a reproductive device that radically transforms the genetic system and the possibilities of variations. As soon as sexuality becomes obligatory, each genetic programme is no longer formed by exactly copying a single programme, but by reassorting two different programmes. The genetic programme is then no longer the exclusive property of one line of descent. It belongs to the collectivity, the group of individuals who communicate with each other by means of sex. Thus a kind of common genetic fund is set up, drawn on by each generation for making new programmes. This common fund, this population united by sexuality, forms the unity of evolution. Instead of the sameness imposed by the strict reproduction of the programme, sexuality offers the diversity produced by a reassortment of programmes at each generation. So great is this diversity that, with the sole exception of identical twins, no individual is exactly like his brother. Sexuality obliges programmes to cover all the possibilities of the genetic combinative system. It therefore compels change. In order to convince oneself that sex plays such a role in evolution, that it is itself an object of evolution open to continuous refinement, it is enough to consider the subtleties, the rites and the complications which accompany sexual practices in higher organisms.

The other necessary condition for the very possibility of evolution is death. Not death from without, as the result of some accident; but death imposed from within, as a necessity prescribed from the egg onward by the genetic programme itself. For evolution is the result of a struggle between what was and what is to be, between the conservative and the revolutionary, between the sameness of reproduction and the newness of variation. In organisms reproducing by fission, the dilution of an individual caused by the rapidity of growth is sufficient to erase the past. But in multicellular organisms, with differentiation into somatic and germ lines, with sexual reproduction, individuals have to disappear. This is the resultant of two opposite forces: an equilibrium between sexual effectiveness on one hand, with its cortège of gestation, care and training; and the disappearance of the generation that has completed its role in reproduction on the other. The adjustment of these two parameters by the effect of natural selection determines the maximum duration of life of a species. The whole system of evolution, at least in animals, is based on such an equilibrium. The limits of life cannot be left to chance. They are prescribed by the programme which, from the moment the ovule is fertilized, fixes the genetic destiny of the individual. The mechanism of ageing is not yet known. The theory at present most favoured considers senescence as the result of accumulated errors, either in the genetic programmes contained in somatic cells or in the way these programmes are expressed, that is, in the proteins produced by the cells. According to this theory, the cell might cope with a certain number of errors, but once beyond this point, it would be doomed to die. In time, errors accumulated in an increasing number of cells would cause the inevitable extinction of the organism. The very way the programme is executed would, therefore, determine the length of life. However this may be, death is an integral part of the system selected in the animal world and its evolution. Much may be hoped from what today is called 'biological engineering': the cures for many scourges, cancer, heart disease, mental illness; the replacement of various organs with grafts or artificial parts; a cure for some failings of old age; the correction of certain genetic defects; even the temporary interruption of active life to be resumed at will later. But there is very little chance that it will ever be possible to prolong life beyond a certain limit. The constraints of evolution can hardly be reconciled with the old dream of immortality.

The arsenal of genetics favours mainly changes in quality of the programme, not in its quantity. In fact, evolution is first expressed by increased complexity. A bacterium is the translation of a nucleic-acid sequence about one millimetre long and containing some twenty million signs. Man is the result of another nucleic-acid sequence, about two metres long and containing several thousand million signs. The more complicated the organization, the longer the programme. Evolution became possible, through the relationship established between the structure of the organism in space and the linear sequence of the genetic message. The complexity in integration is then expressed by the simplicity of an addition. The known mechanisms of genetics, however, favour variations of the programme but hardly ever provide it with any supplement. There are certain copying errors that repeat certain segments of the message, genetic fragments that viruses can transfer or even supernumerary chromosomes. But these processes are not very effective. It is hard to see how they could be sufficient to cause some of the major stages in evolution: the change in cellular organization from the simple or 'procaryotic' form of bacteria to the complex or 'eucaryotic' form of yeasts and higher organisms; or the transition from the unicellular to the multicellular state; or the appearance of vertebrates. Each of these stages, in fact, corresponds to a rather important increase in nucleic acid. These sudden increases can have occurred only by making the most of some exceptional chance event, such as an error in reproduction providing extra chromosomes, or even some exceptional process, such as a symbiosis of organisms or the fusion of genetic programmes from distinct species. The fact that symbioses can indeed take part in evolution is now proved by the nature of 'mitochondria', these organelles responsible for producing energy in complex cells; by all biochemical criteria, they bear the stamp of bacteria. They even have their own nucleic-acid sequence independent of the chromosomes of the host cell. In all likelihood, they are vestiges of bacteria that once associated with another organism to form the ancestor of our cells. As to fusions of genetic programmes, they are known in plants, but not in animals, which are protected by a safety mechanism from the effects of the 'abominable couplings' dear to antiquity and the Middle Ages. Cells from different species, however, have recently been fused in laboratory cultures, human and mouse cells, for example. Each possessing both the human and mouse programmes, these hybrid cells multiply perfectly. What abnormal couplings between different species cannot achieve may nevertheless be accomplished in other ways. Were such encounters able, even exceptionally, to have consequences, this is enough to provide an opportunity for very profound changes. In practice, nothing proves that such accidents occur in nature; but in theory they are not impossible. There is no regularity in expansions of programme. There are sudden changes, unexpected increases, unexplained decreases, with no relation to the complexity of the organism. Very unusual events are required to fit enlargements of programme into the rhythm of evolution. This shows how illusory any hope of estimating the duration or evaluating the probabilities of evolution are today. One day perhaps, computers will calculate what the chances were of man appearing on earth.

Expansion of programme is caused by the tendency to increase interactions between the organism and its environment, a characteristic feature of evolution. There are many ways an organism can multiply exchanges with its surroundings. Already protozoa succeed in doing so. Their outfit of specialized organelles shows a surprising degree of complexity for a single cell. But there is a limit to the number and size of structures compatible with reproduction. Beyond a certain threshold, to increase the number of cells and differentiate them becomes a way of economizing. While some cells look after nutrition, others can deal with perception, locomotion or integration. Diversifying and specializing cells means freeing each from the constraints imposed by the necessity of having to accomplish *all* the reactions of the organism. It means allowing each cell to do less, but to do it better, so long as activities are coordinated. If they are to specialize, cells must therefore communicate with each other.

There are several ways cells can communicate: by direct contact or through the mediation of the nervous system and the hormones. Little is yet known of the nature of the molecular interactions that take part in such regulatory circuits. In fact, we are beginning to 'understand' the cell, but not the tissues or organs. Nothing is known of the logic of the system controlling the execution of complex programmes such as the development of a mammal. The formation of a man from an egg is a marvel of exactitude and precision. How can millions of millions of cells emerge, in specialized lineages, in perfect order in time and space, from a single cell? This baffles the imagination. During embryonic development, the instructions contained in the chromosomes of the egg are gradually translated and executed, determining when and where the thousands of molecular species that constitute the body of an adult are to be formed. The whole plan of growth, the whole series of operations to be carried out, the order and the site of syntheses and their coordination are all written down in the nucleic-acid message. And in the execution of the plan, there are few failures: the accuracy of the system may be measured by the rarity of abortions and monsters.

During development, each cell receives a complete set of chromosomes. But according to their specialization, different cells produce different types of messengers and proteins. Although it contains the whole programme, each cell translates only part of it and carries out only certain instructions. There is thus a precise sequence of chemical events during which the very expression of the genes is modified as the cells differentiate. Through the interplay of regulatory circuits segments of the message in each cell-line are activated or inhibited. Not only are these regulatory circuits more complex in multicellular organisms than in bacteria, they also fulfil different requirements. First, because in these organisms there must be systems that can differentially activate sets of genes in a permanent, instead of reversible manner. Also, because finding one gene among a million, and not one among a thousand, requires a more elaborate mechanism, such as successive sorting of sub-sets. Finally, because a bacterium and a cell in a multicellular organism operate under very different conditions. The bacterium has to maintain its functional equilibrium while adapting to different environments. The cell must also preserve a precise state of equilibrium; but in addition, it must coordinate its activities with those of its neighbours. Only in this way can the organ fulfil its functions, which in turn are subject to regulation by the organism as a whole.

In the end, it is always the logic of the organism, its individuality, its purpose which control its constituents and their systems of communication. In the network that coordinates such a complex group of chemical activities as a mammal, however, there are many opportunities for errors or false manoeuvres. Some are without importance; others have major consequences. Cellular multiplication, for instance, is subject to control by the organism. Swift at first during development of the embryo, it ceases completely when the organism reaches maturity, only resuming in response to injury. The genetic programme does not simply prescribe the plan of cellular divisions; it also sets a limit to them. This coordinating network seems to combine two kinds of circuits: one direct, mediated by actual contact between the cells; the other indirect, mediated by hormones. In each case, however, it is through specific receptors on its surface that the cell receives the signals. Were a receptor inactivated, were a signal not transmitted, then one of the circuits ensuring the social behaviour of molecules and cells would be interrupted. A cell may thus be led into a state of anarchy: deaf to signals limiting its growth, it is no longer a member of the community. It may invade neighbouring tissues and cause a tumour. With the notion of genetic programme, the old controversies about the origin of cancer have lost much of their significance. Whether the lesion starts in the nucleus or the cytoplasm, whether it be the consequence of a somatic mutation, of the presence of a virus or of a defect in a circuit, anything which prevents reception of a signal can put the cell outside the laws of the community. To understand cancer is to gain access to the logic of the system which imposes on cells the constraints of the organism.

All these complications caused by the multiplicity of cells and by their differentiation are determined by the increased exchanges between the organism and its environment. To heal a wound after injury, or to regenerate a limb after amputation is already to adjust the responses of the organism. Greater flexibility of the programme thus allows certain types of aggression to be warded off. In the course of evolution, however, what has developed above all is the ability to collect outside information, to treat it and to adjust the reactions of the organism accordingly. All possible solutions are tried out, subject to the control of natural selection. Some organisms feel their environment, others hear it, or see it, or smell it. The ability to react to stimuli and the latitude in the choice of response increase in parallel. It is not enough to acquire a few impressions here or there; there must also exist the capacity to integrate them and to draw the conclusions. It is an advantage, for example, to be sensitive to light. So great is indeed this advantage that the eye has been 'invented' several times during evolution: the compound eye of insects, and the lens eye, which has arisen independently on at least three occasions: in certain molluscs, in spiders and in the earliest mammals. But what would be the use of a precision instrument capable of defining shape, of judging distance, of determining the direction of movement, if not for locating a predator or a prey and making the appropriate response? For all that, it is essential to have the means of identifying the signals received, of comparing them with shapes recorded in a 'memory', of distinguishing friend from foe, of swimming, running or flying; in short, of 'choosing' a reaction. Means of perception, of reaction and of decision must evolve in harmony.

Increased exchanges between organism and environment are based on the development of the nervous system. But our present knowledge of this system is on a par with the knowledge of heredity in the nineteenth century. We have some information about certain electric or biochemical properties of the nerves; we have very little concerning specificity of the connections, or the organization and construction of the network. How is information coded, transmitted, recorded and deciphered? What logic underlies the activity of the brain, the memory or the acquisition of knowledge? In these areas, we are still almost completely ignorant. One fact seems beyond dispute, however: the anatomy of the nervous system is in some fashion fixed by heredity. The brain is like other organs: its structure is determined down to the last detail by the genetic programme. In many mutants of the mouse, alteration of one particular gene produces both an anomaly in behaviour and a specific lesion of the brain. During regeneration of severed nerves in certain organisms, the path adopted by the fibres, the establishment of the connections, the constitution of the circuits – in short, the entire organization of the network is carried out according to the original plan. Special centres exist, in fact, in the brain of mammals, not only for receiving various sensations and putting various muscles into action, but also for controlling sleep, or dreams, or attention, even for producing affective states. For example, there is a centre for 'punishment' in the rat, another for 'pleasure': fitted with correctly implanted electrodes and given the means of activating this centre at will, a rat satisfies itself until it collapses from sheer exhaustion! But we do not yet know how acquired circuits are superimposed on the heredity network, nor how the innate and the acquired fit together. For today the latter two are no longer antagonistic, but complementary. Ethologists consider that when behaviour involves acquired experience, it is dependent on the genetic programme. Learning comes into the framework fixed by heredity. Undoubtedly, it will soon become possible to analyse the molecular mechanism of synapses, the articulation of the nervous cells, the unity of anatomical connection on which is based the whole arrangement of the nervous system. And we can be sure that to the biochemist the characteristic reactions of brain activity will appear as ordinary as digestive reactions. But it is quite another matter to describe a feeling, a decision, a memory, a guilty conscience in terms of physics and chemistry. There is nothing to show that it will ever become possible, not only because of the complexity, but also because since Gödel we know that a logical system is not sufficient for its own description.

With the development of the nervous system, with learning and memory, the rigour of heredity is relaxed. In the genetic programme underlying the characteristics of a fairly complex organism, there is a closed part that can only be expressed in a fixed way and another open part that allows the individual a certain freedom of response. On the one hand, the programme rigidly prescribes structures, functions and attributes; on the other, it merely determines potentials, norms, frameworks. Here it commands; there it permits. As what is acquired increases in importance, the behaviour of the individual changes. This is apparent in the various ways by which birds recognize their like. In some, like the cuckoo, the species is identified in a way rigidly laid down in the genetic programme. All that is necessary is the mere sight of shapes and movements. Raised in the nest of its adoptive parents such as hedge-sparrows or warblers, as soon as the young cuckoo becomes independent it joins company with other cuckoos, even if it has never seen any in its life. With geese, on the contrary, identification is much more subtle. It works through a mechanism that ethologists call 'imprinting'. After hatching, the young gosling follows the first object it sees moving and hears calling. Usually, it is its real mother that the gosling follows. But if, by chance, it is another organism, Konrad Lorenz, for instance, then the gosling considers Konrad Lorenz as its mother and follows him everywhere. The genetic programme, therefore, determines shape in one case, and the ability to receive the imprint of a shape in the other. The animal world contains many examples of this kind. The growing importance of the open part of the programme gives a direction to evolution. Together with the capacity of response to stimuli, the degrees of freedom left to the organism in the choice of responses also increase. In man, the number of possible responses becomes so high that one can speak of the 'free will' so dear to philosophers. But flexibility has its limits. Even when the programme gives the organism only an ability, that of learning, for instance, it imposes restrictions on what can be learnt, on when learning is to take place and under what conditions. The genetic programme of man gives him an aptitude for language. It gives him the power of learning, understanding and speaking any language. But man must still be in a favourable environment at a certain stage of his development in order to fulfil this potential. After a certain age, deprived of speech, of care and of maternal affection for too long, a child will never learn to speak. The same restrictions apply to memory. There are limits to the amount of information that can be recorded, to the length of time it can be stored and to the power to retrieve it at will. But this boundary between rigidity and flexibility in the programme has hardly yet been explored.

As exchanges increase during evolution, new systems of communication appear that no longer operate within the organism, but between organisms. A network of relations is thus established between individuals belonging to the same species. Originally, these communication systems were directly connected with the purpose of reproduction. Without them, sexuality would scarcely be efficacious. As long as it is not necessary for reproduction and remains merely an auxiliary function, nothing favours the union of the sexes. There is no 'sex-appeal' among bacteria. Opposite sexes meet by chance in random collisions. So it is with certain lower organisms that, being hermaphrodite, use sexual intercourse only occasionally. But as the independence of the organism increases, as sexuality becomes the only method of reproduction, then individuals of one sex must have a way of spotting those of the other. So long-distance communication systems appear that link selectively the opposite sexes of the same species. They are usually specific signals emitted by one sex and received by the other. Some insects use olfactory signals: they produce a volatile substance that is picked up, identified and interpreted by others provided by their genetic programme with a receptor sensitive to this molecular structure. Other insects use auditory signals: only the males sing. Fish and birds use visual signals: one of the sexes, usually the male, has a complex equipment of shapes, colours and iridescent ornaments that provide specific stimuli for the opposite sex. These visual signals, connected by hormones to the chemistry of the organism, activate all that part of behaviour concerned with reproduction. This sets off the succession of activities leading to copulation, nest-building, incubation and so on. There again, the whole series of operations, rites and ceremonies to be performed are all written down in the genetic message. The sight of the opposite sex acts merely as a signal. It only sets in motion the execution of an already prepared scheme for reproduction.

Obviously, these systems of signals have been selected to favour reproduction. They are nonetheless methods of communication between individuals of the same species. They make possible the formation of integrons at a higher level than the single organism. Up to mammals, however, integration rarely exceeds the temporary formation of a couple, the unit of reproduction. It is exceptional for groups of animals with coordinated behaviour to be set up, such as shoals of fish or flocks of birds during migration. The principal exception is found among certain insects, ants, termites or bees, that form true integrons transcending the individual. The old comparison of the organism and society becomes real in the ant-heap, the termitary and the beehive. Yet each of these structures is primarily a reproduction unit. The queen and the males play the role of sexual cells, the workers that of somatic cells. There again, the unity of these systems is rigidly determined by the genetic programmes that control, not only the morphology and physiology of each type, but also the nature and series of operations each has to perform. When the programme opens and a new system of communication such as the dance of the bees is established, it is in order to transmit information necessary for one function of the system: the search for food.

The structure of the genetic message therefore imposes the structure of animal communities. But with mammals the rigidity of the programme of heredity becomes less and less strict. The sense organs become refined. The means of action increase, particularly with the ability to grasp. The capacity to integrate becomes greater at the same time as the brain. One even sees the appearance of a new property: the ability to do without objects and interpose a kind of filter between the organism and its environment: the ability to symbolize. Gradually the signal becomes a sign. Even a rodent can learn to distinguish a triangle from a square or a circle and to associate shape with its quest for food. A cat can learn to count stimuli. Although a chimpanzee cannot speak with its larynx, it seems able to learn some elements of the code-language of gestures that deaf and dumb use for communication. The chimpanzee thus manages to recognize certain signs, interpreting and miming them, even combining some of them in groups to make short 'sentences' and express itself. It is not, therefore, at one stroke, by a sudden jump, that the small area of the brain controlling gesture and speech was developed. It is not even by a single series of successive stages, by a continuous chain, that man became man. It is by a mosaic of changes in which each organ, each system of organs, each group of functions, has evolved in its own way and at its own pace. Long foetal life and slow development, walking on two feet and freeing the forelimbs, formation of the hand and the use of tools, increase of brain size and aptitude for speech, all this leads not only to a greater autonomy with regard to environment, but also to new systems of communication, of regulation, of memory, which function at a higher level than the organism. All the conditions are then fulfilled for new integrations to occur in which coordination of elements no longer depends on the interaction of molecules, but on the exchange of coded messages. A new hierarchy of integrons is thus set up. From family organization to modern state, from ethnic group to coalition of nations, a whole series of integrations is based on a variety of cultural, moral, social, political, economic, military and religious codes. The history of mankind is more or less the history of these integrons and the way they form and change. There again appears a tendency towards growing integration made possible by the development of new means of communication. As long as it is confined to speech, the transfer of information is limited in space and time. With writing, communication can break free of time and the past experience of each individual can be stored in a collective memory. With electronics, with the means of preserving picture and sound and transmitting them to any point on the globe at a moment's notice, all restrictions in time and space have disappeared.

In the cultural and social integrons, new objects appear which function according to principles unknown at lower levels. The concepts of democracy, property and wages are as void of meaning for a cell or an organism as the concepts of reproduction and natural selection for an isolated molecule. This means that biology is diluted out in the study of man, just as is physics in the study of the cell. In this domain, biology represents merely one approach among others. Since the appearance of a theory of evolution, sociologists – starting with Herbert Spencer – have often tried to interpret the variations and interactions of social or cultural integrons by means of purely biological models. As the mechanisms governing the transfer of information obey certain principles, the transmission of culture through generations can be considered as a kind of second genetic system superimposed on heredity. It then becomes tempting, particularly for biologists, to compare the processes at work in both systems and draw analogies; to compare the ways ideas and mutations crop up; to contrast the novelty of change with the conservatism of the copy; to explain the disappearance of societies or cultures, like that of species, by blind alleys due to over-specialized evolution. The parallel can even be made in detail. Reproduction, then, lies at the centre of both systems, for codes of culture and societies as for the structure and properties of organisms: the fusion of cultures is like that of gametes; the university in society plays the role of the germ line in the species; ideas invade minds as viruses invade cells; they multiply and are selected for the advantages they confer on the group. In short, the variation of societies and cultures comes to be based on evolution, like that of species. All that has to be done, then, is to define the criteria of selection. The trouble is that no one has yet succeeded.

For with their codes, their regulations, their interactions, the objects that form cultural and social integrons transcend the explanatory schemes of biology. Once more, they involve integration of components that are themselves already integrated. But although there are further stages and discontinuities of phenomena and concepts, there is no complete break with the levels of biology. The objects of observation fit one inside the other. Physiology, for example, studies individually the functions of the organism and their coordinating mechanisms. At the level above physiology, behavioural science disregards the internal processes so as to grasp the complete reaction of the organism to its environment. At a still higher level, the dynamics of populations and sociology ignore the behaviour of individuals and study the behaviour of whole groups. One day, the different levels of observation will have to be brought together and related to each other. Once again, there is no hope of grasping the system without understanding the properties of its components. This means that although the study of man and societies cannot be reduced to biology alone, it cannot do without biology any more than biology can do without physics. It is not possible to account for cultural and social transformations by a selection of ideas. But it is not possible either to forget that the human organism is the product of natural selection. Of all living organisms, man has the most open and flexible genetic programme. But how flexible is it? How far is behaviour dictated by the genes? What constraints does heredity impose on the human mind? Obviously such constraints exist at some levels; but where should limits be drawn? According to modern linguistics, there is a basic grammar common to all languages; this uniformity would reflect a framework imposed by heredity on the organization of the brain. According to neurophysiologists, dreaming constitutes a necessary function not only for man, but for all mammals; it is controlled by a centre located in a precise area of the brain. According to ethologists, aggressiveness represents a form of behaviour selected in the course of evolution. Already present in most vertebrates, it gave man a selective advantage when living in small groups and constantly competing for food, women and power. Today, it is no longer natural selection that plays the leading role in transforming man, at least in certain societies. It is culture, more efficient, more rapid, but also very recent. Consequently, many aspects of man's behaviour today find their origin in some selective advantage given to the species when it emerged. Many traits of human nature must be inserted in the framework established by the twenty-three pairs of chromosomes that make up the common inheritance of man. But how rigid is this framework? What restrictions does the genetic programme impose on the plasticity of the human mind?

With the accumulation of knowledge, man has become the first product of evolution capable of controlling evolution. Not only the evolution of others, by encouraging species of interest to him and eliminating bothersome ones, but also his own evolution. Perhaps one day it will become possible to intervene in the execution of the genetic programme, or even in its structure, to correct some faults and slip in supplementary instructions. Perhaps it will also be possible to produce at will, and in as many copies as required, exact duplicates of individuals, a politician, for instance, an artist, a beauty queen or an athlete. There is nothing to prevent immediate application to human beings of the selection processes used for race-horses, laboratory mice or milch cows. But it seems desirable to know first the genetic factors involved in such complex qualities as originality, beauty or physical endurance. And above all, agreement has to be reached about the criteria for the choice. But that is no longer the concern of biology alone.

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There is a coherence in the descriptions of science, a unity in its explanations, that reflects an underlying unity in the entities and principles involved. Whatever their level, the objects of analysis are always organizations, systems. Each of them is used as an ingredient by the one above. Even that old irreducible protagonist, the atom, has become a system. And physicists still cannot say whether the smallest entity known today is an organization or not. The word 'evolution' describes the changes that occur between systems. For what evolves is not matter blended with energy into one permanent whole. It is organization, the unit of emergence, that can always associate with its like to integrate into a system by which it is dominated. Without this property, the universe would be insipid: an ocean of identical particles, both inert and unaware of each other; something like the oldest rocks on earth, whose molecules and relationships have not changed for thousands of millions of years.

Integration changes the quality of things. For an organization often possesses properties that do not exist at the level below. These properties can be *explained* by the properties of the components; they cannot be *deduced* from them. This means that a particular integron has only a certain probability of appearing. All forecasts about its existence can only be statistical. This applies equally to the formation of beings and things; to the constitution of a cell, an organism or a population, as well as of a molecule, a stone or a storm. It is therefore on contingency that the unit of explanation is based today. In organisms, however, the effects of chance are immediately corrected by the requirements of adaptation, reproduction and natural selection. Hence a paradox. For in the inanimate world, the chances of events occurring can be statistically predicted with accuracy. In contrast, with living beings, which are indissolubly linked to a history whose details will never be known, the deviations introduced by natural selection make any prediction impossible. How could the appearance and development of certain living forms rather than others be predicted? How could, in the Secondary era, the sudden end of the large reptiles and the success of mammals have been foreseen?

Ultimately all organizations, all systems, all hierarchies owe their very possibility of existence to the properties of the atoms described by Clerk Maxwell's electromagnetic laws. There are perhaps other possible coherences in descriptions. But science is enclosed in its own explanatory system, and cannot escape from it. Today the world is messages, codes and information. Tomorrow what analysis will break down our objects to reconstitute them in a new space? What new Russian doll will emerge?