THERMODYNAMICS OF FLOW AND BIOLOGICAL ORGANIZATION

by A. Katchalsky

The fundamental questions facing mankind since time immemorial, "Who am I?" "Where do I come from?" "Where am I going to?", continue to haunt modern man, despite his scientific sophistication. We are still suffering from pain, from phobias and frustrations, and looking for reassurance and comfort, for hope and inspiration, in our struggle for existence. As pointed out by Durkheim, the major problem of prescientific man was to overcome the hostile forces of nature in order to survive. The advent of a scientific technology made man a master of nature, but in the process he lost interest in life itself, and the new mastery only increased his insecurity and frustration.

Previous generations found consolation and guidance in mythological beliefs, which reinforced man's ego and provided life with meaningful mission. There is, however, at present no retreat to the mythological world, and anyone who has been infected with the analytical method of science is doomed to the search for cognitive solutions for meaningful behavior, without the support of mystical revelation. It is this recognition which drives many honest thinkers to raise the classical problems of value and humanistic attitudes also with the scientists—and it is the presence of the inner struggle within our generation which underlies our symposium on science and human values.

On a priori grounds it would seem reasonable to direct our questions regarding foundations for a moral system in a scientific society to the philosophers or to the psychologists. Experience has, however, discouraged this approach, and during the last century there has been a growing tendency to regard science itself as a philosophical foundation for human behavior, a foundation which could provide the dictum for a meaningful, satisfying, and decent life. It is true that for many centuries the scientists themselves were very reluctant to indulge in problems of an ethical nature. There is an old maxim in the history

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of science that Greek science was destroyed by the Platonic search for answers to the questions "Why?" or "What for?" Since the Renaissance, therefore, science confined its activities to asking "How?" and "What is the mechanism?" without seeking to explore the ultimate, or divine, aim of natural phenomena. Thus, even today the greater number of scientists are ready to leave the value judgments to the humanists, the lawyers, or the politicians, without troubling themselves about the consequences of their own activities.

Whatever may be the justification for this prevalent attitude, it cannot be considered tenable in the face of the dangerous results achieved by modern science—results which may eradicate all of mankind, including the "Olympic" scientists themselves. A generation ago it was the atomic scientists who recognized that atomic weapons are their responsibility since, as Lloyd George already stated during World War I, "War is too earnest a business to be handed over to the generals. . . ." Today, with the recognition of the potential dangers of genetic engineering, the impact of medical sciences on the population explosion, and with the overall participation of all science in global pollution, there is no scientific group which can shake off responsibility and avoid a direct confrontation with value judgments.

For several decades, the search for adequate foundations on which a moral system could be constructed was directed toward the physical sciences. The assumption underlying these efforts was that the laws of physics represent the "foundations of nature," and if—and what a huge if—human ethics should conform to natural requirements, then a set of weighty commandments could evolve from this study. Some of the better-known consequences of these considerations are the fine study of Bronowski[1] on the moral foundations of the whole structure of science and the famous attempt of Niels Bohr[2] to show that the principle of complementarity of atomic physics suffices for a new approach to human understanding and may serve as a basis for international complementary relations between contradictory cultures. Despite the excellence of Bohr's work and the intellectual satisfaction provided by its insight, the analysis of foundations did not succeed in providing a moral dictum which could guide people in their behavior and provide answers to the problems imposed by our times. The distance between the principle and the operational requirements was too great. Hence, it is understandable why during recent years an increasing number of thinkers are turning their attention to the biological sciences in the hope that the understanding of living organisms will provide man with a way of understanding himself.

To be sure, such an approach might be promising only if there were something new in biology, and in particular in the biology of humanoid relatives, which is not deducible from the physical properties of the molecular constituents of living beings. For, if we accept the assumption of the reductionists that all living phenomena are potentially implied in the elementary components, there is no point in looking for answers in the more complex systems—we should continue with the study of physical foundations. The reductionist approach became very prominent through the outstanding success of molecular biology in providing the explanation for the genetic code and indicating how cellular organization may be grasped in terms of a molecular cybernetics. It is still, however, an open question whether these achievements negate a hierarchical structure and permit the reduction of all the phenomena of life to molecular processes.

There is, of course, no doubt that all living beings are made up of molecules and that the molecular constituents obey the laws of physical chemistry. Our problem is whether the laws governing the behavior of *single* particles suffice for the treatment of organized *assemblies* of particles—even assuming that our knowledge of the laws were complete. It is not that the laws of assemblies are nonphysical or beyond the grasp of natural science—only that they are different and *cannot* be derived from the laws characterizing the behavior of single particles. The negation of reductionism has nothing to do with vitalism or with the concept of special forces operating in the living systems. Since it does not seem possible to reduce the behavior also of nonbiological assemblies to the properties of single atoms, clearly additional concepts and laws are required to make the transition from one organizational level to another. It is difficult to avoid the impression that reductionism is based on a belief similar to that in the Laplacian demon, a belief in the absolute powers of scientific deduction. One is tempted to support the statement of Mayr that "enthusiastic but poorly informed physical scientists have lately tried very hard to squeeze all of biology into the straight jacket of a reductionist physical-chemical explanation"[3]—arriving at somewhat doubtful results.

Indeed, as was pointed out by von Neumann,[4] what matters in systems of higher organization is not so much the energy and forces, but the *patterns* which result in *persistent configurations*. Energy, force, etc., are the major properties of *individual components* (and the domain of the physical sciences), whereas configuration is the domain of cybernetics, of logics, and of information theory. Thus, the transition to higher levels of organization means the introduction into natural sciences of "humanistic" concepts which may act as a bridge between the impact of the sciences and the ethical imperative.

The simplest transition step from the single to the assembly, from the elementary to the complex, is via the science of thermodynamics. In this discipline we encounter for the first time the concept of entropy, which is a typical "social" concept and cannot be attributed to single particles. Indeed, entropy is nonconservative and is closely related to such abstract notions as information and organization. With thermodynamics, we are enabling the first step to be taken toward those forms of complexity in which the expression of individual uniqueness is arrived at and in which the conceptual approach of science merges with that of the humanities. As will be shown later, despite the fact that the level of our discussion lies somewhere between the microscopic and the macroscopic, the treatment of the thermodynamics of flows will be very much to the point and will provide us with additional insight into the nature of living organization.

THERMODYNAMICS OF FLOW PHENOMENA

Anyone who has been exposed to the classical thermodynamic treatment of heat engines may feel that the attempt to relate thermodynamics to "human values" is rather artificial. Historically, however, this is not the case, for already in its earliest stages—during the mid-nineteenth century—thermodynamics exerted a powerful influence on the religious outlook of intellectuals. The recognition that all work phenomena are united through a common and universal factor, *energy*—the realization that there exists an all-embracing unity behind the diversity of energetic forms—was the first scientific evidence that the monotheistic attitude not only is based on prophetic vision, but is a well-documented, objective reality. In the thrill of this discovery, energetic characters were attributed to mental and emotional phenomena, and the father of physical chemistry, Wilhelm Ostwald, with the well-known evolutionist Ernst Haekel, laid the foundations of a new "scientific religion"—the *monistic approach* to man and nature.[5]

Although from a religious point of view, subsequent developments in thermodynamics were less dramatic, they did not lose their intellectual appeal, and by the end of the nineteenth century thermodynamics was considered the "logics of natural science." Its abstraction and universality were generally appreciated; as someone said, "In thermodynamic treatment you do not know what you put in, you do not know what you get out—but the results are always correct."

Classical thermodynamics is, however, too limited for the treatment of the dynamic structures which are so important in biology and which are the subject of the present discussion. It is a theory of *equilibria* which makes only vague statements on systems in flow. The notion of "equilibrium" in thermodynamics deserves some clarification: it is a terminal state reached ultimately by aged systems in which all processes have stopped. The equilibrium of thermodynamics is independent of the path which leads to it and is therefore a "memoryless state," which does not carry the imprint of the developmental history and is determined only by the overall characteristics of the system. "Equilibrium" should be carefully distinguished from a "stationary state"—in which it is by means of the balancing of forces that a system does not change with time. In a stationary state, processes go on and the history of the system will be reflected in the values of the steady parameters. Thus, whenever psychologists speak about "equilibria," they surely do not mean the dead end of thermodynamics reached by living systems only a long time after death. When Janet, Freud, or Piaget invoke the concept of equilibrium in their theory of effective regulation, or when Claparède considers "satisfaction" as a state of equilibrium, they clearly have in mind stable stationary states. Indeed, it is this restriction to terminal equilibria which makes classical thermodynamics such a weak tool in the treatment of biological systems—and this despite its remarkable success in the analysis of the molecular components of cells and tissues. Moreover, the basic laws of thermodynamics hold for *closed* systems, while a living organism is an *open* system, exchanging matter and energy with its surroundings. Hence, when we are dealing with the thermodynamics of living phenomena, attention should be devoted to irreversible processes, and in particular to processes proceeding in open systems far from equilibrium.

Throughout the end of the nineteenth and the beginning of the twentieth centuries, numerous attempts were made to develop a thermodynamics of nonequilibrium systems. The first useful theory was proposed in 1931 by Lars Onsager,[6] who succeeded in correctly describing linear processes close to equilibrium. During the postwar years, nonequilibrium thermodynamics became a well-organized discipline due to the work of Prigogine, of Meixner, of de Groot,[7] and of many others. Since 1958 my colleague O. Kedem and I[8] have applied this new science to various biophysical systems and have found that it is a very useful tool for the treatment of coupled flows passing through biological membranes. Despite its achievements and coordinating value, the validity of nonequilibrium thermodynamics in biology is limited to the fact that it deals only with systems close to equilibrium and requires a linear relation between flows and forces. Living organisms are based on coupled chemical reactions, which are generally nonlinear and rather far from equilibrium. Further attempts therefore had to be made to proceed into the difficult but rewarding field of nonlinear processes.[9]

On a priori grounds, we might suspect that coupled nonlinear flows far from equilibrium may lead to unstable states which could result in the breakdown of the original symmetry of the system and in the formation of new structures, dynamic structures based on the coupling of rapid flows.

DYNAMIC FLOW STRUCTURES

In his attempt to provide a rationale for Darwinian evolution, the well-known British philosopher Herbert Spencer[10] adduced the hypothesis that the driving force of evolution is the transition from homogeneous to nonhomogeneous structures, a transition which he considered equivalent to the development of organizational complexity. To explain his view, Spencer indicates that there exists simple experimental evidence for his statement: Place a drop of a solution of shellac in light petrol on a smooth glass surface. In a short while, as the solvent evaporates, the surface of the varnish becomes marked with polygonal divisions which first appear on the edges and spread toward the center of the drop, converting the whole into a honeycomb structure. The evaporation process has evidently broken the homogeneous symmetry and converted the system into a more complex organized structure. The quantitative analysis of Spencer's experiment should presumably follow the theoretical consideration of Pearson,[11] who attributes pattern formation to an interplay of surface and viscous forces. From our point of view it is, however, important that already a hundred years ago Spencer recognized the existence of symmetry-breaking instabilities which may lead to structural and evolutionary progress.

The first careful experiments on pattern development through the interaction of thermodynamic flows was performed by Bénard in 1900.[12] This classical study is basic to our further discussion and deserves more detailed consideration. As in many other classical experiments Bénard's observation is based on a very simple arrangement. He kept a heavy liquid in a shallow dish which was carefully heated at the bottom. Since the experiment was performed seventy years ago, Bénard was not pressed to report to a granting authority and could follow slowly and carefully the processes taking place in the liquid. He found that at a critical temperature an instability set in and rings appeared near the wall of the dish (fig. 1). These rings, indicating cylindrical tubules in the liquid, increased in number and moved toward the center, filling up the whole volume with a honeycomb structure (fig. 2). On further heating, the Bénard structure disappeared indicating that its existence is limited by a lower and upper boundary. The interpretation of the Bénard phenomenon was given in 1916 by

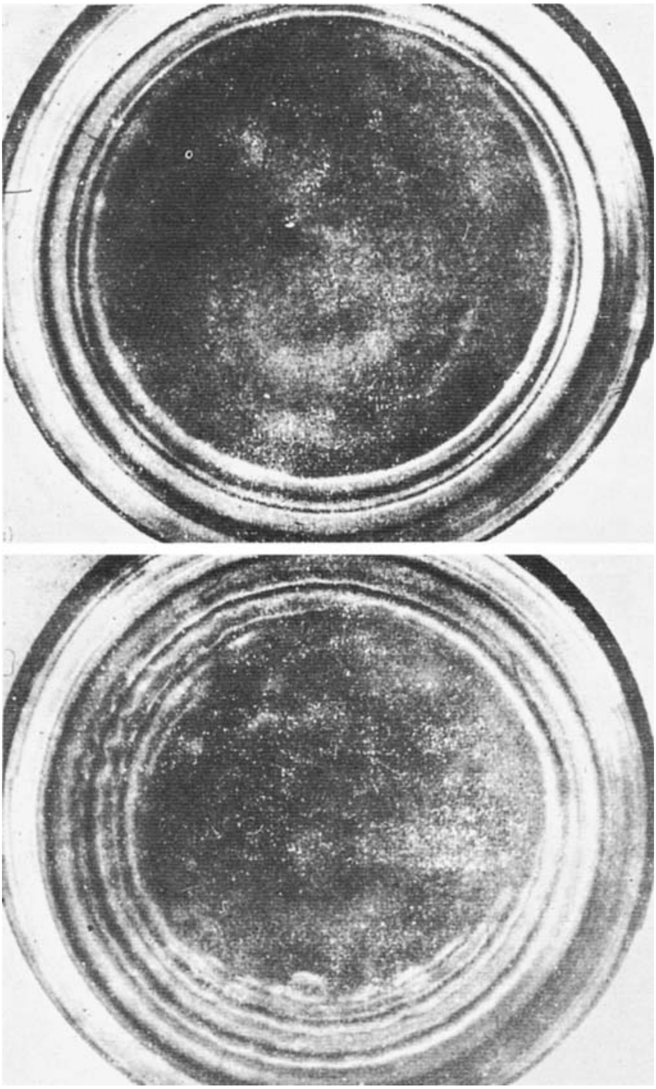


FIG. 1.—The development of the Bénard phenomenon, early stage (from John I. Gmitro and L. E. Scriven, "A Physicochemical Basis for Pattern and Rhythm," in *Intracellular Transport,* ed. Katherine Brehme Warren, Symposia of the International Society for Cell Biology, vol. 5 [New York: Academic Press, 1966], p. 222; by permission of E. L. Koschmieder and Academic Press).

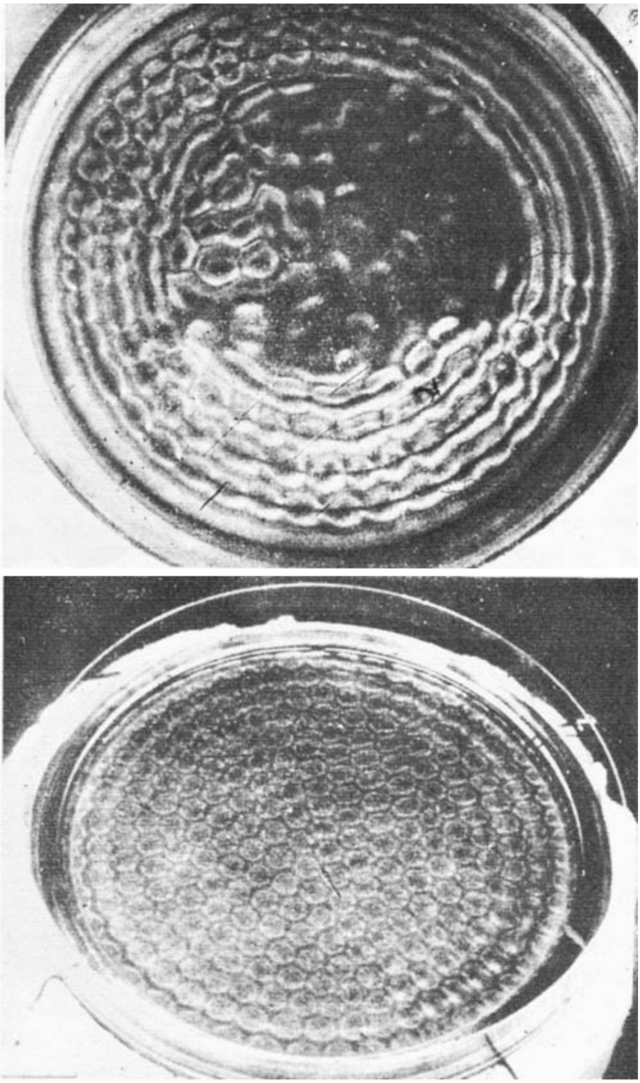


FIG. 2.—The development of the Bénard phenomenon, advanced stage (from John I. Gmitro and L. E. Scriven, "A Physicochemical Basis for Pattern and Rhythm," in *Intracellular Transport,* ed. Katherine Brehme Warren, Symposia of the International Society for Cell Biology, vol. 5 [New York: Academic Press, 1966], p. 223; by permission of E. L. Koschmieder and Academic Press).

the seventy-year-old Lord Rayleigh, who recognized that the pattern is due to the interaction of two flows: the heating of the bottom of the dish establishes an upward heat flow which tries to *destabilize* the system; but since the liquid at the hotter bottom of the dish has a lower density than the liquid at the cooler surface, a convection current arises which attempts to stabilize the behavior and to moderate the effect of the heat flow. Indeed, each volume cylinder, seen as a circle in the surface of the honeycomb structure, represents a flow circulation as shown in figure 3. Thus, the flow pattern is a compromise between stabilizing and transforming factors which maintain a balanced existence within a narrow temperature range.

Other flow structures are known to the hydrodynamicist—but all of them have some common characteristics: they survive only on energy input which is dissipated in the maintenance of structure. Hence, it is appropriate to denote them according to Prigogine as "dissipative structures."[13] It is in this dissipation that the flow patterns differ from "equilibrium structures"—such as the furniture in this room—which do not require energy investment, are based on strong bonds, and are more stable at low tempartures. The dissipative structure may sometimes be fixed by the development of covalent bonds or by crystallization; the initial realm of their stability is, however, always limited, and the depletion of energy input is generally destabilizing.

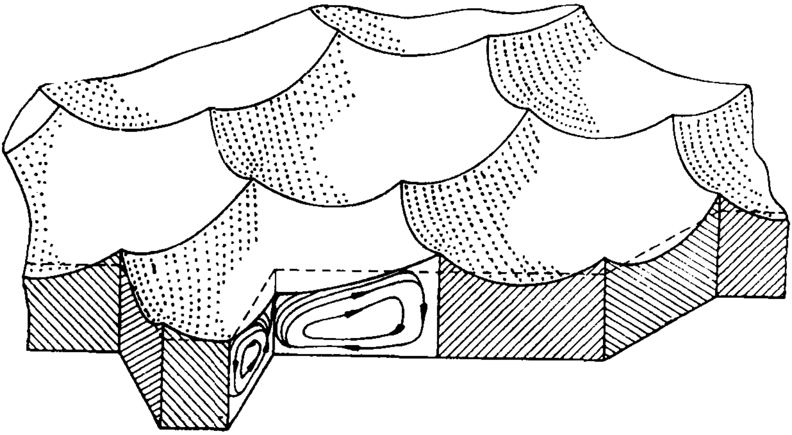


FIG. 3.—Schematic diagram of Bénard cells showing streamlines of flow within a cell (from John I. Gmitro and L. E. Scriven, "A Physicochemical Basis for Pattern and Rhythm," in *Intracellular Transport*, ed. Katherine Brehme Warren, Symposia of the International Society for Cell Biology, vol. 5 [New York: Academic Press, 1966], p. 225; by permission of the authors and Academic Press).

There are such close similarities between the behavior of dissipative structures and the properties of living organisms that it is intriguing to look also for patterns based on interaction of flow in biological systems. On a priori grounds it is clear that the "flows" of interest cannot be heat flows and rarely convection flows. Plausible flows would be the rates of coupled chemical reactions and diffusional propagation, so that our next step will be to consider dissipative structures based on biologically valid processes.

Several decades ago, Lotka in the United States and Volterra in Italy predicted the possibility of a symmetry-breaking mechanism for coupled chemical reactions.[14] They came to the conclusion that processes in which the product of reaction of one process is a reactant for another may enter an oscillatory regime and thereby get rid of the homogeneous behavior *in time*. Indeed, Volterra's model was based on analysis of the fluctuation in the number of edible fish (x) in the Adriatic Sea. If this number is regulated by fish of prey (y) whose reproduction is out of phase with the edible fish, the system will be governed by the nonlinear system of equations

$$dx/dt = k_1 x - k_2 \cdot xy \; ; \quad dy/dt = k_2 \cdot xy - k_3 y \, , \qquad (1)$$

which represents a periodic oscillation. The values of x and y may represent also chemical species participating in coupled reactions so that equation (1) would in principle describe a chemical oscillation. For many years, however, nobody succeeded in translating the equation into a real process which would simulate a biological clock and would represent a flow structure in time.

In 1964 Britton Chance and his co-workers[15] succeeded in isolating from the glycolytic cycle a set of enzymes which showed a clear-cut oscillatory behavior. The process is demonstrable in a lucid manner in the periodic transition of DPNH to DPN accompanying the glycolysis of trehalose by the enzymes of *Saccharomyces carlsbergensis*.[16] It was further studied theoretically by Sel'kov,[17] who showed that the oscillation is based on the fact that the main enzyme involved in the process—phosphofructokinase—is an allosteric enzyme, activated by the products of the reaction (ADP and fructose diphosphate) and inhibited by an excess of the reactant (ATP).

While the first time-dependent structure has been isolated from living cells, Zhabotinsky in Russia[18] discovered a simple man-made system which can be readily studied in any laboratory and may be used as a student demonstration for chemical clocks. Zhabotinsky's reaction is an oxidation of some organic acids, such as citric, malonic, or bromomalonic, by potassium bromate in a solution of strong sulfuric acid (3*N*). To make the reaction progress, catalytic quantities of cerium sulfate [$Ce_2(SO_4)_3$] were added (10^{-3} mol). Now the catalytic action is based on the fact that the Ce^{3+} ion is oxidized first by the BrO_3^- to a tetravalent ion Ce^{4+}, and it is this ion which oxidizes the malonic acid and reverts to its original trivalent state. Schematically, the catalyst participates in two coupled reactions

$$Ce^{3+} \xrightarrow{KB_rO_3} Ce^{4+} \quad \text{and} \quad Ce^{4+} \xrightarrow{\text{malonate}} Ce^{3+} ,$$

and, since the reactions are out of phase, an oscillation develops which is easily followed spectroscopically. Since at 3,650 Å, Ce^{4+} absorbs strongly while Ce^{3+} does not absorb any ultraviolet light, the process observed spectroscopically is as shown in figure 4. Since Zhabotinsky's process is strongly temperature dependent, it is not a real model for biological clocks, which are only slightly dependent on *T*. It is, however, an important introduction to chemical dissipative structures and deserves further consideration. As shown by Zhabotinsky and his colleagues, the range of oscillatory phenomena is limited to a certain

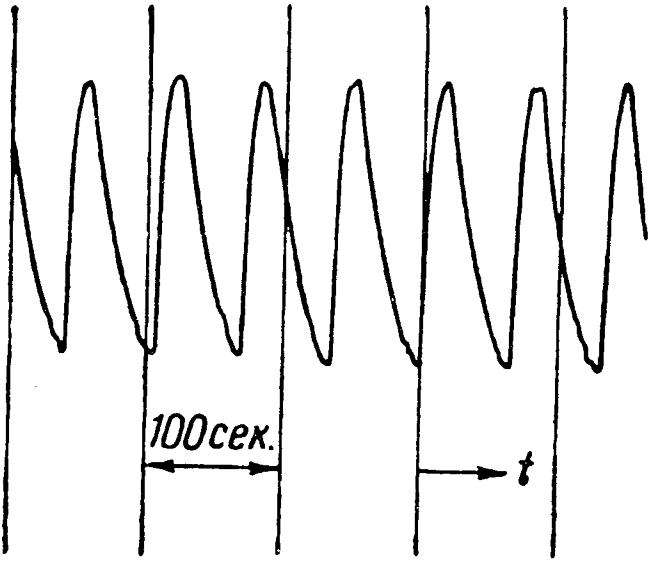


FIG. 4.—The oscillation of light absorption (wavelength 3,650 Å) caused by the concentration oscillation of cerium ions Ce^{4+} (from A. M. Zhabotinsky, *Oscillatory Processes in Biological and Chemical Systems* [Symposium in Puschtchino-na-Oke, March 21–26, 1966] [Moscow: Nauka, 1967]).

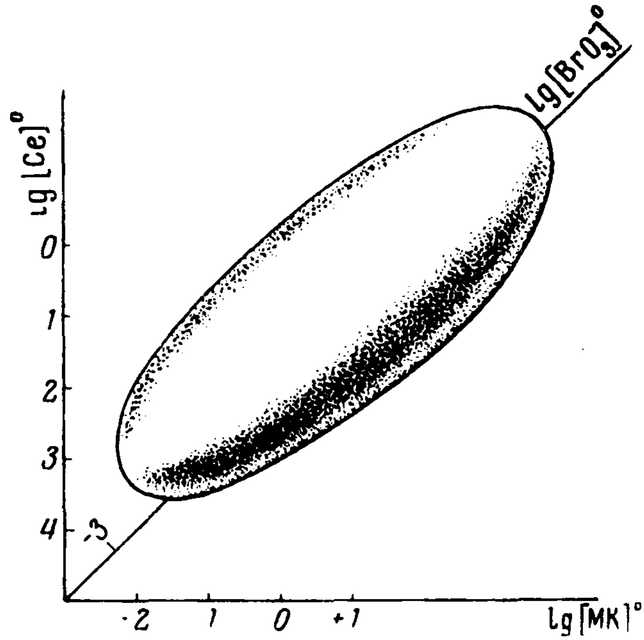


Fig. 5.—The realm of the oscillatory regime in the space of the initial concentration of cerium, malonic acid, and bromide.

realm of concentrations, as shown in figure 5. Thus, the first condition for structures dependent on energy supply is fulfilled by this experiment. There was, however, another striking finding which provides a bridge between the oscillatory properties and geometrical patterns of the Bénard type: it was observed in Russia, and corroborated by Prigogine's group in Brussels,[19] that oscillation in time is obtained only when the solution is stirred; if the reaction mixture in a test tube is left undisturbed, the catalyst establishes a layer structure, with layers of trivalent cerium alternating with those of the tetravalent. Thus, the full-fledged dissipative structure is a tetra-dimensional pattern in both time and space. By choosing the experimental conditions, we may observe either the oscillation in time or the regular organization in space. This interesting discovery leads us to the major theoretical paper published in 1952 by A. M. Turing,[20] a paper the title of which envisions the ability of chemical processes to structure matter in morphogenetic patterns.

"The Chemical Basis of Morphogenesis"

To appreciate the significance of Turing's work we must look again at stationary states. It will be recalled that any system left to age without the interference of external forces ultimately reaches a state of thermodynamic equilibrium. If, however, some constant forces continue to operate on the system, the aging process will lead not to an equilibrium but to a steady state. When stationarity is reached, fluxes will continue to flow in the system but their effect will be such that the local parameters of state, such as local temperatures, concentrations, or pressures, will not change with time. Since systems evolve spontaneously toward stationary states, the general feeling was that stationary states are *stable*. Indeed, some ten years ago Prigogine[21] showed that stationary states close to equilibrium are stable in regard to fluctuations; that is, if a small perturbation acts on a steady system, forces develop which bring the system back to stationarity. Moreover, he was able to show that quasi-equilibrium stationary states obey a variational principle, namely, that entropy produced by a steady system is minimal as compared with all nonsteady neighboring states.

For several years, the principle of minimum entropy production gave the impression of being a major physical foundation for the phenomenon of life. It is well known that physical sciences are strongly attracted to variational principles; already in the seventeenth century Maupertuis declared that the fact that all mechanical movements follow the principle of least action is the experimental proof that the universe is governed by a divine mathematical wisdom. Despite all criticism, variational principles retained their importance throughout the ages, and, as pointed out by Max Planck, the principle of least action proved in both relativity theory and quantum mechanics to be more powerful than the parent equations of Newton. Now the search for a variational principle underlying biology is quite natural, and the belief that biological systems develop toward a steady state made the principle of minimum entropy production a major highlight in the theoretical study of life. There were two reasons which favored its acceptance: on the one hand, most organisms are endowed with homeostatic mechanisms for maintaining an approximately stationary state, and, on the other, the minimization of entropy production was eminently reasonable. Everyone is aware of the fact that life is an antientropic struggle against the dissipative forces of nature. Since all real processes require, however, a positive production of entropy, life has chosen the least evil—it produces entropy at the lowest rate.

The trouble with this fine principle is that it holds only close to equilibrium, while living beings are always far from equilibrium. And it is here that Turing presented his crucial question: are *all* stationary states really stable, or can we envisage unstable stationary states in a region far from equilibrium?

To answer the question, Turing investigated a simple model of reaction and diffusion which we shall discuss in some detail. The simplest case consists of two cells connected by a permeable wall. In each cell, a chemical reaction takes place in which x is converted into y according to the fictitious mechanism

$$dx/dt = 5x - 6y + 1 \; ; \quad dy/dt = 6x - 7y + 1 \, . \tag{2}$$

Moreover, x can diffuse from cell 1 to cell 2 according to the rate process $-0.5(x_1 - x_2)$ while y diffuses out from 1 to 2 according to the rate process $-4.5(y_1 - y_2)$. Thus, the total change in the contents of, say, cell 1 is

$$\begin{aligned} dx_1/dt &= 5x_1 - 6y_1 + 1 - 0.5(x_1 - x_2) \, , \\ dy_1/dt &= 6x_1 - 7y_1 + 1 - 4.5(y_1 - y_2) \end{aligned} \tag{3}$$

(see fig. 6). It is readily seen that for $x_1 = x_2 = 1$ and $y_1 = y_2 = 1$, that is, for a homogeneous distribution of matter,

$$dx_1/dt = 0 \quad \text{and} \quad dy_1/dt = 0 \, .$$

Since x_1 and y_1 do not change with time, the state is steady and may remain so ad infinitum if no random fluctuation occurs which might shift x or y from one cell into another. If, however, a fluctuation of a few percent occurs, a rather important change will take place in the

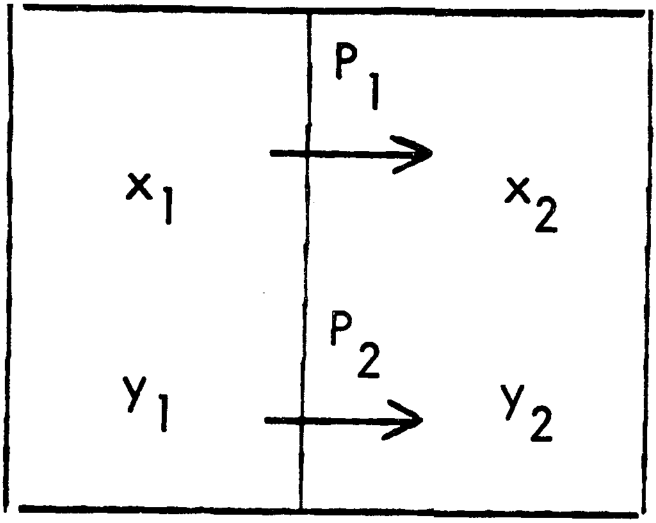


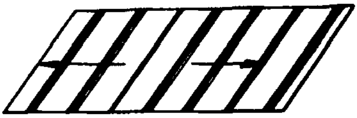
FIG. 6.—Two communicating reaction boxes for the demonstration of the Turing phenomenon. $P_1 = 0.5$, *permeability coefficient of the x-component*; $P_2 = 4.5$, permeability coefficient of the y-component.

system. Consider, for example, a shift of x_1 from 1 to 1.06 and of y_1 from 1 to 1.02. Since the total amount of matter in both cells is constant, x_2 will change from 1 to 0.94 and y_2 from 1 to 0.98. Inserting the new values into equations (3), we find that $dx_1/dt = 0.12$ and $dy_1/dt = 0.04$. This means that a positive fluctuation in x_1 and y_1 does not result in a negative value of the derivatives with time but in the opposite: both dx_1/dt and $dy_1/dt > 0$, that is, x_1 and y_1 will continue to increase, the amount of matter in cell 1 will rise, while the amount in cell 2 will fall, until a new steady state is established. Thus, the intial homogeneous steady state is unstable and the system will develop spontaneously toward a nonhomogeneous stable steady state. Or, in Turing's words, "A system although it may originally be quite homogeneous may later develop a pattern or structure due to an instability of the homogeneous equilibrium, which is triggered off by random disturbances."[22] Thus, Turing's work is a forecast of Zhabotinsky's dissipative space structure mentioned above.

It seems that the theoreticians of chemical engineering were the first to recognize the importance of Turing's considerations for the interpretation of the instabilities which develop in technical systems and for the practical utilization of dissipative strucures. Since engineering systems are generally continuous, there is no need to treat them as a sequence of discontinuous cells, but it is possible to obtain the spatial distribution of matter by the solution of the continuity equation as applied to a system of coupled reactions. Some of the solutions obtained by Scriven and his colleagues are given in figures 7 and 8. It will be observed that the patterns developing under given boundary conditions are truly morphogenetic and comply with Turing's prediction that the interaction of diffusional and chemical flows leads to a distribution of substances which might play an important role in the processes of differentiation and morphogenesis.

For our purpose, however, there is a special interest in the work of Prigogine and his school.[23] Prigogine recognized that the destabilizing factor in Turing's model is an autocatalytic process and that the fictitious scheme (eq. [3]) could be brought closer to reality by writing a more plausible sequence of reaction, such as that give in equation (4):

$$\begin{array}{cl} A \rightarrow X & \\ 2X + Y \rightarrow 3X & \text{which is the autocatalytic step,} \\ B + X \rightarrow Y + D & X \text{ and } Y \text{ are intermediates,} \\ X \rightarrow E & \\ \hline A + B \rightarrow D + E & \text{overall reaction scheme.} \end{array} \tag{4}$$



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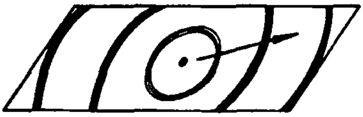
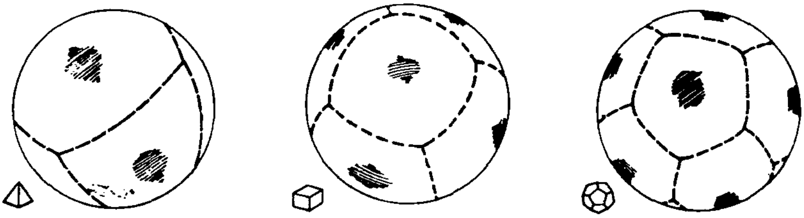


POINT SOURCE

Lineal and circular waves propagating on a plane.



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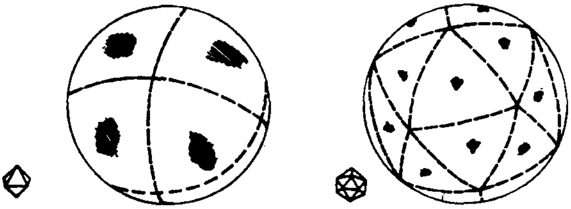

OCTAHEDRAL ICOSAHEDRAL

Fig. 7.—Dissipative structures developing on different geometrical bodies (from John I. Gmitro and L. E. Scriven, "A Physicochemical Basis for Pattern and Rhythm," in *Intracellular Transport*, ed. Katherine Brehme Warren, Symposia of the International Society for Cell Biology, vol. 5 [New York: Academic Press, 1966], p. 250; by permission of the authors and Academic Press).

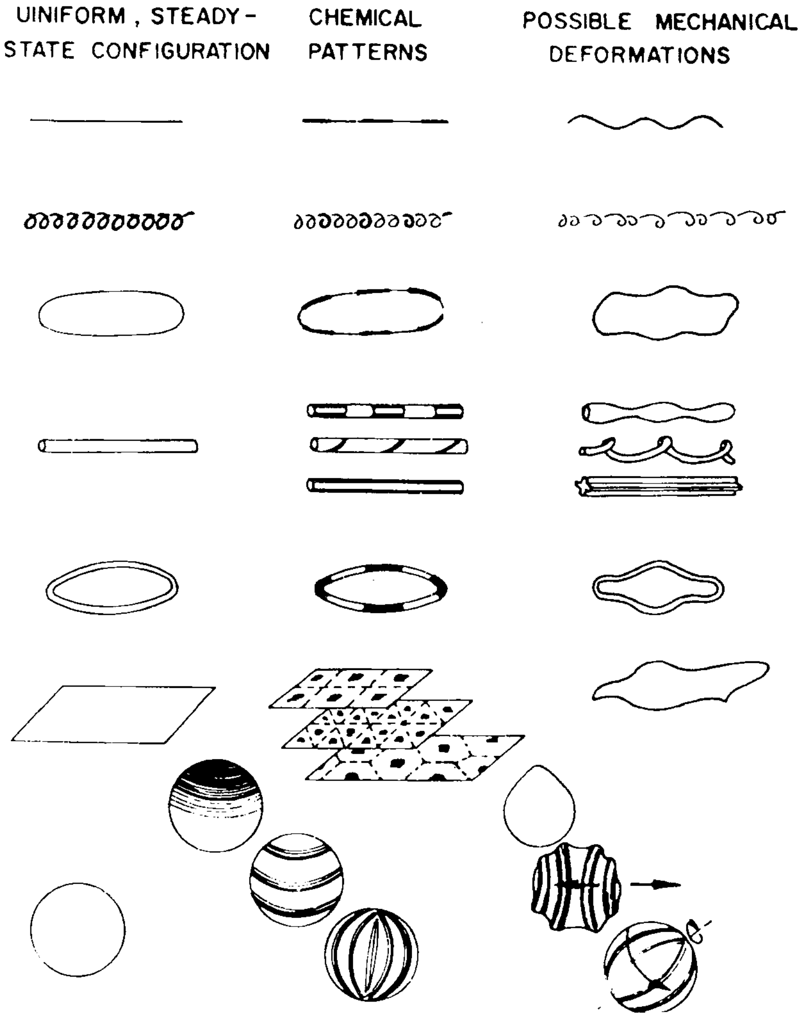

Fig. 8.—Dissipative structures in media which develop mechanochemical patterns (from John I. Gmitro and L. E. Scriven, "A Physicochemical Basis for Pattern and Rhythm," in *Intracellular Transport,* ed. Katherine Brehme Warren, Symposia of the International Society for Cell Biology, vol. 5 [New York: Academic Press, 1966], p. 249; by permission of the authors and Academic Press).

In this model the reactant *A* is kept constant by an external supply, as are the reaction products *D* and *E,* which are removed at a constant rate. The variable of the process is the reactant *B,* the concentration of which determines the amounts of *X* and *Y* formed in the process.

Now, if a set of equations for reaction and diffusion is written, it is found that for small values of B there are single stationary values of X and Y corresponding to B. At a given critical concentration, B_{crit}, however, there is a split and for each value of B two stationary values x and y can be evaluated, indicating a breakdown of symmetry and the formation of dissipative structures (fig. 9). Closer inspection of the results reveals that, in addition to the flow separation of material, not every solution is stable. All values of X and Y close to equilibrium represent stable solutions; on the other hand, values of X and Y corresponding to B's larger than B_{crit} may be either stable or unstable (see dashed regions in fig. 9).

By applying thermodynamic criteria of stability, it was possible to identify the first stable region, beyond the realm of quasi-equilibrium phenomena. It is, however, intriguing to speculate that further from equilibrium, in the far range of nonlinear phenomena, there exist still other stable stationary states the structures of which are as yet unknown. Moreover, if such a discrete spectrum of stable states exists, it

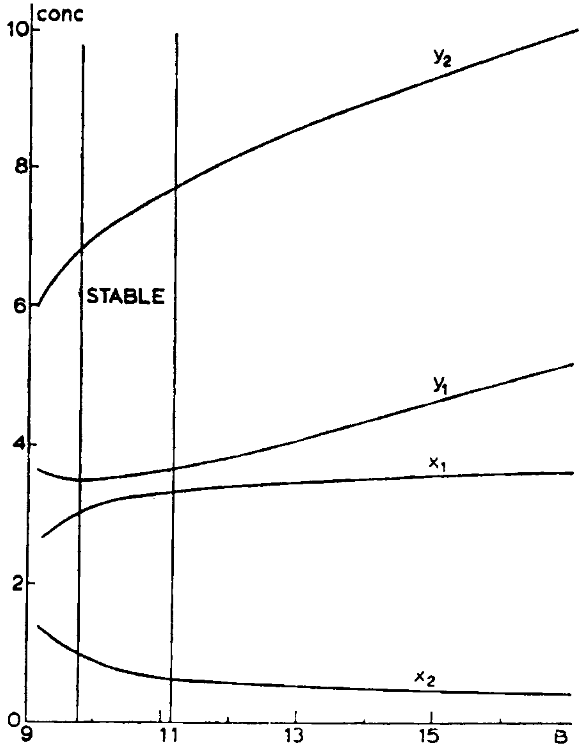

FIG. 9.—Steady states for systems beyond the critical point

may underlie the discontinuous transition from one dissipative structure to another accompanying input of energy. As we shall see below, in biological structures, the discontinuous jump from one level of organization to another is of frequent occurrence, and it is intriguing to speculate that the stratified stability of the levels is the basis of the organizational transitions.

BIOLOGICAL AND PREBIOLOGICAL DEMONSTRATION

The existence of morphogenetic patterns of the Bénard type has been recently demonstrated in various branches of biology. Rather striking is the organization of various microorganisms in honeycomb structures, as shown, for example, by the growth of *Euglena viridis* in shallow dishes (fig. 10).[24] If the protozoan is grown in tubes, a wave structure similar to the Bénard pattern develops. Similar patterns of organization were observed in the Tetrahymena and in the larvae of the sea urchin *Arbacia*.[25] The study of Loefer and Mefferd[26] revealed the remarkable fact that the pattern is independent of pH, of temperature, or of osmotic pressure, of surface tension, of the viscosity of

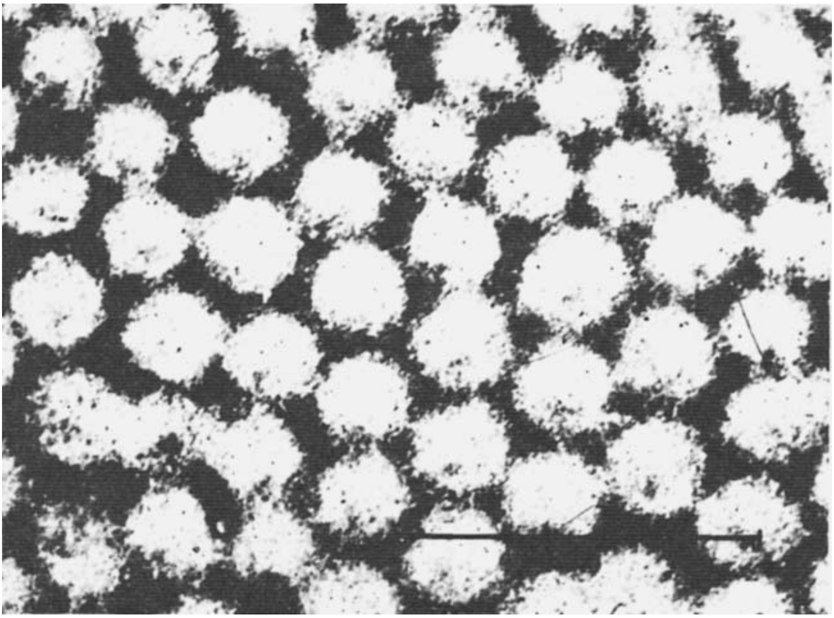

FIG. 10.—Two-dimensional pattern of *Euglena gracilis* (from Klaus Brinkmann, "An Phasengrenzen induzierte ein- und zweidimensionale Kristallmuster in Kulturen von *Euglena gracilis*," *Zeitschrift für Pflanzenphysiologie* 59 [1968]:368; by permission of Gustav Fischer Verlag).

the medium, or the age of the organism. There is, however, little doubt that it is a coupling of flows which leads to these dissipative structures, and a recent study of Hartman[27] indicates that the causative agents in the case of Tetrahymena are flows of carbon dioxide and ammonia. The metabolic liberation of CO_2 acts as an attractive agent, or as a positive chemotactic reagent, which causes aggregation of the cells. With cell accumulation, the local CO_2 concentration increases so that the chemotaxis is autocatalytic. The process is, however, moderated by the liberation of NH_3, which repels the microorganisms and tends to homogenize their concentration. Thus, the formation of pattern is similar to the interaction of a transforming heat flow and a moderating convection flow in the Bénard case, only here the equivalent flows are those of chemical metabolic products.

Recently, Keller and Segel[28] carried out a fine analysis of the experimental results of Bonner and his co-workers on the initiation of the formation of a multicellular fruiting body in the slime mold *Acrasia*. The transition takes place from the freely moving amoebae produced in the germination step which are first homogeneously dispersed in the growth medium; subsequently they aggregate, however, in collection points and form multicellular structures. Here, too, there is a good indication that the organizational process is due to the nonlinear interaction of an autocatalytic attractive step and a moderating step out of phase with the transforming step. There is substantial evidence that the positive chemotactic agent is acrasin (presumably cyclic 3′-5′ AMP), counteracted by the action of the enzyme acrasinase, which splits acrasin.

The field is, however, still open for a fuller study of the morphogenetic processes within the cells themselves. All morphogenesis starts, of course, on the fixed equilibrium structures whose coded organization represents the history of the species. But the genes may serve as centers for the development of chemicodiffusional processes which interact in the far-from-equilibrium range and form transient dissipative structures underlying cellular growth and differentiation. A promising study in this direction was carried out by my colleague R. Blumenthal with P. Changeux and R. Lefever.[29] This work treats the excitability of nerve membranes from the point of view of comparative transitions of "protomeric units" comprising the membrane. It was shown that the resting state of an excitable membrane corresponds to a far-from-equilibrium stable organization beyond a dissipative instability. Excitation follows a small perturbation which causes the system to jump from a higher energy level to another structure—close to equilibrium. The quantitative treatment shows that the "assisted phase transition" of the membrane structures exhibits most of the properties of nerve behavior.

In concluding this section it is worth mentioning that dissipative structures seem to govern also some of the prebiotic processes which lead to the primeval synthesis of high polypeptides and proteins. Over several years my co-worker M. Horowitz and I studied the polycondensation of amino-acid adenylates under physiological conditions, that is, in aqueous media, at neutral pH, and at room temperature.[30] The adenylates were chosen since they constitute the first activated form of the amino acids participating in normal protein synthesis and since, as shown by us, they can form spontaneously under the conditions of a primeval sea from the ATP and amino acid which form prebiotically. For a long time the polycondensation led only to low molecular polypeptides—of some four to eight amino acids which did not look like promising candidates for primeval proteins. However, when we added a special kind of clay—montmorillonite—very high polypeptides of chains of up to forty-eight amino acids formed rather rapidly according to the scheme of figure 11.[31] Moreover, as we found

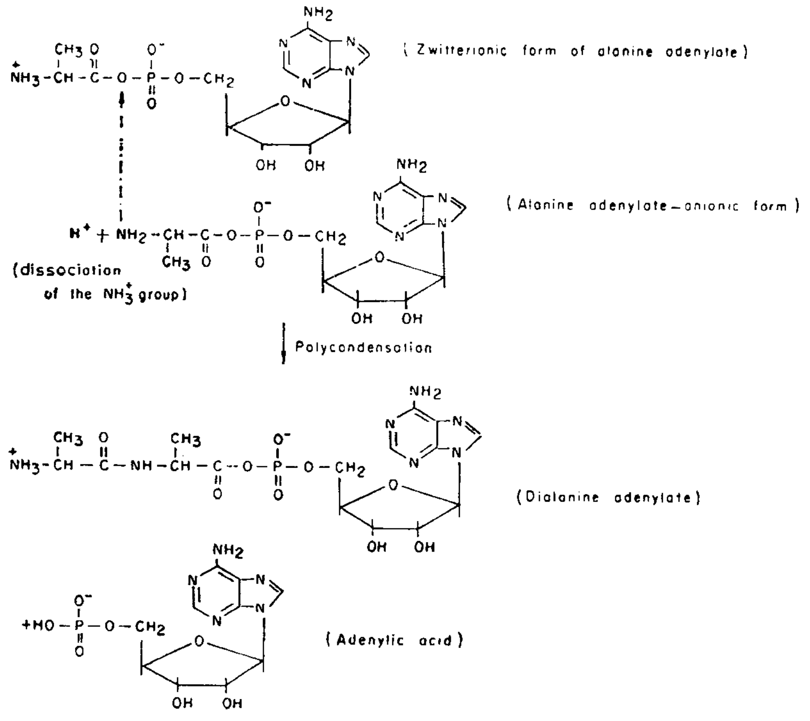

FIG. 11.—The polycondensation of alanyl-adenylate

recently, there is even no need to start the process with amino-acid adenylates, for if a mixture of two clays—the permutites and montmorillonites—is added to the aqueous medium, it is possible to start the processes with an amino acid and ATP, which combine and subsequently form long polypeptide chains. To be sure, the choice of clay as heterogeneous catalyst was dictated by the biblical statement that life started from the clay of the earth, but it has, however, the authoritative support of J. D. Bernal,[32] who stated as far back as 1948 that clays are the most probable absorption and accumulation sites and the protective agents for the primeval synthesis of the biopolymers.

A closer inspection of the polypeptides formed in the process revealed a rather peculiar distribution of their molecular weights. It was found that the chain lengths are not distributed continuously in a Poissonian or Gaussian pattern, but constitute a discrete spectrum, as shown in figure 12. This distribution is most probably due to the cooperation of diffusion and polycondensation which leads to the establishment of a dissipative periodic structure on the surface of the clay particles, and it is this structure which is fixed in the spectrum of molecular weights. The fact that the distribution is not continuous provides a mechanism of selectivity and of choice for the right chain length. Since selectivity is one of the foremost requirements of living

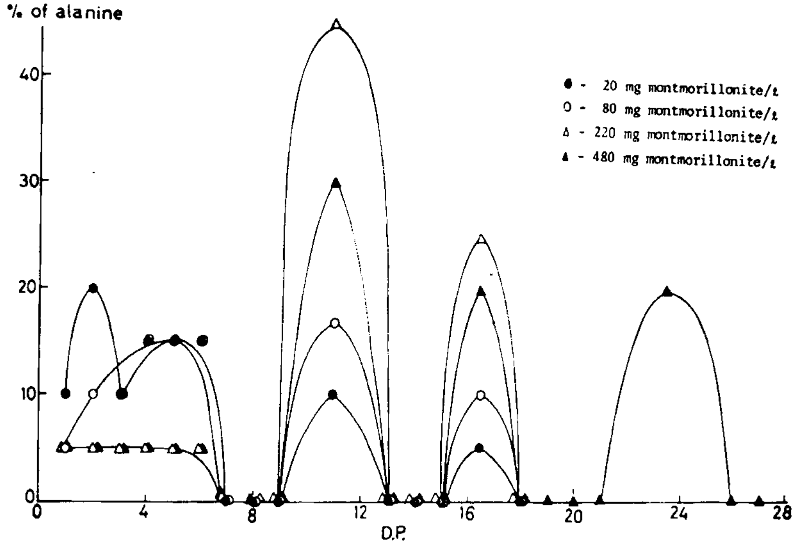

FIG. 12.—Distribution of the molecular weights of polyalanines, obtained when alanine-adenylate is introduced into an aqueous solution at pH 8.5 in the presence of various amounts of montmorillonite.

organization, it is of some interest that dissipative polymerization is endowed with the ability to isolate polymers of given properties.

CONCLUDING REMARKS

There are several striking similarities between dissipative structures and living systems. The very fact that the spatial organization of a dissipative structure is based on the interaction of coupled flows suggests that it is an elementary case of the biological identity between function and organization, in which function is not the product of structure but is another expression of living texture. Moreover, the phenomenon of life is maintained on energy input, and dissipation accompanies every aspect of active maintenance. It should be realized that, beneath the dynamic organization of cells, there exists in addition the hidden framework of a permanent structural setup. It is well known, for instance, that bacterial cells may be desiccated under the condition of high vacuum and liquid-air temperature to a dry lyophilized powder. The bacterial powder has no metabolic activity and is dead to all intents and purposes, except that when water is added and the temperature is raised, the cells revive and begin to metabolize and reproduce. Living cells are therefore not only loose dissipative structures in the continuous medium of a test tube, but a *dynamic pattern* superimposed on a *fixed network,* the organization of which is dictated by the genetic code. Thus, the flow structures of cells are confined to preordained limits which represent the evolutionary history of the species.

Within these limits, however, the characteristics of dissipative organization are clearly discernible. An important fact is that, in a manner similar to that described previously for dissipative processes, life has sharp upper and lower boundaries. When the boundaries are crossed, rapid death ensues, as is shown for instance in the mortality curves for marine algae found by A. Thorhaug.[33] Although slow death may be caused by a gradual accumulation of mistakes, the sharp transitions, shown in figure 13, indicate an unstable transition from one pattern to another, from living to dead matter.

It is interesting to speculate whether the jump from a lower to a higher level of organization across a range of instability can be assumed to be basic to biological evolution also. Thus, the accumulation of micromutations within a species, as the accumulation of mistakes in an individual organism, is generally insufficent to shift a species from one level to another. The evolution of species seems to be a sequence of larger jumps in a discontinuous spectrum similar to the transition spectrum of dissipative structures. Thus, the accumula-

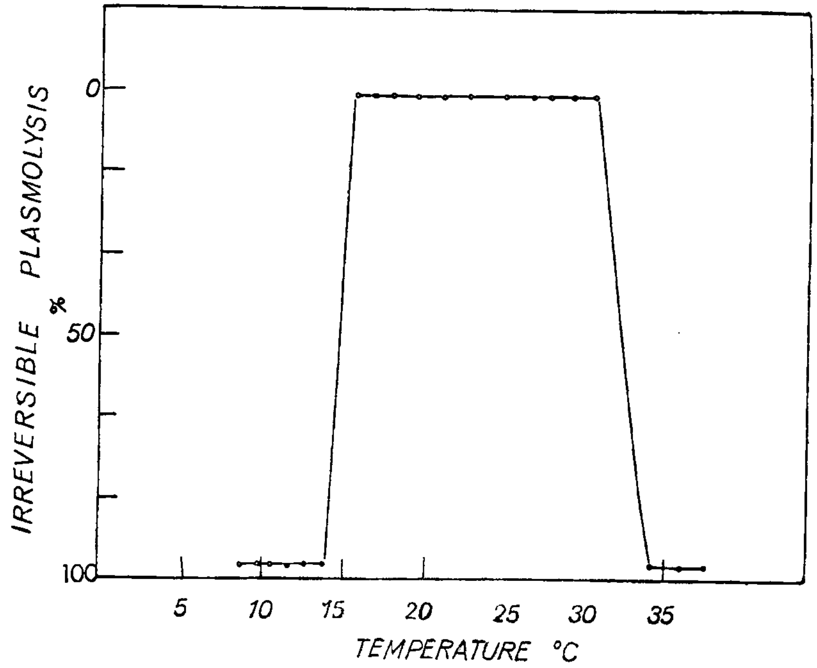

FIG. 13.—Percentage irreversible plasmolysis versus temperature for *Valonia macrophysa* exposed to the given temperature for three days. Each point represents the mean of twelve cells.

tion of micromutations would act as a destabilizing factor which disturbs the fine balance of the flow process, creating a tension within an existing flow pattern and, when stability is fully undermined, leading to a finite jump to a new organizational setup; to use the expression of J. Bronowski in a recent article, life comprises hidden strata of stability, one above the other, and the evolutionary process consists in the climbing up the strata one by one.[34]

For the purpose of our discussion, there is a special interest in the discontinuous transitions accompanying the formation of new brain patterns leading from animal to man and underlying the development of intellectual and moral capacity. I am well aware of the danger of projecting the concepts of one discipline into another and of using analogies instead of careful analysis of the system under consideration. For instance, "evolution" and "relativity" have been misused so often that there is no need to add "dissipative structures" and "discontinuous jumps" to the vague vocabulary of those speakers looking to natural sciences for authoritative support. There is, however, a deeper justification for the use of the notions developed above also in the sociopsychological domain. In the study of abstract customs, it was shown that, in addition to the macroscopic flows of thermodynamics, it is possible that nonphysical *flows of information* are also comprised and that these may participate in the establishment of new patterns.

Thus, the general conceptual framework holds also in a wider domain of phenomena which have a bearing on man and his development. Several anthropologists have indeed indicated that the very transition from the "animal" to the "human" was not a continuous process but a jump toward a *"Homo symbolicus."* As pointed out by Leslie White, the ontogenetic counterpart of the phylogenetic processes came to a clear expression in the development of Helen Keller. According to the report of Anne Sullivan, young Helen lived for several years in a quasi-animal state; and although she started to grasp the significance of concepts, these did not unite into a single structure. The transition to an intelligent human being came suddenly, in a critical transition which endowed Helen Keller with her pronounced human characteristics. Indeed, the profound studies of Jean Piaget[35] on the process of intellectual growth of children lend strong support to the belief that the process is a step function, a series of transitions from one hierarchical level of mental organization to another, a set of irreversible jumps toward the sophisticated pattern of high intellectual activity.

The recognition of the intellectual and moral structures of the mature personality is the road to self-recognition and a fulfillment of the dictum of the Pythia of Delphi—"Gnothi seauton."[36] Here the scientific analysis of macroscopic flow phenomena and the study of thermodynamic structures merge with the eternal search for convincing answers regarding the meaning of our life and our position in nature. As pointed out by J. Bruner,[37] it is only within the framework of well-developed intellectual structures that our concepts and strifes gain meaning and can be interpreted. The picture of an infinite spectrum of dissipative intellectual structures indicates, however, that the road never ends and that future patterns which we cannot predict are possible wherein man will find new answers and will experience a higher integration of human and natural phenomena in structures of profounder unity.

NOTES

1. J. Bronowski, *Science and Human Values* (New York: Harper & Bros., 1956).
2. Niels Henrik David Bohr, *Atomic Physics and Human Knowledge* (New York: John Wiley & Sons, 1958); *Essays, 1958–1962, on Atomic Physics and Human Knowledge* (New York: Interscience Publishers, 1963).

3. Ernst Mayr, "Scientific Explanation and Conceptual Framework" (commentary on Garland E. Allen's "Hugo de Vries and the Reception of the 'Mutation Theory' "), *Journal of the History of Biology* 2 (1969): 124.

4. John von Neumann, *The Computer and the Brain* (New Haven, Conn.: Yale University Press, 1958).

5. Cf. Erwin N. Hiebert, "The Uses and Abuses of Thermodynamics in Religion," *Daedalus* 95 (1966): 1046–80.

6. Lars Onsager, "Reciprocal Relations in Irreversible Processes—Part I," *Physical Review* 37 (1931): 405–26; "Reciprocal Relations in Irreversible Processes—Part II," ibid., 38 (1931): 2265–79.

7. S. R. de Groot and P. Mazur, *Non-Equilibrium Thermodynamics* (Amsterdam: North-Holland Publishing Co., 1962).

8. O. Kedem and A. Katchalsky, "A Physical Interpretation of the Phenomenological Coefficients of Membrane Permeability," *Journal of General Physiology* 45 (1961): 143–79; also A. Katchalsky and O. Kedem, "Thermodynamics of Flow Processes in Biological Systems," *Biophysical Journal* 2, no. 2, pt. 2 (1962): 53–78.

9. Recently my co-workers G. Oster and A. Perelson and I have developed a network thermodynamic theory which holds for nonlinear, nonhomogeneous flow systems ("Network Thermodynamics," *Nature,* in press).

10. Herbert Spencer, *First Principles of a New System of Philosophy,* 2d ed. (New York: D. Appleton & Co., 1879).

11. J. R. A. Pearson, "On Convection Cells Induced by Surface Tension," *Journal of Fluid Mechanics* 4 (1958): 489–500.

12. Henri Bénard, "Les tourbillons cellulaires dans une nappe liquide," *Revue générale des sciences pures et appliquées* 11 (1900): 1309–28; "Les tourbillons cellulaires dans une nappe liquide transportant de la chaleur par convection en régime permanent," *Annales de chimie et de physique,* ser. 7, 23 (1901): 62–144.

13. I. Prigogine, "Structure, Dissipation and Life," in *Theoretical Physics and Biology: Proceedings,* ed. M. Marois (Amsterdam: North-Holland Publishing Co., 1969), pp. 23–52.

14. Alfred James Lotka, *Elements of Mathematical Biology* (New York: Dover Publications, 1956); Vito Volterra, *Leçons sur la théorie mathématique de la lutte pour la vie* (Paris: Gauthier-Villars, 1931).

15. B. Chance, R. W. Estabrook, and A. Ghosh, "Damped Sinusoidal Oscillations of Cytoplasmic Reduced Pyridine Nucleotide in Yeast Cells," *Proceedings of the National Academy of Sciences* 51 (1964): 1244–51; Britton Chance, Brigitte Schoener, and Sigrid Elsaesser, "Control of the Waveform of Oscillations of the Reduced Pyridine Nucleotide Level in a Cell-free Extract," *Proceedings of the National Academy of Sciences* 52 (1964): 337–41; Britton Chance, A. Ghosh, J. J. Higgins, and P. K. Maitra, "Cyclic and Oscillatory Responses of Metabolic Pathways Involving Chemical Feedback and Their Computer Representations," *Annals of the New York Academy of Sciences* 115 (1964): 1010–24; Joseph Higgins, "A Chemical Mechanism for Oscillation of Glycolytic Intermediates in Yeast Cells," *Proceedings of the National Academy of Sciences* 51 (1964): 989–94; Joseph Higgins, "Dynamics and Control in Cellular Reactions," in *Control of Energy Metabolism,* ed. Britton Chance et al. (New York: Academic Press, 1965), pp. 13–46.

16. Benno Hess, Karl Brand, and Kendall Pye, "Continuous Oscillations in a Cell-free Extract of *S. Carlsbergensis,*" *Biochemical and Biophysical Research Communications* 23 (1966): 102–10; B. Hess and K. Brand, Abstracts, Third Federation of European Biochemical Societies Meeting, Warsaw, 1966, F108.

17. E. E. Sel'kov, "Self-Oscillations in Glycolysis," *European Journal of Biochemistry* 4 (1968): 79–86.

18. A. M. Zhabotinsky, *Oscillatory Processes in Biological and Chemical Systems,* Symposium in Puschtchino-na-Oke, March 21–26, 1966 (Moscow: Nauka, 1967), pp. 149, 181, 199, 252.

19. I. Prigogine, private communication.

20. A. M. Turing, "The Chemical Basis of Morphogenesis," *Philosophical Transactions of the Royal Society of London* B237 (1952): 37–72.

21. Cf. n. 13.

22. See n. 20 above.

23. R. Lefever, G. Nicolis, and I. Prigogine, "On the Occurrence of Oscillations around the Steady State in Systems of Chemical Reactions Far from Equilibrium," *Journal of Chemical Physics* 47 (1967): 1045–47.

24. Klaus Brinkmann, "An Phasengrenzen induzierte ein- und zweidimensionale Kristallmuster in Kulturen von *Euglena gracilis*," *Zeitschrift für Pflanzenphysiologie* 59 (1968): 364–76.

25. John R. Platt, "'Bioconvection Patterns' in Cultures of Free-swimming Organisms," *Science* 133 (1961): 1766–67.

26. John B. Loefer and Roy B. Mefferd, Jr., "Concerning Pattern Formation by Free-swimming Microorganisms," *American Naturalist* 86 (1952): 325–29.

27. K. B. Hartman, private communication.

28. Evelyn F. Keller and Lee A. Segel, "Initiation of Slime Mold Aggregation Viewed as an Instability," *Journal of Theoretical Biology* 26 (1970): 399–415; John T. Bonner, *The Cellular Slime Molds*, 2d ed. (Princeton, N.J.: Princeton University Press, 1967).

29. Robert Blumenthal, Jean-Pierre Changeux, and René Lefever, "Membrane Excitability and Dissipative Instabilities," *Journal of Membrane Biology* 2 (1970): 351–74.

30. A. Katchalsky and G. Ailam, "Polycondensation of Amino Acid Phosphoanhydrides—Theoretical," *Biochimica et Biophysica Acta* 140 (1967): 1–13; M. Paecht-Horowitz and A. Katchalsky, "Polycondensation of Amino Acid Phosphoanhyrides—Polymerization of Proline Adenylate at Constant Phosphoanhyride Concentration," *Biochimica et Biophysica Acta* 140 (1967): 14–23; R. Levinsohn, M. Paecht-Horowitz, and A. Katchalsky, "Polycondensation of Amino Acid Phosphoanhyrides—Polycondensation of Alanyl Adenylate," *Biochimica et Biophysica Acta* 140 (1967): 24–36.

31. M. Paecht-Horowitz, J. Berger, and A. Katchalsky, "Prebiotic Synthesis of Polypeptides by Heterogeneous Polycondensation of Amino-Acid Adenylates," *Nature* 228 (1970): 636–39.

32. John Desmond Bernal, *The Physical Basis of Life* (London: Routledge & Kegan Paul, 1951).

33. A. Thorhaug, "Thermal Effects on Membrane Phenomena" (Ph.D. diss., University of Miami, Coral Gables, Fla., 1969).

34. J. Bronowski, "New Concepts in the Evolution of Complexity: Stratified Stability and Unbounded Plans," *Zygon* 5 (1970): 34.

35. Jean Piaget, *The Language and Thought of the Child*, 3d ed., trans. Marjorie Gabain (London: Routledge & Kegan Paul, 1959); also, Bärbel Inhelder and Jean Piaget, *The Growth of Logical Thinking from Childhood to Adolescence*, trans. Anne Parsons and Stanley Milgram (New York: Basic Books, 1958).

36. "Know thyself."

37. Jerome S. Bruner et al., *A Study of Thinking* (New York: John Wiley & Sons, 1956); *Studies in Cognitive Growth* (New York: John Wiley & Sons, 1966).