ENTROPY, THE HEART AND THE LIVING SYSTEMS

EDUARDO CÉSARMAN; NORMAN BRACHFELD;
BRUNO ESTAÑOL

ABSTRACT. There is a certain parallelism between the physiologic phenomena of the heart analyzed from the point of view of view of thermodynamics and some aspects of cellular development and evolution. The pumping heart cycles from a biological "active" state during systole to a mechanical "resting" state during diastole. But from a thermodynamic point of view the heart is active during relaxation or diastole and passive during contraction or systole. This profile is similar to that of dividing blastomeres supposing that heart muscle cells have used their developmental trajectory to set up contraction instead of cytokynesis. The diastolic cell would be viewed as being in a relatively immature condition and the systolic one as relatively senescent.

KEY WORDS. Heart, entropy, termodynamics, diastole, systole, muscle, mechanic, electric, metabolic, energy.

It is possible to construct a theory of the cardiac cycle by analyzing its physiologic phenomena from the point of view of thermodynamics (Césarman and Brachefeld, 1976). The theory proposed corresponds to some, as yet unexplored, aspects of the natural behavior of the heart. Classic thermodynamics is applied to the non-living world (Fast, 1970; Fermi, 1956; Grünbaum, 1955); the challenge of biology is to integrate thermodynamics, a discipline that deals with the simplest possible systems, such as ideal gases, with the performance of complex living systems. Today this endeavor is possible because the theoretical instruments exist (Bertalanffy, 1960; Bertalanffy, 1968; Laborit, 1959; Lehninger, 1971; Nicolis and Prigogine, 1977; Schrödinger, 1945; Szent-György, 1957). The distinct property that characterizes living systems, as opposed to non-living things, is their capacity of self-maintenance and self-reproduction. Within the theory of non-equilibrium thermodynamics of irreversible processes in dissipative systems, as well as with information theory and cybernetics (Wiener, 1961), we are capable to simplify our conception of

---

Prolongación Paseo de la Reforma num. 19, 1er piso, México, D. F., 01330, México.
eduardocesarman@hotmail.com

Ludus Vitalis, vol. X, num. 17, 2002, pp. 163-174.

complex systems and to create a new perspective of the cardiac cycle and reach a better understanding of what makes the heart beat.

The heart works continuously to supply oxygen and nutrients to all the body, including the heart itself, and to remove waste. It propels unoxygenated blood to the lungs and delivers oxygenated blood to the peripheral tissues in accordance to their metabolic needs. The heart requires a constant input of energy, ultimately derived from the radiant energy of the sun. This energy is stored and utilized at a relative fixed temperature and pressure. The heart is an aspirating-impelling muscular pump that functions in a highly integrated, near optimal, manner and performs at a high level of mechanical and metabolic efficiency. It is self-regulated by sophisticated control mechanisms. The heart works as the pulsating pump of a highly durable hydraulic system. It has the unique property of transforming chemical energy into work with more efficiency than any machine ever engineered by man (Kolin, 1972).

Traditional physiologic studies of the heart distinguish three qualitatively different processes in each cycle of the heart. These are the mechanic, electric and metabolic transformations. A fourth process can be added: the thermodynamic phenomena that occur in each heart cycle, mainly heat production and entropy changes (Césarman, 1990). By incorporating thermodynamics to the study of the heart beat it is possible to formulate a theory that associates some of the basic laws of nature with those that govern the behavior of the heart.

The most recognizable unique inherent quality of the heart is its mechanical ability. Until recently, diastole and systole were the only terms used to designate the mechanical phases of the heart cycle. The first physiological function of the heart to be studied was its pumping activity. The rhythmic alteration between mechanical contraction and relaxation has long provided the framework for physiological and clinical descriptions of normal and abnormal function (Brutseart and Sys, 1989; Rushmer, 1961; Wiggers, 1950).

The mechanical components of the contraction form but one subsystem in a highly integrated mechano-chemical process. Indeed, this component is in all respects dependent upon another subsystem, the energy-liberating chemical reactor that provides the sources of energy for such contraction. Nonetheless, one may challenge the appropriateness of the terminology applied to the events of myocardial contraction and derived from purely mechanical considerations (Césarman and Brachfeld, 1980; Césarman and Brachfeld, 1981).

The heart may be conceptualized as a thermodynamic system with rhythmic and cyclic contractility, with an input and output of energy and matter that behaves as a dissipative structure. The phases of the cardiac cycle correspond to a continuous alternation between states of uphill decreasing entropy during diastole (thermodynamic activity towards non-equilibrium) and downhill increasing entropy during systole (thermodynamic passivity towards equilibrium). Thus entropy is greatest at peak systole, when the system is furthest removed from its normal thermodynamic non-equilibrium state. Entropy is reduced again during the subsequent diastole and relaxation, when the system regains its thermodynamic non-equilibrium, and excitability is restored. Many properties of the heart are related to these entropy changes (Césarman and Brachfeld, 1977).

The cardiac muscle is an excitable tissue in which impulse formation and mechanical contraction become thermodynamic processes that are invariably accompanied by an increase in entropy. The bioelectric activity and the systolic contraction are a consequence of the previous negentropic diastolic process, during which free energy and information were stored in the system. Although entropy cannot be directly measured in biological systems, the changes in entropy can be estimated by measuring the different forms of energy consumption and production of heat, and evaluating the efficiency of the system.

The heart comprises less than one percent of the body weight, but utilizes one-tenth of the total oxygen and energy consumed. The heart-muscle is an open biological system that is traversed by energy and matter in a cyclical fashion. This inflow of energy and matter results from the coronary blood supply to the heart and the oxygen consumption, which are mostly diastolic events. Thermodynamically, this phasic input of energy and matter maintains the heart at two different levels: an upper steady state during diastole or ventricular relaxation, when the inflow of blood is maximal, and the lower steady state during systole or ventricular contraction, when the inflow of blood is minimal. Any obstacle to a proper supply of oxygen to the heart will make diastolic recovery from systole difficult or, in extreme cases, impossible. If the heart could receive a continuous input of nutrients and oxygen, without the intermittences of systole, it would stay indefinitely in diastole.

The non-lineal cyclic variations of the input and output are governed by complex built-in, closed loop, subsystems of control (Russek and Cabanac, 1983). Thus, the heart oscillates between two possible steady states, the upper diastolic and the lower systolic, with a threshold in each level. These respond to regulatory mechanisms of aperture and closure of the system and to the necessary combinations of negative and positive feedback and feedforward processes. These subsystems maintain the heart open and thermodynamically stable during diastole, and assist the heart in order to recover its diastolic level once it has fallen into the isolated and static equilibrium of systole.

During the mechanical contraction of systole the heart performs exogenous or external work and is integrated as a subsystem of the body. During diastolic muscle relaxation the heart performs endogenous internal reconstructive work and functions as a system-in-itself (Brachfeld and Césarman, 1980). Mechanical and mostly exergonic works predominate in systole while metabolic and mostly biosynthetic and endergonic works predominate in diastole. Fuels are burned in systole and in diastole, but the heart refuels mostly during diastole.

A major conceptual conflict between mechanical and thermodynamic definitions of cardiac function lies in the identification of the resting and active states (Césarman and Brachfeld, 1976). A thermodynamic evaluation requires a revision of many of our concepts of mechanistic cardiac physiology. Thus, the heart may be shown to be thermodynamically active during mechanical relaxation (the diastolic "resting" state) and thermodynamically passive during mechanical contraction (the systolic "active" state). Thermodynamically, the phase of the cardiac cycle that corresponds to mechanical relaxation is actually the most active bioenergetic state of the heart. This is shown by the fact that the heart is excitable only during diastole.

Both diastole and systole tend towards irreversibility, but each one corresponds to a different kind of irreversibility. During diastole, the heart tends to remain in an irreversible far-from-equilibrium (or non-equilibrium) upper stationary steady state with low entropy, while during systole the heart tends to remains in an irreversible close-to-equilibrium lower stationary steady state with high entropy.

The heart will remain stable, at any level, if the input of energy and nutrients remains equivalent to the input of heat, carbon dioxide and water. The heart will become unstable if there is a variation either in the input or the output. The diastolic stability of the heart is broken when there is a closure in the input and the system is "pushed" downwards towards an increase in entropy. On the other hand, the systolic stability of the heart will be broken when the system opens to the flow of energy and nutrients, and is "pulled" upwards towards a decrease in entropy (Césarman, 1991).

The heart will remain in the upper steady state of diastolic non-equilibrium unless a perturbation occurs capable of releasing the stored energy. This perturbation is the stimulus that ignites electrical depolarization towards osmotic equilibrium and starts systolic muscle contraction.

Two critical moments may be identified in each cardiac cycle. One is the beginning of diastole and the other is the beginning of systole (Césarman, 1992). Each of these moments constitutes a turnaround, in the opposite direction, of all the processes that occur during the cardiac cycle.

The beginning of the diastolic process is one of the most intriguing phenomena of the cardiac cycle. It is the moment when the heart opens to energy inflow and is pulled upwards to a higher-level steady state. The maximal aperture of the system, after its relative closure during the previous systole, is the necessary and essential condition for the origin of diastole. With the inflow of energy the heart is ready to perform as a self sustained dissipative thermodynamic system capable of maintaining an upper steady state with dynamic stability. Information makes the beginning of diastole possible. The only way that the myocardial cell can reconstruct itself and recover the upper steady state of diastole is by having information. Without information, left only to chance, it would be statistically most improbable for the diastolic recovery to occur once the heart has reached its maximum level of entropy during the previous peak systole and thermodynamic nadir (Brillouin, 1951; Shannon and Weaver, 1949; Singh, 1946; Tribus and McIrvine, 1971).

The main feature of the beginning of diastole is the change, in an opposite thermodynamic direction, of all the several phenomena that have occurred in the previous systole (Césarman, 1992). From a thermodynamic point of view, the cardiac cycle originates with diastole, and systole occurs as an epiphenomenon of diastole. The first processes to suffer a turnaround, at the origin of diastole, are those related to the initiation of the recovery of the transmembrane osmotic, ionic and electrical gradients. Practically all the duration of the cardiac cycle corresponds to this diastolic uphill, energy-requiring, recovery of the transmembrane gradients and the maintenance of the upper steady state.

Diastole originates: 1) as a transition from a close-to-equilibrium lower stationary and high entropy state, to a far-from-equilibrium upper stationary and low entropy state. 2) With a shift pointing to the use of free energy: from exogenous-mechanically oriented to endogenous-metabolically oriented. 3) As a transition from thermodynamic passivity during mechanical contraction and depolarization, to thermodynamic activity during mechanical relaxation and repolarization. 4) As a self-generated process in which there is a built-up, a loading of the system with energy. Diastole replenishes the energy stores that were depleted during systole.

The recovery period of diastole is a process of self-organization towards the upper steady state in accordance with the non-equilibrium thermodynamics of the irreversible processes. Diastole is analogous, in many ways, to the irreversible and spontaneous tendency of life itself (Césarman, 1993). The beginning of diastole is possible due to self-regulated control mechanisms, while the phenomenon of the origin of life was possible due to self-designed mechanisms and self-evolved processes (Kruger and Kissel, 1989; Salthe, 1991). Trying to understand the biogenesis of diastole is trying to know what makes the heart beat.

The transition from the lower steady state of systole with high entropy (mechanical contraction), to the upper steady state of diastole with low entropy (mechanical relaxation), corresponds to the process of myocardial cell self-organization. The phenomena occurring during the cardiac cycle correspond to a very high scalar level in biological evolution, and they are very distanced, in time and hierarchy, from the phenomena that originated life. Nevertheless, the self-organizing phenomena that occur during diastole are structurally similar to the prebiotic self-organizing processes. The modern concepts dealing with the origin of life and evolution, from the point of view of self-organization, deal with theories such as developmental biology (Blum, 1951; Salthe, 1993), thermodynamics of the irreversible processes (Prigogine and Stengers, 1984), cybernetics and the evolution of biological macromolecules (Küppers, 1987).

Systole is constructed during diastole. The heart will neither become excitable nor contractile until its internal milieu has been restructured. Systole is a transient perturbation of diastole that starts with the ignition of the energy accumulated during diastole. Only by changing its open-system status to a less open or relatively closed-system condition, is it possible for the heart to fall from the upper steady state of diastole to the lower steady state of systole. During systole the heart performs as an isolated system, utilizing its reserves of free energy. The heart would remain mechanically contracted and stable, as long as the system remains isolated, without exchange of energy and matter. Injury and death of the myocardial cells would be the result of a prolonged isolation.

Each beat of the heart is the result of the alternating action of two opposite forces of nature. One is the uphill force against thermodynamic equilibrium and the other is the downhill force towards thermodynamic equilibrium. This can only occur if the heart, during diastole, behaves as an open thermodynamic system and, during systole, as an isolated thermodynamic system. The tendency during diastole is towards an upper steady state with a decrease in entropy and during systole towards a lower steady state with an increase in entropy. Thus, it is convenient to consider as diastolic all the mechanical, metabolic, electric and osmotic processes of the cardiac cycle that accompany the system towards the upper steady state and to consider as systolic these processes when they accompany the system towards the lower steady state.

The heart seems to be an unusual case of hybridism, a system that obeys to different laws of thermodynamics. While at systole the heart behaves as an isolated system that complies with the classical laws of thermodynamics, those that embody the principle of conservation of energy and define the concept of entropy; at diastole a fundamental change occurs when the heart opens and it becomes a system that obeys a different set of laws, those of non-equilibrium thermodynamic for living systems.

In 1989, two physiologists, Dirck Brutsaert and Stanislas Sys, referred to these ideas in a masterful note in an article on the "Relaxation and diastole of the heart":

> The traditional notion that the pumping heart cycles from a biological 'active' state during systole to a biological 'resting' state during diastole is deserving of a critical reexamination. Césarman and Brachfeld correctly recognized that this is a thermodynamic misnomer since the heart may be shown to be thermodynamically active during mechanical relaxation and diastole and thermodynamically passive during contraction. If the pumping heart behaves as a dissipative structure, then entropy would be greatest at peak systole when the system is furthest removed from its normal thermodynamic nonequilibrium state and would be reduced again during relaxation and subsequent diastole when the supersystem regains this nonequilibrium with restoration of maximal excitability. Hence thermodynamically, the true physicochemical driving force of cardiac contractions, or for the performance of external work, is the downhill tendency toward a state in which the entropy of the system is maximized. During the contraction phase, the heart may be thought of as having lost a marked degree of differentiation, contractile integrity, and energy; it has simultaneously increased its degree of randomness and has become unexcitable and more stable of physicochemical equilibrium. At the end of the contraction phase, the heart will not contract again without restoration of membrane excitability and unless the intracellular contractile milieu is restructured by active bioenergetic metabolic processes. Mechanical relaxation corresponds to an uphill thermodynamic process during which entropy decreases and order increases and is actually the bioenergetically most important phase of the cardiac cycle. During subsecuent diastole, the heart has regained a state of maximal differentiation and order, with maximal excitability and maximal capability to perform work. Hence this state of maximal excitability and thermodynamic instability during diastole can hardly be considered as merely "resting"; instead, a constant input of free energy liberated by substrate oxidations is utilized to maintain this high degree of orderliness with minimal entropy production.

Thus it is possible, as I said in the beginning of this work, to construct a physiological cardiac cycle theory from a thermodynamical standpoint that it will answer to yet unexplored heart performances. As for the non-living world application of classical thermodynamics, the question here is to incorporate this discipline to the biological complex system organization.

This attempt is now possible due to several theoretical instruments: Through thermodynamics, information theory and cybernetics we can conceive complex systems and thus create a new frame of the cardiac cycle and comprehend what makes the heart beat.

UPHILL DIASTOLE COMPARED WITH DOWNHILL SYSTOLE

1. *(Diastole)* The cardiac cycle originates at the beginning of diastole.
   (*Systole*) Systole is an epiphenomenon of diastole.
2. *(Diastole)* Mechanical relaxation is the most obvious phenomenon of diastole.
   (Systole) Systole is defined by the mechanical contraction of the heart.
3. *(Diastole)* It is possible to consider "diastolic" all those processes that are related to the mechanical diastole such as the electric, osmotic, metabolic and thermodynamic changes that occur during the cardiac cycle.
   (Systole) It is possible to consider "systolic" all the electric, osmotic, metabolic and thermodynamic processes that coincide with the mechanical contraction of the heart.
4. *(Diastole)* While at diastole there is a prolonged opening to the inflow of energy and matter.
   (Systole) While at systole there is a brief closure to the inflow of energy and matter.
5. *(Diastole)* During diastole the heart captures and stores free energy which is utilized for internal metabolic recovery and maintenance work.
   (Systole) During the mechanical contraction of systole the heart consumes stored free energy.
6. *(Diastole)* Diastole is characterized by self-generated and self-organized internal processes toward replenishment of cellular energy stores and reconstitution of the internal cellular milieu.
   (Systole) Mechanical contraction of systole delivers blood to the heart itself and to the other organs and tissues of the body. It is a form of externally oriented work.
7. *(Diastole)* Free energy is used to reach and preserve optimal transmembrane cation gradients.
   (Systole) During systole there is passive tendency toward transmembrane osmotic equilibrium.
8. *(Diastole)* During diastole muscle relaxation internal energy-requiring work is performed to suppress myosin-actin interaction and pumping calcium back into the sarcoplasmic reticulum.
   (Systole) Systolic electric activation alters membrane permeability to extracellular calcium, releases calcium stored in the sarcoplasmic reticulum.
   Calcium is bound to troponin which permits the interaction between actin and myosin.
9. *(Diastole)* Repolarization and the maintenance of the repolarized state are the electrical manifestations of diastole.

(Systole) Sudden depolarization is the brief electric expression of systole.

10. *(Diastole)* Heat produced during mechanical relaxation is minimal. Metabolic processes of diastole are more efficient than those of systole.
    (Systole) During mechanical contraction free energy is degraded into heat and is dissipated in the surroundings of the system. Systole is less efficient than diastole.
11. *(Diastole)* During diastole there is an uphill decrease in entropy.
    (Systole) During systole there is a downhill increase in entropy.
12. *(Diastole)* Information, as a form of negentropy, makes the beginning of diastole possible. Statistically, the beginning of diastole is a most improbable process to occur spontaneously.
    (Systole) Systole tends to occur spontaneously and does not need information.
    It is, from a statistical point of view, a most probable phenomenon.
13. *(Diastole)* Diastole tends towards a far-from-equilibrium, irreversible higher level state.
    (Systole) Systole tends towards a close-to-equilibrium, irreversible, lower level steady state.
14. *(Diastole)* Excitability begins when metabolic and thermodynamic recovery has been reached.
    (Systole) When the myocardial cell approaches systolic thermodynamic equilibrium it becomes relatively stable and invulnerable. It becomes refractory to stimulation.
15. *(Diastole)* When thermodynamic non-equilibrium is reached, diastole becomes unstable and vulnerable because the heart-as-a-system is "pushed downward" toward thermodynamic equilibrium.
    (Systole) At the end of systole, the system opens to the inflow of free energy.
    It becomes unstable as the system is "pulled upward" toward thermodynamic non-equilibrium.
16. *(Diastole)* Diastole is the active metabolic and thermodynamic process that provides order and prepares the heart for systole.
    (Systole) Systole is the passive thermodynamic process toward a non-ordered and random process.
17. *(Diastole)* During diastole the heart behaves in accordance with the laws of non-equilibrium thermodynamics of the irreversible processes.
    (Systole) During systole the heart behaves in accordance with the laws of classic thermodynamics.

In 1993, Stanley Salthe referred to my ideas on thermodynamics of the cardiac cycle in a scholarly book. I was stimulated to see how these were applied to biology to explain some aspects of cellular development and evolution. Salthe states:

> Césarman (1977,1990) viewed heart muscle cells from the point of view of thermodynamics. On this view diastole is a time when the cell undertakes recovery from systole, a period when it does internal work to replenish its high-energy stores and reestablish its membrane resting potential. At this time of cycling cells, it is open to an inflow of nutrients. In systole, the cell cuts off communication with other cells and expresses 80 percent of its stored high-energy bonds in externally directed mechanical work. More than 75 percent of this energy is released as heat at this time.- Since this energy profile is similar to that of dividing blastomeres, with systole mapping onto cytokinesis, it seems to me that heart muscle cells have used their developmental trajectory to set up contraction instead of cytokinesis. The diastolic cell would be viewed as being in a relatively immature condition and the systolic one as relatively senescent. Such a formulation emphasizes that senescence is not necessarily a terminal situation for a given material system… I am suggesting that the rhythmic contractions are homologous with those of muscle cells.- Along these lines, one can see that the diastolic recovery period is metabolically like growth even though the muscle cell does not physically enlarge.- Final cause, however, because of its unfamiliarity in these contexts, requires careful exploration. In the context of multicellular organisms the cell cycle is enlisted in various functions, any of which could be viewed as a final cause of cell division for each kind of cycling cell, just as the functioning of the heart could be viewed as a final cause of heart muscle contraction. Semiotically, muscle contraction would be an interpretant generated by the organism in one of its interpretations of the cell cycle. In free-living cells, the perpetuation of their kind might be viewed as the final cause of cell division, and as its interpretation.

REFERENCES

Bertalanffy L. (1968), *General System Theory*. New York: G. Braziler.

Bertalanffy, L. (1960), *Problems of Life.* New York: Harpers, Torchbooks.

Blum, H. F. (1951), *Time's Arrow and Evolution.* New York: Princeton University Press.

Brachfeld, N. & Cesarman, E. (1980), "Entropy and the contractile state." *Adv. Myocardiol.* 2, 249.

Brillouin, L. (1951), "Maxwell's demon cannot operate: information and entropy." *J. Appl. Phys.* 22 (I), 334.

Brutsaert, D. L. & Sys, S. U. (1989), "Relaxation and diastole of the heart," *Phys. Rev.* 69, 1228

Césarman, E. (1990), "The four diastoles. A cardiac cycle model," *Acta Cardiol. XLV,* 15.

Césarman, E. (1991), "A theory of the heartbeat. Open diastole and closed systole," *Acta Cardiol. Suppl.* XXX, 9.

Césarman, E. (1992), "The origin of diastole. At the edge of the cardiac cycle," *Acta Cardiol, XLVII,* 205.

Césarman, E. (1993), "Thermodynamic model of the heart. A process of diastolic self-organization," *Ludus Vitalis* I, 47.

Césarman, E. & Brachfeld, N. (1976), *A Redefinition of the Resting State of the Myocardial Cell.* México, D. F.: Pax-México

Césarman, E. & Brachfeld, N. (1980), "Bioenergetics and thermodynamics of the cardiac cycle," in *New Horizons in Cardiovascular Disease. Part I.* Kones, R. J. (ed.). New York-Mount Kisko: Futura.

Césarman, E. & Brachfeld, N. (1981), *Termodinámica del corazón y del cerebro.* México, D. F.: Consejo Nacional de Ciencia y Tecnología.

Césarman, E. & Brachfeld, N. (1977), "Thermodynamics of the myocardical cell: a redefinition of its active and resting status," *Chest* 72, 296.

Fast, J. D. (1970), *Entropy.* London: McMillan.

Fermi, E. (1956), *Thermodynamics.* New York: Dover.

Grünbraum, A. (1955), "Time and entropy," *Am. Sci.* 43, 550.

Kolin, I. (1972), "The evolution of the heat engine," in *Thermodynamics Atlas.* London: E. Longman.

Krueger, F. R. & Kissel, J. (1989), "Biogenesis by cometary grains: thermodynamic aspects of self-organization," *Origins of Life and Evolution of the Biosphere, 19,* 87.

Küppers, B. O. (1987), "Molecular evolution and the origin of life," in *Evolution and Creation.* Andersen, S.& Peacok, A. (eds.) Aarhus.

Laborit, H. (1959), *Stress and Cellular Function.* Philadelphia: J. B. Lippincott.

Lehninger, A. L. (1971), *Biochemistry.* New York: Worth.

Lehninger, A. L. (1971), *Bioenergetics.* San Francisco: Benjamin.

Nicolis, G. & Prigogine, I. (1977), *Self-organization in Non-equilibrium Systems.* New York: John Wiley & Sons.

Prigogine, I. & Stengers, I. (1984), *Order Out of Chaos.* New York: Bantam.

Rushmer, B. F. (1961), *Cardiovascular Dynamics.* Philadelphia: W. B. Saunders.

Russek, M. & Cabanac, M. (1983), *Regulación y control en biología.* México: CNEB-CESSA.

Salthe, S. N. (1991), "Formal considerations on the origin on life," *Uroboros* 1, 44.

Salthe, S. N. (1993), *Development and Evolution. Complexity and Change in Biology.* Cambridge and London: The MIT Press, Bradford Book.

Schrödinger, W. (1945), *What is Life?* New York: MacMillan.

Shannon, C. E. & Weaver, W. (1949), *The Mathematical Theory of Communications.* Urbana: University of Illinois Press.

Singh, J. (1966), *Teoría de la información, del lenguaje y de la cibernética.* Madrid: Alianza.

Szent-György, A. (1957), *Bioenergetics.* New York: Academic Press.

Tribus, M. & McIrvine, E. C. (1971), "Energy and information," *Sci. Am.* 224, 179.

Wiener, N. (1961), *Cybernetics. On Control and Communications in the Animal and the Machine.* Cambridge: MIT Press.

Wiggers, C. L. (1950), *Physiology in Health and Disease*. Philadelphia: Lea & Febiger.