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CONTROL IN BIOLOGICAL SYSTEMS — A PHYSICAL REVIEW*

A. S. Iberall and S. Z. Cardon

~~*Rand Development Corporation, Cleveland, Ohio*~~

This is a physical review and parenthetical commentary on regulation and control in biological systems. Some prior instances of such interdisciplinary efforts are Burton,[1] Adolph,[2] and Jury and Pavlidis.[3]

I. SUMMARY OF PHYSICAL CONTROL CONCEPTS

Regulation developed from the Industrial Revolution in the steam engine speed governor, instruments with temperature compensation, and such slow devices as temperature or pressure regulators. Discontinuous regulation began with the on-off temperature regulator. Continuous feedback control began with control of properties of active electric networks through 1925, achieved continuity with mechanical feedback control in the 1930's, emerged in the 1940's as a linear or small amplitude servomechanism theory in the electromechanical field. Linear control theory was generalized in the 1950's, and gradually enriched by discontinuous automatic control. At present, generalization of theory is sought.

Introductory engineering bibliography is Considine,[4] Perry,[5] Cosgriff[6]; on servomechanisms, James, Nichols, Phillips,[7] Brown and Campbell,[8] Chestnut and Mayer.[9] Introductions to non-linear control are Flügge-Lotz,[10] Loeb,[11] or, currently, Thaler and Pastel.[12] Broad engineering views are Truxal,[13] Smith.[14] Other modern books are Seifert and Steeg,[15] Horowitz,[16] Gibson.[17] European sources include Oldenbourg and Sartorius,[18] MacMillan,[19] Letov.[20] Computer control is discussed in Leondes.[21] Further systems engineering, cybernetics, or adaptive control theory will not be cited except Weiner[22] because of biological significance. Current status of control can be viewed in JACC 1962 reprints.[23] A physical background to dynamic analysis is Den Hartog,[24] Cunningham,[25] Andronow and Chaikin,[26] Whittaker,[27] Minorsky[28]. Fundamental ideas underlying this material may start from a primary distinction between regulation and control.

A. Regulation

A regulator makes an output slowly respond uniquely to another variable independent of slow disturbances. If the regulator is dynamically stable, it continues to adjust uniquely to a slow changing input. Mathematically, an ideal regulating relation $z = f_0\ (x)$ is sought. Instead, what is available is $z = f\ (x, y_1, \ldots y_n)$ where x = input variable; z = desired regulated output variable; $y_1, \ldots_n$ = disturbance variables. For example, a variation of pressure x to a Bourdon tube causes it to bulge, unwind, and through a

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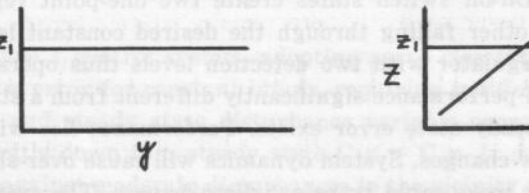
sector and pinion causes an output angular shaft rotation z. A linkage is designed against temperature disturbances y to compensate for this variable. In another example, adjustment of the compressed length x of a spring in a pressure regulator determines the outlet pressure z against disturbance variables of supply pressure y_1 and demand flow y_2. The regulator compensates for such changes.

Regulator design art deals primarily with static characteristics.[29, 30, 31] The compensation is never perfect; there remain "static" errors. If $z = f(x, y_1 \ldots y_n)$, $dz = \left(\frac{\partial z}{\partial x}\right) dx + \left(\frac{\partial z}{\partial y_1}\right) dy_1 + \ldots + \left(\frac{\partial z}{\partial y_n}\right) dy_n$. The quantities $\left(\frac{\partial z}{\partial y_1}\right) \ldots \left(\frac{\partial z}{\partial y_n}\right)$ are not zero. For high quality requirements, considerable study is required to make a design approach the ideal law. Generally, it is required that a change over the entire design range of disturbance variables should not cause more change in the output variable than some permissible small output error. In biological systems it may not be clear what the permissible output errors are. Without full understanding of the function, it is especially difficult to assess regulation as a minor loop effect in an overall complex dynamic system.

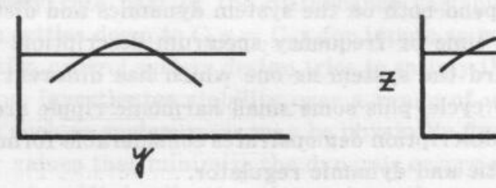
Summarizing, in regulation an expected response is achieved in a slow time scale with only small errors from certain slow disturbances. Transient disturbances will not set the regulating system into uncontrolled oscillation which grow forever, or do not die out to negligible amplitude. The method of testing for regulation consists of exposing the system to a variety of constant input variable states x, at selected fixed values of the disturbance variables y_1. This determines a family of curves that demonstrate the regulation. Stability is noted by causing dynamic upsets, illustratively step functions, or pulse disturbances, and noting the nature of the transient response before the system settles down to its static value.

B. On-Off Regulation

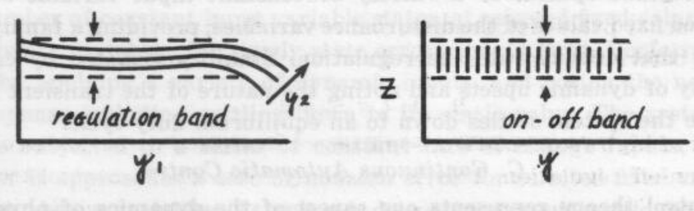
Lack of high frequency transient response and regulator design difficulty led to on-off regulation. This is commonly considered a control technique. While nonlinear characteristics of this type of system preclude the use of linear servo theory, Kochenburger's describing function approach has led to design methods for such discontinuous systems.[9] However, the common foundation is more mathematical than physical. One may note[24] similarities in response of a simple second order linear system with linear "viscous" and with discontinuous "dry friction" damping. While for moderate amplitudes, the two have similar responses, ultimately, fundamental physical differences emerge. For physical reasons it is proposed here to view an on-off system as a regulator that works discontinuously. The previous type of regulator is regarded as static regulation, and the present type as examples of dynamic regulation. In the on-off regulator, there exists a physical system in two or more distinct physical states, in prototype two. The two states are essentially not related. In one state, there is generally an active power element in the system network. In the other, there may be less or no power source. The working idea is that the first state may be "switched" to the second, causing the system to change the state of the output "regulated" variable. This may be expressed as $z = f(x, y_i, p)$. Previously, the p might have been an internal disturbance source. Now it is a two state variable $p = p_1$, or $p = p_2$ which changes z. Alternately, there may be different system functions in the two states $z = f_1(x, y_i, p_1)$, $z = f_2(x, y_i, p_2)$. So far no regulating function has been accomplished. Added



a. A desired regulator property b. A poor 'one point' regulator



c. A better 'two point' regulator d. A 'three point' regulator



e. Static regulator characteristics f. Dynamic regulator characteristics

FIGURE 1. Illustration of regulator performance.

details of regulator theory are shown in FIGURE 1. Suppose a regulator is desired with a property of constant output z_1 independent of a disturbance y. A very poor regulator is first illustrated. This may be called a one point regulator, for at one value in the y range, $z = z_1$. A two point regulator will be correct twice in the range, etc. For a given number of points the objective is to stretch a tolerable regulating band over as wide a disturbance range as possible. On-off switch states create two one-point regulators, one rising and the other falling through the desired constant level. The elementary on-off regulator with two detection levels thus operates in a design band with no performance significantly different from a static regulator. A similar steady state error exists. Performance lies within the design band for slow changes. System dynamics will cause over-shoot outside of the band for more rapid transient disturbances. The system may or may not be dynamically stable. The difference between the static and dynamic regulator is that in the static one the system is confined within a design band, for slow disturbance variations, to fixed performance curves; while in the dynamic one, there tends to be a time dependent repetition rate and duty cycle that depend both on the system dynamics and disturbance levels. This leads to a time or frequency spectrum description. Alternatively, one might regard the system as one which has different average positions over the duty cycle, plus some small harmonic ripple around the average position. This description demonstrates considerable formal equivalence between the static and dynamic regulator.

Summarizing, the dynamic regulator also possesses mean steady state errors, and transient disturbances may not set the regulating system into uncontrolled oscillation. The method of testing for regulation consists of exposing the system to a variety of constant input variable states, at selected fixed values of the disturbance variables, providing a family of duty cycles that demonstrate the regulation. Stability is noted by causing a variety of dynamic upsets and noting the nature of the transient response before the system settles down to an equilibrum duty cycle.

C. Continuous Automatic Control

Control theory represents one aspect of the dynamics of physical systems. In control, there is a referent input state x, established by some physical element of the system, and with common measure, a correlated output variable. The measure difference between output and input is the error signal. It is mathematically operated on by time dependent operations to produce a power output that is capable of driving the element with which the output variable is associated to attempt to reduce the error to zero. The act of driving the error toward zero is one that finally results in no static errors. Design tries to modify an operational relation $0_1 \; (z) = 0_2 \; (x, y_1, y_2 \ldots, y_n, t)$ for the underlying system to produce some desired control relation $z = f(x)$, where z = output controlled variable; x = input signal variable; $z = f(x)$ = an "error" variable; $y_1, \dots y_n$ = input disturbance variables; 0_1 = differential operator that transforms the output into some other time dependent function; 0_2 = operator that transforms the right hand into a time dependent function of input, disturbance variables, and arbitrary, usually stochastic, functions of time. Illustrated in a linear case $A_1z + B_1z + C_1z = A_2x + B_2x + C_2x + 0_3(y_2) + 0_4(y_3) + \dots + f_1(t)$.

A Type 1 control system, adopting servo classifications, ultimately has no static error for constant inputs, requiring indifferently small stochastic inputs and steady state disturbance variable operators. The system can then settle down to a steady state $C_1z = C_2x$. It must be at least locally stable against moderate disturbances in the vicinity of this singular steady state. The same ideas may be applied to nonlinear control systems. A Type 2 control system ultimately has no static error and no velocity error, if the inputs are changing at most by a constant rate. This requires additionally that the first derivative coefficients B are proportional to the C coefficients, the steady rate part of the disturbance variable is small, and that the system settles down to $C_1z = C_2x$ for inputs as variables as $x = \dot{x}_0 + x_0t$. Generally, control system design tries to satisfy the prime requirement for the type, investigates stability over a range of usable parameters (parameters such as system mass may be physically fixed), and then selects parameter values that minimize the dynamic errors arising from time changing inputs. Minimalization determines the quality rather than defines the controller. Excellent illustrations are by Lees.[32] In continuous control systems control functions are performed with continuous, not necessarily linear, operations. Characteristics are determined by exposing the system to a number of constant input variable states, at selected fixed values of the disturbance variables. No steady state errors should exist. Performance is noted by applying a variety of dynamic inputs, and noting the nature of the response including settling down to its static value. The system may also be subjected to a series of constant rate of change inputs, to note whether it approaches a zero or nonzero error for selected fixed values of the disturbance variables. At present, discontinuous automatic control refers to systems that are piece-wise continuous but with different switch states, i.e., physical low-mass switch elements capable of distinct states. Except as an ideal, they do not have zero steady state error, but are really part of a sophisticated dynamic regulator art. In this regard one must study nonlinear control references with considerable care.

D. Physical Concepts Underlying Regulation and Control

Control theory is clearer if the physical dynamics of systems is understood. Some pertinent primitive concepts of the statics and dynamics of physical systems follow: there is a fundamental idea of a static chain of elements linked by mathematical-physical relationships. Quasi-statically, the relations between elements can be verbally or mathematically described. Causality or reciprocity determines the response in one direction or another. In addition the links may have dynamic characteristics, creating dynamic chains of elements. They may respond or be linked by operational relations such as derivatives, integrals, thresholds, or even more complex connections. The linking elements are transducers, since they transform one physical quantity to another. In prototype, they are two terminal passive elements which contain no internal power sources. Two conjugate quantities y and x, are related by an operator 0 , $y = 0(x)$ when the application of x to the "terminals" results in a conjugate response variable. To produce change, either external power must be applied to disturb the chain, or active power sources can be used as two terminal elements. A one or more dimensional chain results. The chain is in an indeterminate state unless closed in one or more loops to form a network. Their mathematical description is in the form of differential equation sets. To continue analysis, one conceptually removes any time varying active elements and replaces them by a quasi-static sequence of potential power sources. One may then determine whether there exists a sequence of stationary states of the network. If so, these states, described as singular states (of motion) of the system, form a state of balance of the chain. They show three kinds of stability behavior. If disturbed, they can settle to a stationary state of balance, they can oscillate "indefinitely" (as long as power is supplied), or they can grow without limit and destroy the system. The latter represents catastrophic transient behavior, and is thus not generally the subject of balanced states, or regulation and control systems, but of dynamic transient analysis. The second case represents behavior of a bounded system with some sort of dynamic balance. Analysis of this type of system (nonlinear limit cycles) is difficult, and is still subject to some arbitrary concepts of its stability, balance, and associated regulation and control criteria. If the oscillations are small or indifferent, then ideas of a static balanced chain are useful. Thus, analysis sets up a conceptual chain, and examines whether small disturbances leave the chain stationary. These closed loops of a balanced stable chain do not make a regulated or controlled system, but a balanced system (like a mechanical force balance system). Electrically, this analysis is the equivalent of a D.C. network analysis. By considering small disturbance steps of various power levels in the chain, information about the stability of the system can emerge. In this discussion, regulation and control is defined with regard to stable chains. One may attempt analogous concepts for systems that are not absolutely stable. However, one must examine the system objectives in each case, as in the problem of discontinuous regulation or control and with more complex frequency modulated, pulse modulated systems, or other fragmentations of the time domain. In examining biological systems, both physical and biological scientists must accept foundations that are far from perfect and often over-simplified.

II. REVIEW OF CONTROL IN BIOLOGICAL SYSTEMS

A. *A System Outline*

The human is a physical-chemical system with complex communications, and power net characteristics. Even in quiescence one finds many sustained internal dynamic phenomena. Electrical, thermal, chemical, mechanical measurements indicate periodic phenomena in a range Kc/sec. to a cycle per century. These nonlinear limit cycles are logical evidence for active internally powered networks. Intermittent recharge need is evidence of storage elements. The "random" nature of its detailed actions, imperfectly correlating with ambient environmental events except for some "circadian" cycles or a longer periodic lifetime cycle, suggests that the system is self-actuated, requiring active prime mover engine elements. Sustained types of dynamic performance that are classed as limit cycles are important properties to be noted in a dynamic systems analysis. Illustrative in the body are brain waves, neural activity, body awareness, muscle tremor, heartbeat, capillary twinkling, eye blink, respiration rate, blood circulation rate, hormonal dynamics, peristalsis, vasomotor pulsing, sweat gland twinkling, thermal cycles, water and food cycles, circadian cycles, menstrual cycles, and seasonal cycles. Such sustained dynamics in the system can furnish a point of departure for a physical analysis. Such characteristics imply nonlinear system dynamics, which may not have anything to do with regulation and control. For example, the pacemaker cells of the heart form an autonomous system. Supplied with a nutrient, they form an approximately constant frequency oscillator. Activity level or chemical environment may change the rate, but within limts, only moderately. Thus, they may be considered a frequency regulator. Alternately, an eye blink cycle might be a nonlinear oscillator or an aperiodic network requiring input trigger signals. A dynamic control analysis of a complex active system starts by delimiting its exterior boundaries, choosing an "isothermal" ambient environment, and then by observation of variables, determining the degree of constancy of their time averages, and the number of active limit cycle oscillators that exist. (In passive systems, testing may be done in either an adiabatic or isothermal environment. In active systems, to prevent overheating, only an "isothermal" environment can be used.) These may simply be autonomous oscillators or used as internal regulators or controllers. It is difficult in current physical methodology, to justify a fundamentally sound first attack on the internal operation, regulation, or control of complex systems other than on its autonomous oscillations.

Control analysis of the human requires a general framework for the system. The main line of biological development of regulation and control is the physiological-biochemical one beginning with Bernard,[33, 34, 35] and Cannon.[36] Smith[37] contributes further advance to the main biochemical line. Wiener[22] developed a physiological-mechanistic offshoot, which has been extended by McCulloch and coworkers Pitts and Lettvin.[38]

Bernard's internal medium masterfully identified and delimited the field in which biological materials, processes, and mechanisms interact, and he advanced the case for the physical-chemical nature and state of balance within the field boundary. Thus, the system can be attacked by physical science. The internal environment preserves the necessary relations of exchange and equilibrium with the external environment, but has become specialized and isolated from the surroundings. This is an improvement biologically in the protecting mechanisms. Further, he disclosed an overall systems point of view: "To succeed in solving these problems we must, as it were, analyze the organism, as we take apart a machine to review and study all its works; that is to say, before succeeding in experimenting on smaller units we must first experiment on the machinery and on the organs." Bernard also devoted himself to biochemical chains, bringing to the field both the materials and processes end of systems analysis, without explicitly defining the regulating and control functions.

An introduction to dynamic chains in the interior and the likelihood of regulation begins with Cannon's concept of homeostasis. In spite of unstable mechanisms, an essential constancy is maintained in the internal field against static and dynamic disturbances from the environment. Though this refers to both regulation and control, he states more precisely that he is not discussing simply the equilibrium state of a balanced chain, but an overall response of the system, which maintains most of the *steady states* in the organism at nearly constant, but adjustable levels. This expresses primary comprehension of regulation, in which moderate bounded steady state errors are tolerated. (Cannon attributes recognition of regulation to Bernard. "Bernard — clearly perceived that just insofar as — constancy is maintained, the organism is free from external vicissitudes. 'It is the fixity of the milieu interieur which is the condition of free and independent life', he wrote, and 'all the vital mechanisms, however varied they may be, have only one object, that of preserving constant the conditions of life in the internal environment.' 'No more pregnant sentence' in the opinion of J. S. Haldane 'was ever framed by a physiologist.' ") Thus, an examination of biological regulation fairly begins with these men.

Cannon's outline of biochemical regulation is useful.[36] He describes elements in the chain of mechanisms and processes that create balances, regulators, or controllers in the interior, primarily ones that handle the fluid matrix. Discussed are some response elements that tend to restore blood pressure, basically if the disturbance is the amount of fluid in the system, but the changes are cataclysmic rather than the systematic changes within a normal operating range for viewing regulation. Sensing is at "some sensitive nerve endings in the blood vessels high in the neck near the brain." (Discovery of a sensing transducer involved in a process should not be confused as the end of characterizing a chain or regulator). He mentions two sensors, thirst and stomach hunger pangs, as tending to assure water and energy supplies for the fluid matrix. Stomach pangs form a repetitive periodic cycle. He began studies of a chemical level trigger, possibly blood sugar, for the hunger pangs.

(Such elements are more likely aperiodic alarm mechanisms than regulators. They are actuated when reservoirs of water or energy are depleted, and set the entire system into free spatial self-motion to seek out supplies. The alarms should not be confused with level regulators. A regulator is a specific mechanism that achieves a certain performance band for particular ranges and types of disturbances. To test water level regulation, for example, requires holding constant environment potentials, supplying water at various constant rate inputs, and determining the steady state water level response. Instead of such simple regulation type experiments, more commonly difficult experimental situations of the self-actuated system engaged in a variety of complex tasks are viewed for evidence of regulation, or the response to such drastic steps as tearing out the walls investigated. While valid biological states, they are not valid elementary physical states for examining regulation and control. The hunger alarm is an oscillator, tied into the system in a fashion usual for alarm systems. Its network has adjustable parameters that may put it into stable or unstable states. Reich (1961)[39] illustrates network instability. As an alarm, a network itself is a limit cycle oscillator, but is used in an aperiodic mode. If by other means a larger chain is closed, then this on-off alarm characteristic may be used as part of a dynamic regulator, or even controller. However, without complete description of the chain, its function is unknown. Thus these problems have exposed two oscillators, and some unexplored ideas on stability of the networks.)

Cannon points to the kidney as the excess regulator of water content in the organism, as an "overflow," or peak level regulator. (The combination of a storage element and an on-off resistance element, like a flush valve, does not of itself create a regulator, but an aperiodic relaxation network which may be used in a more complete chain for balancing, regulation, or control.) More likely the desired effect is precisely maintaining consistency of the blood even when excess water is taken into the body, or none is supplied. In the latter case, water stored in the muscles and skin may be used. Storage level may shift with pH. (Regardless of details, there likely exists a large chain zero water rate regulator, i.e., against a range of slow disturbances, the rate at which water enters some regulated zone is nearly the rate at which water leaves. The unbalance may not be measured directly as a rate, but by a parameter proportional to the rate, such as fluid pressure, distension, or concentration change in a reference volume.)

A similar regulator is proposed for salt content constancy. Excess is gotten rid of through the kidneys. In deficit, there is withdrawal from storage. (Likely a zero rate or an on-off regulator is actually involved.) Cannon then discusses regulation of blood sugar, normally near 100 mg. of blood sugar per 100 cc. of blood. Two "force balance" elements, adrenin from the sympathico-adrenal apparatus brings sugar from liver storage, and insulin from the insular apparatus depresses blood sugar concentration, possibly involving sugar stored in liver and muscles. (While the pair furnish a "restoring force" toward a balance, it is not clear whether this tends to regulate by a continuous restoring force, or as a two position on-off dynamic regulator. Another point in regulator theory may be pertinent. A "spring" is commonly used to create a force balance near a desired regulating point, with considerable design art aimed at a high spring rate to make regulating point deviations small. A two position band-determining on-off switch generally is designed to be a nonlinear restoring spring that does not quite have an "exact" balance point. In this context, reference to on-off control as a dynamic regulating system may be better understood.)

Below 70 mg. per 100 cc. sugar level, possibly down to 45 mg., low sugar reactions occur. One symptom is hunger pangs. (Again, pangs are an alarm function that may be used in a larger regulating or control chain, reasonably a larger "voluntary" chain, under central nervous control that acts on all of these "alarm" signals to produce a control function in an external feedback loop. However, this has nothing to do with much more localized regulating or control chains with small operating ranges that only signal alarms when not able to continue their function. At this point, an overall view of the complex biological system begins to emerge. There must be local automatic regulating and control links. These have operating ranges. When the operating ranges are exceeded, alarms are set off. There must be a panel board in the central nervous system in which various alarm states are indicated. In the central nervous system there must be a computer control system. According to some schedule or algorithm, regardless of how complex, the computer determines a corrective course, which may or may not take care of all alarms at that time, and actuates the system to corrective action. Whether a new biological concept or not, it would not be considered new within the scope of physical control theory. However, it is proposed as one that might suit both physical and biological scientists. The details of the processes and mechanisms are biological; the abstracted characteristics of processes and mechanisms are physical).

There is likely an overflow at 170 mg. into the liver since large charges of sugar into the system appear to stop at this level, below a kidney threshold (whether a regulating chain is really involved is not indicated). There is likely a second overflow level at 180 mg. into the kidney, indicating serious malfunctioning of the system. Cannon then turns to blood protein regulation. Protein nitrogen is stored to a large extent in the liver. Protein in the plasma is held constant. If a step decrease of plasma is made, there is a relaxational rise, with a time delay of the order of a day, in which material is restored likely from the liver. Possibly the thyroid gland is important in controlling both storage and release. Touching blood fat regulation, fat is increased in the blood after eating, and is stored in the system. The regulation of its storage and its release is obscure. He discusses blood calcium regulation. Referring to its regulated precision in the blood, there are concentrations down to 7 mg. per 100 cc. with no parathyroid gland, and up to 10-20 mg. with repeated injections of gland extract. At the high end, the blood becomes extremely viscous. Below the low end, convulsions appear. Calcium is stored in the long bones. Storage may be depleted by secretions from the thyroid or from the pituitary gland. Secretions from the parathyroid seem to be the main associated agent. Deficient secretion reduces blood calcium (raises phosphorus), while excess secretion does the opposite. If the glands are lacking, there is defective calcium deposition. Though the balance is not described, nor fully determined, regulation likely exists. For example, blood osmotic pressure, dependent on the concentrations of glucose, salt, protein, and calcium, largely on salt, only showed a half-percent variance from a fixed level for a sizable test group, after a few minutes at quiescence. Oxygen supply is then dealt with. While food and water are stored and can be drawn upon for days, storage of ozygen is essentially not provided for. Body activity requires continuous oxygen delivery "to permit the burning of the waste products of those activities" (this latter phrase seems surprising). Regulation is achieved by speeding up the delivery process. Requirements may vary from 250 - 300 cc. per minute quiescent, to 15 lpm in severe effort; likely four lpm is the maximal sustained amount. As a result of high muscle activity, lactic acid accumulates in the muscles. It must either be burned or transformed back into glycogen. The body works beyond the limit set by available oxygen, Hill's oxygen debt, taking up enough oxygen later to burn the accumulated waste. Oxygen regulation to remote cells is only provided during moderate activity. The respiratory and circulatory system adjustments are not adequate to prevent acid development. Other devices are brought into play to maintain neutrality. To supply the extra oxygen, various mechanisms are used. For example, the respiration becomes deeper and more frequent. However, the main element is more rapid elimination of carbon dioxide. Its increased partial pressure in the arterial blood, as it passes a respiratory center, sends signals that result in more vigorous respiratory muscle action. This pumps out the extra carbon dioxide in the lung space. A small percentage increase in the level causes large changes in ventilation, suggesting carbon dioxide regulation. Vigorous muscle activity involves the sympathico-adrenal system which leads likely to secretions that increase both breathing depth and rate. In the deep lung spaces, an exchange oxygen partial pressure is thus maintained even with increased oxygen use. Oxygen transfer takes place at the pulmonary capillaries by partial pressure exchange. Added oxygen can be carried only by increase in the rate of red cell carriers in the blood, mainly by increase in blood rate, as pump action of limb muscles, the diaphragm, and the heart all change both rate and stroke. For example, for a ten-fold increase of oxygen delivery, the heart can double its stroke volume, and more than double its rate. There is an increase in arterial blood pressure by constricting blood vessels to the abdominal organs, expanding capillaries where the greater oxygen supply is needed, and also making more oxygen available. Increase of carbon dioxide and temperature in the muscles can result in a more complete unloading of oxygen from the red cell carriers. Thus the muscles are prepared to use the increased flow. When the blood leaves the lungs, it may carry up to 18 cc. of oxygen per 100 cc. of blood in violent exercise. It may only use up three to four cc. in outlying capillaries in a quiet state, but only return five cc. in active regions.

(Expressing no judgment on the biological validity of the complex dynamic problem that has been outlined, it is an inadequate foundation for a mechanistic model of the oxygen supply chain. Particularly misleading would be to encourage engineering efforts of superficial system analogues. Exchanges between disciplines must be observed with caution. It is of no more help to the physiologist to get back half-baked physiological descriptions of his processes as physical analogues simply because they are in mathematical terms, than for him to have furnished half-baked physical descriptions of physiological processes. Some physical problems can be illustrated. System self-actuation depends on the ability to quickly shift muscles from doing internal to external work, requiring that they be active engines. While all body cells require fuel and are tied likely into rhythmic cycles, they all do not have the requirement of transforming energy both for their own function and others. Thus, enginering thought would seek the muscle prime mover engine cycle to "explain" oxygen demand, since a "combustion" engine is implied. Since there is no storage for combustion oxygen, but for the sugar fuel in general inundation mass of the body or the liver, a proportioning fuel-oxygen mechanism is needed. In any particular muscle action (lift of foot, etc.), the external load and work is indeterminate. For these short strokes, does the body draw on storage? Physical engines for example use flywheels and phased cycles to smooth power over each cycle. Over what period is an essential fuel-oxygen equilibrium established? Does a hormonal signal — say adrenalin — push the muscle system into "high gear," capable of supplying high external demand power if needed? If so, is it possible that appreciable power transients exist? Thus isn't the concept of oxygen debt misleading even though it is perfectly valid that fatigue products are stored, and require a second chemical step for equilibrium? It is not that these are valid questions, but that a much more complete dynamic chain is needed to describe even the steady state chain during a given activity level in which external and internal work is being done and heat is flowing.)

Cannon returns to the regulation of blood neutrality. Work, resulting in lactic acid and carbon dioxide, acidifies the blood. Base radicals in food can render the blood alkaline. Blood is slightly basic at *p*H 7.4. At *p*H 6.95 coma and death ensue. At *p*H 7.7 tetonic convulsions ensue. If too acid, the heart relaxes and ceases to beat; if too alkaline, it contracts and ceases. Acid reacts with sodium bicarbonate to form more carbon dioxide which stimulates the respiratory center, causing pump out of carbon dioxide. Another buffer, alkaline sodium phosphate, reacts with acid to give acid sodium phosphate. Both forms are almost neutral, but the latter is slightly acid and may not accumulate. By absorption and concentration in the kidney tubules, much of the acid is excreted. With alkaline blood a respiratory stimulus is lacking and the carbon dioxide developed by the persistent active organs cumulates. Thus, precise regulation in the chemical composition of the blood is quite urgent. The combination of sensitive respiratory center, blood buffers, and kidney act continuously to prevent swings away from the normal state. (Because many of the likely mechanisms that are needed for the regulating or control chain are identified, and their function important, the need exists for complete regulation or control data upon which to found or complete mechanistic chain.)

Discussion proceeds to the constancy of body temperature, maintained in the deep body near 37° C. Drugs and fever interfere. Above 42° C. brain disturbances occur. Below 24° C. deep lethargy prevails. Internal processes tend to obey an Arrhenius law of doubling the chemical process rate per 10° C. rise. Heat is continuously produced by activities involving the organs, and is transferred through the body. It is remarkably constant in normal people at standard conditions. From the consumption of oxygen and production of carbon dioxide during a test period, a basal metabolism representing the heat produced by burning fuel can be computed. Only variations of a few per cent on individual subjects is the rule. Metabolism is likely directly influenced by the thyroid gland, and to a lesser extent by the pituitary and the cortex of the adrenal gland. What keeps the thyroid gland constantly active is not known. Regulation of body temperature, like oxygen supply rate, is achieved by modifying a process speed. Constant temperature is maintained by changes in heat production and heat loss. With vigorous work, vasodilation brings larger quantities of blood warmed by the active muscles to the surface. Warm temperatures induce sweating through skin glands with an evaporative heat loss. Heat is lost in evaporating water to saturate the breath. When body temperature starts to fall, heat is conserved by reducing perspiration, by contracting the surface vessels, by lifting hair to enmesh a thicker air layer, and by clothing. At low temperature, it is also likely that adrenal secretion to the blood is called forth. There are successive defenses which are set up against a shift. If dilation of the skin doesn't stop body temperature rise, sweating, and even panting take place. If constriction doesn't prevent temperature fall, there is a more rapid metabolism called for by the secretion of adrenin, and if not sufficient, greater heat production by shivering is resorted to. Thus, there must be a sensitive thermostat. In the diencephalon are the central stations for the secretion of sweat and for shivering, automatic reactions which govern the production and loss of heat. This thermostat may be affected by the blood temperature, or by nerve impulses from the surface.

(Except for moderate changes in details, this picture of temperature regulation is essentially the same as is accepted today.[40, 41] Does it model the temperature regulating chain? Here the authors have some background.[56] Once again, energy actively required to satisfy both temperature regulation and external work requires an engine cycle. Temperature constancy precludes the cycle from being active through all body cells, unless there is a hormone mechanism that actively coordinates the metabolic activity at all cells. Under quiescent conditions, for example, data such as Cannon discusses does not make this probable. Thus, more likely cycle exists. Physical reasons, particularly the body temperature distribution, suggest more likely an engine localized at the site of muscles and other active organs. One would expect active oscillator-type engine cycles rather than the astonishing uniformity of basal metabolism that Cannon discusses, or that even Benziger[41] implies. Experiments verified the expectation and uncovered a power cycle of about 1 cycle per two minutes. This is the system's engine cycle. The constancy of mean metabolism is only evidence that the power cycle is regulated in an undisclosed fashion, although one may suggest that the anterior hypothalamus temperature controls the amplitude of an action potential carrier wave of about 10 cps. that stimulates a sustained muscle tremor as one basic element in temperature regulation. While this statement may suggest considerably enriched possibilities in construction, it still does not complete the regulating chain.)

Other subjects discussed are aging, body defenses to alarm by such devices as the conditioned or unconditioned reflex, the significance of the role of the sympathico-adrenal system in regulation. (Sympathectomized animals continue to live without apparent difficulty, but various regulation defects show themselves.) In an attempt at general assessment of ideas of Meltzer (1907) on the margin of safety in the system, whether the body is organized in a general or limited plan, essentially whether the system operates with quality regulation, Cannon decides that the system operates with gross regulation, copious material, and a considerable amount of redundancy. (This valuable message represents a view comprehensible in old-fashioned chemical plants or production lines. A very uniform product comes out of the plant, pound after pound of breakfast cereal, etc. The internal line does not consist of closely regulated or controlled systems, but systems with a large degree of play and redundancy. At greater throughput, problems of stability and of critical regulation and control of sub-elements arise, and such systems are inoperative.)

As summary, general features of body stabilization are discussed. The elements are naturally unstable. Regulation in the fluids stabilize the system. The system has alarms. There are automatic regulators with measure sensors. Materials and processes are regulated. An important element in material regulation is storage of both short time and long time nature, as is overflow in the fluid field. Many process regulators, such as for temperature, oxygen supply, pH, are automatic. The sympathico-adrenal apparatus automatically makes many of the adjustments, preserving normal internal conditions both for various individual conditions and as a unified system. Cannon reviews some tentative regulation propositions that he stated in 1926. In the open loop body response, there are many regulating functions, as exhibited by their steady state constancy; the quality of regulation exists because of large restoring forces to the disturbance sources; the regulating mechanisms may be multiple to increase their effectiveness; and the restoring mechanisms occur in pairs, i.e., since they tend to be unidirectional chemical reactions, a pair is required to create a restoring "spring" force. Higher animals tend to have the more complex or complete regulation mechanisms. The higher self-actuated animal is free to go about more complex tasks because it lives with a regulated fluid internal medium. Automatic corrections act, in the main, through a special portion of the nervous system which functions as a regulatory mechanism. For the regulation it employs storage of materials as a means of adjustment, and changed rates of processes. Finally, there is a philosophic discussion of whether the same principles of regulation exist in the social system.

(To physical scientists, occupied with regulation and control, Cannon[36] offers great, friendly and familiar thoughts. Clearly, if Bernard isolated the important physical-chemical field, Cannon understood the primacy and need for regulation, and even likely identified major elements of the regulation. However, the missing ingredient in the work and of most subsequent investigators is the systematic exposition of the system characteristics of each proposed regulator under a large variety of steady state input environmental conditions, and of control functions under conditions of transient response. The validating data are measurements at a series of steady state "disturbance" levels to determine the steady state response of the system. The major disturbance input variables for the human are temperature, position, oxygen partial pressure, water vapor, total pressure, rate of water intake, rate (and type) of "food" intake, and light level. Regulation among body variables has to be tested with regard to changes in these variables. If argued that it is not pertinent to hold all of the input variables constant, the burden of proof, in each case, is on the investigator. In nonlinear systems, the lack of a principle of superposition does not permit automatic correlation between different type signals. Each correlation must be experimentally examined.)

Proceeding now along the main biochemical chain of regulation, as viewed by Smith,[37] the kidneys are the master chemical engineers of the internal environment. Their balance function keeps it regulated. Other organs tend to perform one function; the kidney has a variety of tasks. (This summary is so elegant, that it was adopted as the thread of continuity. The one addition to be considered is the likely need to embed some major mechanisms in the milieu so well regulated by the kidneys.) Smith[37] traces the evolutionary story of the kidney. Early vertebrates evolved in fresh water, but an internal salt milieu was needed for the elaboration of complex organs and mechanisms, making tenacious salt conservation a most primitive kidney function. A second problem of water conservation arose when they left the water. He depicts kidney evolution from a tube stuck into the body cavity draining it by means of an open mouth; to adding a tuft of permeable capillaries, through which the pressure in the arterial blood filtered water out of the tuft, with subsequent drainage out of the body through the open mouth; then with the tuft inserted in the tube, possibly with a separate open mouth; and then finally with the tuft inserted into a blind end of the tube with no mouth. This is the glomerulus of the adult kidney. Ludwig (1842) showed evidence that the tuft acts as a filter. Cushing (1917) published the first definitive work on urine formation. Experimental work then demonstrated the reality of filtration theory. Later studies by Marshall and Edwards exhibited tubular excretion in vertebrates without glomeruli. To aid in water balance, later amphibia have a mechanism for reducing glomerular filtration (and thus water excretion) rate when out of water, and also a mechanism for varying skin permeability to water. These are governed by the pituitary gland. Studies on aglomerular forms proved that the tubule could excrete all the important constituents of urine, including creatinine, creatine, uric acid, magnesium, calcium, potassium, sulfate, iodide, nitrate, many dyes and synthetics, but not carbohydrates or protein. In reptiles, a change in protein metabolism produces uric acid which requires only half as much water for the same amount of protein metabolized, conserving water. However, uric acid is insoluble. Reptiles deposit it by tubular excretion in the urine in very high concentrations, such as 3,000 times the blood concentration. Mammals also void a urine more concentrated than blood. A temperature regulated system required an increased blood circulation and blood pressure, and thus increased glomerular filtration, requiring tubular reabsorption of valuable constitutents from the filtrate, with a capacity to conserve water by making a very concentrated urine even with urea. This unique functional ability was accompanied by two anatomical changes; a bending into a hairpin loop, and the disappearance of a venous blood supply to the tubules. He describes the function of the mammalian kidney in man. The individual nephron consists of capillaries from the renal artery, balled into an elastic membrane capsule to form the glomerulous; the capillary network leaves to interlace the tubule and depart to the renal vein; the tubule in a complex winding hairpin turn connects the membrane to an outlet tube that leads to the bladder. The glomeruli have a total surface of ¾ sq. meter and filter about 50 gallons per day, the kidneys receiving about 500 gallons per day of blood. The daily filtrate contains 2½ pounds of salt, of which only 5 per cent is excreted in the urine and 95 per cent reabsorbed by the tubules. A pound of sodium bicarbonate and ⅓ of glucose are also filtered. More than 99 per cent of both are reabsorbed. Also filtered and reabsorbed are potassium, calcium, magnesium, phosphate, sulfate, amino acids, vitamins, and many other substances of body value. Of the 50 gallons of filtrate that enter the tubules only 1½ quarts of final wastes, water and waste material which may have been concentrated a hundredfold or more, is excreted. The total circulating fluids, of about three gallons, are thus filtered about 16 times per day. Once the filtrate enters the capsule, it is effectively outside of the body. The main filtered and reabsorbed ingredients are salt and water. (A mechanistic chain of how such complex functions are achieved, by what appears to be nearly a passive mechanism, is physically intriguing.) Most of the salt and water is absorbed in the first segment of the tubule. Thus, in this segment the urine retains the same osmotic concentration as in blood. In the subsequent descending and ascending thin segment of tubule, reabsorbed salt transferred to the interstitial fluid draws water osmostically from the tubule in the presence of an antidiuretic hormone (ADH) of the pituitary gland. The urine emerges thus with the osmotic pressure of the interstitial fluid around the loop. Under conditions of dehydration, urine flow is minimal, and osmotic concentration maximal. During hydration, in the absence of ADH, the last segment of tubule is less permeable, so that free water is unabsorbed and is excreted as a dilute urine. This represents a theory of pores in the last segment of tubule under control of ADH. Receptors in midbrain and the pituitary gland are affected by osmotic pressure in the blood via ADH to increase or decrease the excretion of water, so that osmotic pressure changes in the blood not more than 1 or 2 per cent. With a large drink, urine flow starts as soon as water is absorbed from the intestines, reaches a maximum in 30 minutes, and within an hour the body is back in water balance. However, one can drink at a rate faster than the body can excrete. Because of 85 per cent reabsorption in the early part of the tubule, urine flow cannot exceed 15 per cent of the glomerular filtrate, or seven gallons per day. (It is not quite clear whether the system is thus regulated against input water rates, or controlled. If osmotic pressure is controlled, there would be negligible change in osmotic pressure at any input rate up to seven gallons per day of water, possibly with some lower limit otherwise set. If regulated, there would be some shifts in the osmotic pressure.)

While this completes Smith's kidney discussion, a few more ideas are abstracted. He mentions Bernard's later thoughts and those of Fredericq's, that higher organisms are so constructed that when disturbed they react to restore a balance, and the higher the organism the more numerous and complex are the regulatory mechanisms. The fundamental problem is not the essentially passive but regulated fluid, but ultimately the "living" mechanistic unit, the cell. (This "atomistic" approach does not solve the macroscopic problems, only avoids them. Illustratively, a solution of the classical equation of continuum hydrodynamics do not await a solution of the molecularly cast Boltzmann equations. Thus, there is more taste for the views of D'Arcy Thompson. This is no objection to atomistic problem solving, but is a caution that science cannot use only one extreme or another.) Smith touches on the nervous system. It has only four basic operations — conduction over protoplasm; conduction over the nerve fiber; excitation or inhibition of cell action through fluids; transmission across nerve junctions. From these arise its capacity for complex reactions. Many body activities — circulation, digestion, excretion, temperature control — are taken care of by an autonomic nervous system organized to handle a very great number of details. In higher animals the nervous system is the most adaptable organ. (The impression is left that it represents a great number of patch networks in which all sorts of chains — balancing, regulatory, control, oscillator, alarm chains — are locally created to coordinate desired functions. Viewed from a network, plant, or systems background, it suggests a loose coupling among chains so that minor loops cannot transmit very much that will upset the overall system stability. These properties enlarge the scope of the problem to more modern and abstract automatic control theory. However, there clearly must be major systems that work almost independently to permit main system stability. This could be in physical controversy for a long time. It is clear that much of the patching, as learning, uses adaptive control mechanisms.) In discussing consciousness, the concept of "mind" is replaced by an episodic, but continuous excitation of the cortex by incoming nerve signals. These signals travel with a velocity of 10-100 feet per second, with .003 second time delays at nerve junctions. Thus, the time delay from external signal to "awareness" ranges from 0.1 to 1 second. There is also a memory. A contribution of Freud's is that recall from memory to awareness may be resisted. In complicated patterns of even voluntary activity, consciousness may play a very limited role. Piano playing is cited in which 70-80 distinct motor actions per second, many involving power, can be executed. For example, 20 power strokes (playing notes) per second under control have been observed. At 30 notes per second, the play becomes ragged. (These are levels of 400-600 motor actions per second.) It is likely that there is a constant shifting between the "automatic" and the aware. However, awareness is not a prerequisite for nervous system functioning. More fully, consciousness is an awareness of exterior and interior environment, of neuromuscular activity with choice of self-actuation, and of a time binding quality that makes time continuous over the individual internal events. It is a function not only of the cortex, but of the brain stem and peripheral nervous system. The neurosurgeon has explored the cortex in detail by stimulation and has identified numerous areas that have some specific involvement in sensory or motor activity, and of specific parts of the body. This localization is more functional than anatomical and begins with very little. During infant growth, the cortex acts as if it controlled a big sucking mouth, a tongue, a big nose, and hands. Later hands and mouth regions shrink as eyes, ears, feet, etc. come in. There are puzzling silent areas such as the frontal lobes. Removal reduces restraint, judgment, initiative and tact. The subject becomes fat, carefree, and a little silly.

In summary, while the significance of the kidney has been stressed, an adequate description has not been given either for its balancing chain or regulating function. That it is still uncertain is apparent in Zinsser,[42] who states in part that analysis of the kidney process is just barely begun and that warring generations of physiologists have still not validated any hydrodynamic analysis of the nephron. There are some models. For example, he shows a set of equations for a mechanical analogue. (The equations in both referenced papers are not essentially correct. They are linear, or nearly so, general process representations, rather than specific functional models. Engineering background of such engineering analogue studies may be viewed in Karplus and Soroka.[43] They lack sufficient wide range applicability to account validly for all of the singular states of motion, and the stability near the singularities.) While such efforts as Smith's likely complete the main biochemical materials regulation line of description, a view of a chemically regulated fluid matrix is not satisfactory as a complete system model. Major operating mechanisms that are essentially regulated or controlled must be identified. They are likely engine cycles to permit the function of system self-actuation. Since oscillators will be discussed later, discussion of these mechanisms will be deferred. However, it is appropriate that Smith ended on the nervous system, for there are coordinating, communications, and computing functions that have to be performed. These fit into automatic control views. The nervous "communications" system, and the signalling hormonal system are likely two main line systems that require consideration.

Primary exposition of the communications system may be attributed to Wiener,[22] although the detailed foundations are due to neurophysiologists. As background to his synthesis, he mentions involvement in an informal interdisciplinary study program with Rosenblueth (Cannon's collaborator), contact with the differenential analyzer development, and work in electric network analysis. In part in common with others, Wiener visualized high speed computation, using digital (arithmetic rather than analogue functions such as the differential analyzer), binary, electronic elements in a complete electromechanical chain (rather than with human links) and with a rapid short time memory. This represented a first problem in programming "equivalently" to a human. Finally, in a tracking problem involving prediction of path in a chain involving a human, the suggestion arose that the element of feedback (i.e. servomechanism theory) is essential to human operation. (Picking up a pencil is illustrated in which the hand acts as a servo follow-up mechanism to the tracking eye and may show oscillations. Seeking for an illustration of an uncontrolled oscillation in a biological system as an unstable control loop, an example was found and the interdisciplinary nature of automatic control and biological systems was joined.) It appeared that the central nervous system is not a passive, nor a D.C. net receiving sensory inputs and discharging outputs. There must be active circulating signals. Therefore, the performance of the nervous system as an integrated whole must be examined. The primary need was not for an A.C. network analysis, but a communications theory for "signals" (i.e. time series) as a statistical science. A unified view was sought for the problems of communications, control, and statistical mechanics for both machine and biological system, including a background in mathematical logic. Thus, the concept of cybernetics, as a theory of guiding mechanisms, was born. (What was new about this was not the concept of feedback, binary computation, the use of memory, control optimalization, but application of these ideas to biological systems.) These ideas were widely communicated to physical and social scientists. An example of work attempted at Massachusetts Institute of Technology (1946) was the dynamics of an isolated muscle-nervous system reflex in a living animal, analyzed as a control system. Wiener points to the need for a communications, low power, rather than power network point of view. He presents a formalistic discussion on the nature of the ergodic hypothesis (the reason why averages in phase space and in time are equal). The formalism of Gibbs is questioned. (In applied physical problems, it is generally only the physical result that is desired, not the formalism. For many degrees of freedom systems, it is Boltzmann results that are used to ascertain the nature of the approach to equilibrium. In reality, phenomenalogical equations are used to replace the nonequilibrium Boltzmann equations. It is true that a standoff is reached in systems with large statistical fluctuations. However, there always is a race whether statistical or continum descriptions have greater success when there are only moderate fluctuations. A chapter on time series theory furnishes apt illustrations. Wiener proposes that such problems as the turbulent field or the weather field are to be thus most hopefully treated. It is this that may be challenged.)

Wiener discusses feedback and oscillation. From illustrations of biological control instability (ataxia), he proceeds to on-off thermostat regulation, and steam engine governing as illustrations of feedback, in particular negative feedback. An elementary discussion is given of linear systems from this point of view. Whether regulation or control is meant is not discussed. Instead the follower type characteristic (i.e. linear servo theory) is discussed generally with some attention to stability. (Available servo theory books are not referenced.) Similar, but more complex follower action by feedback is implied in biological mechanisms, as in hand motion. Differences between linear and non-linear dynamics are indicated. (It is not clear whether in general limit cycle oscillations are being discussed. To be countered is an example that an organ pipe driven by "D.C." air source can be explained by crude linear theory as opposed to a more precise nonlinear theory. This imprecision is not permissible, particularly since what can easily be involved are stability questions.) In general, nonlinear systems of equations are hard to solve. (They are also hard to formulate when no "exact" science exists.) It is suggested that physiological tremors may be treated roughly as perturbed linear systems. (The authors question this except for small tremors. Most real tremors in the biological system likely arise from nonlinear mechanisms.) The section concludes that the feedback systems of control discussed and the compensation schemes discussed previously are competitive. (The dual allusion appears to be recognition of a difference between regulation and control, here linear.) They both lead to a follower characteristic. The feedback (control) system does more than this, and has a performance relatively independent of the controller element. (While acceptance is indicated of a distinction between regulators and controllers, a belief common in automatic control theory is repeated that constancy of characteristics is only necessary in the regulator. In both cases, nullity, whether in error measuring or force balancing, depends on the precision of transformation of physical variables through mechanistic elements.) Possibilities of combining regulators and controllers exist. Examples are regulating an input, or staging. Feedback loops thus become bigger, and more complex. (The user generally has different applications for a regulator and controller. Typically, large slow fluctuations or changes are reduced in output amplitude by a regulator. If insufficient, a second stage may be used. If residual transient disturbances are troublesome, then a controller may be used for these time dependent disturbances. Wiener illustrates this, and it is useful to call the point of view to biological attention.) More complex types of feedback networks involving regulators and controllers are also discussed. Illustratively, one of them, control by informative feedback, involves testing the network by an injected high frequency impulsive signal, and from the segregated high frequency information, modifying the adjustment of a regulator to monitor the stability. Examples are given as particular cases of a very complicated and yet imperfect theory, which should get more attention. (The subject has received more attention. It is pertinent to cite H. Ziebolz, as likely innovator of the two time scale control network in a great variety of complex forms, such as the process and short time scale independent analogue loop with interconnected information feedback. Such efforts led to computer control and adaptive control.) Important application of feedback is to physiological homeostatic mechanisms. However, these mechanisms tend to be slower than feedbacks involving the nervous system. (A basic point arises here. It is possible, but not really useful, to involve a concept of "feedback" in regulator design, which is generally concerned only with force balance coupling and means for achieving compensation. To identify it as "feedback" is a convenient label that derives from linear feedback theory, where there is hardly any purpose in distinguishing between regulation and control. Cannon clearly defined homeostatic mechanisms as regulators. With their slow response, they likely are. Thus, the problem exists of identifying whether they really are regulators. On the other hand, as Wiener already discussed, the continued circulating information feedback in the nervous system, suggests controller action. The problem is to find them. The two intrinsically different classes of mechanisms do have dynamic behavior in common, but this arises from the basic presence of masses and inertias, and not from feedback, but from coupling.)

Discussing computing machines and the nervous system, Wiener points to the elementary algebraic character of the digital computer, the equivalence of this to switching, and to logical addition and multiplication. The neurons are ideally suited to act as electric relays, with states of firing or resting. Nerve action is characterized in more detail in functions of both a temporary and permanent memory in the nervous system (by temporarily circulating a train of impulse signals around a closed circuit), the use of triggers acting similarly to repeaters to feed in new messages for continued short time storage, the problem of long time storage. Many believe that long time storage is tied to the threshold of the synapse, that the total neuron content is established at birth, and the chief changes, representing memory, are increased in thresholds. He considers the brain, as the computer, to be a logical machine. Based on the work of Turing and Post, he believes that the study of logic and the logical machine, whether nervous or mechanical, are equivalent. Discussion continues on relating logical and psychological characteristics of the mind and some of the logical difficulties, a need for dynamics in mental activity, the salient nature of the Pavlovian reflex, the pleasure-pain principle, some modelling of a conditioning process, and a duality of a nervous communications net and a hormonal communications net. It is suggested that such properties as conditioned reflexes, or storage by synapse threshold could be accomplished in computers. The problem is tackled of assigning a neural mechanism to how the system specifically identifies an object from incomplete or distorted information, illustratively for vision. There likely is a visual-muscular feedback system. For example, a negative phototropism drives worms into the darkest region accessible. In a human, there are same regulators, such as pupil opening. There is a reflex feedback to bring some function of the input field into focus on the fovea. Object images are brought into standard position and orientation in the eye and cortex. The eye recognizes outline drawings, likely involving enhanced sensitivity at boundaries. There may be comparison between an outline and a standard stored in memory. However, the aspects of the object image seem to form a complex involving permanent subassemblies. A feasible subassembly is visualized in one mathematical form of group theory, in terms of group transformations. In such complexes may lie the Gestalt of the object image. An illustration is a reading mechanism for a blind person, in which letter forms are standard but type size may vary, requiring identification of form independent of size. A group scanning scheme involving an array of photocells and actuated oscillators of various pitches which was proposed by McCulloch is described. It was loosely identified with the fourth layer of the visual cortex by von Bonin. Other necessities for group scanning is a widespread synchronism in the cortex by some clocking mechanism as the alpha rhythm of the brain. (This represents primitive talk about coding of input complexes that are no longer one dimensional, but have a complex field character. It does not really deal with mechanisms, but with some of the preliminary logical ideas. Further development of the logic is found in subsequent works of von Neumann and Ashby.)

Discussion on computer malfunctions and psychopathology is not of present concern except to note the reliability in performance required by the long neural chains in man and that the prefrontal lobes may have control over the circulating memory. Wiener further speculates on higher cell, group, race organizations; chemical, hormonal communication; lack of stability in political and social organizations; a theory of games in which only limited regulation exists; regulation in the social past; on the nature of society, etc. A 1961 supplement deals with learning and self-reproducing machines, from the point of view of a theory of games, and of a nonlinear mathematical theory. Finally, electric signals of the brain wave, and some aspects of correlation theory are discussed. (It is surprising that thorough earlier application of correlation theory to such nonlinear processes as turbulence is dismissed so briefly. It is through these studies that the use of correlation techniques in physical fields has commonly reached physics, and that their use for nonlinear fields was found to produce less than perfect results.) A harmonic spectrum is shown with a rather sharp band in the vicinity of 10 cps. (specifically a very sharp cut-off at 9.05 cps.). This is taken as evidence for an accurate clock mechanism. However, the alpha rhythm can be modified. Some general discussion is given about synchronization in nonlinear networks, possibly capable of generating a self organizing system as in brain waves, and thus containing the idea of a dynamic template. (These later remarks fit in with modern thinking. However, the authors have certain reservations. In experience with diverse problems involving time series, ranging from heat power cycles in the temperature regulation of the human, to the spectrum of turbulence, to studies in frequency division, to the Chandler wobble of the earth, as viewed from physical training, they have been reluctant to use stationary time series results. Thus, the statistical correlation analysis that Wiener has popularized has limited appeal. Their view remains a deterministic mechanics with certain indeterministic input elements. With small samples of data, it appears very difficult to determine, *a priori*, which philosophy will give better answers. The problem is noted by authors like Munk and MacDonald,[44] with reference to the Chandler wobble of the earth. From limited data, it is difficult to distinguish between a monochromatic response with a wide stationary dispersion, and a monochromatic response that wanders. They allude to discussions by Melchior (1958), Rudick (1953, 1956), Walker and Young (1955), and a rather classic doubt expressed with regard to correlation analysis of dynamic phenomena by Jeffries.[45] The problem is quite chaotic when dealing with nonlinear systems. Jeffries cites much earlier discussion in Goudny Yule (1927). The same criticism may be documented in turbulence. With regard to synchronization or to nonlinear resonance, time is well spent with Minorsky,[28] Chapters 18 and 19. It is only very simple nonlinear problems, mainly electrical networks, or mechanical systems, that have been treated quantitatively and with any degree of system.)

Thus, Wiener developed a mathematical-physical-logical view of nervous system organization and its response complexes, analogous autonomic ideas in the digital computer, and including communications theory. This increased future likelihood of interpreting the functioning, regulation, and control of the complex biological system. McCulloch with Pitts and Lettvin,[38] partially under the impact of Wiener and von Neumann, attempted the detailed attack on neurophysiological problems from a communications point of view. The importance of this work is in the philosophy, the details of their reasoning, and their accomplishments. Accepting a regulated interior, with materials regulation, and a guiding mechanistic-logical mechanism for self-actuated and autonomous processes, there remains need to view physiologically significant mechanisms and organs.

B. Oscillator Mechanisms

A dynamic analysis of an unknown system separates analyzable phenomena with measurement techniques that create neglible interference without disconnecting. One starts from steady states of the system. If it contains internal prime movers converting stored energy to energy in flux, the system ultimately degrades its energy to heat. Only a sequence of isothermal states in which potentials and source fluxes in the environment are kept constant or at constant rate are plausible. If periodic significant power transforming cycles are found in the fluxes passing out of the constant potential boundary, they are indications of unstable steady states, the limit cycles of Poincaré. Minorsky states, "A stable limit cycle represents a stable stationary oscillation of a physical system in the same way that a stable singular point represents a stable equilibrium." They are fundamental in nonlinear nonconservative systems. (The property also refers to clocks, engines, oscillators, rhythms, D.C.-A.C. converters. Distinctions are that a clock has a pure timing phase; an engine involves considerable power transformation, generally to mechanical form; an oscillator, generally electronic, is viewed as a frequency regulator rather than as a time regulator; a D.C.-A.C. converter is a specific form of oscillator, generally of low frequency and of electromechanical nature; a rhythm has become the biological term for repetitive cycles—sometimes not even limit cycles.) One must uncover elements of this type to expose what else goes on.

1. *The Nervous System Clock (The Brain Wave):* Orientation for nervous system waves may exist in the development of A.C. electrical power transmission for which D.C. was given up and a frequency, commonly 60 cps., chosen in the face of conflicting requirements. This is generated and monitored by central prime movers to run home and plant. Local equipment may or may not be synchronous. While most A.C. motors are not, quality uses are. Most equipment show effects partially correlated to 60 cps.; some even show subharmonic resonance, or frequency division. However, 60 cps. noise is pervasive. Similarly, near 10 cps. "fundamental" is likely embedded in the body structure. The timing function is possibly accurately established; and if so, by the general theory of clocks.[26] A primary

timing impulse in the biological clock might be obtained from the time delay of a signal running around an electrically distributed line, where the return of an impulsive signal triggers another one. Thus, timing accuracy could depend on a propagation velocity, which might require temperature regulation.

Brain wave data are like sounds from a busy switchboard. A hash of noise, equipment, etc., are all intermingled. One attends for predominant harmonic and transient behavior signals, but it is difficult to get all the process details from outside, particularly if the signals are small communications rather than power signals from which it is possible to infer prime mover properties. Prevalance of 10 cps. in and about small brain waves can only suggest prime significance without detailing functions. Action potentials and muscle tremor are in the 10 cps. frequency range. (In tremor an actuator power element is involved.) A 0.1 - 0.2 second reflex character suggests a single pulse selection by nonlinear synchronization rather than a general propagation time holding for many body paths. Smith's musical examples are apt. Ten independent power strokes can be done by well-trained amateurs at near 1 - 1 correspondence to a primary impulse rate. The skilled can do 20 strokes per second. As interpretation, a player learns to sequence pairs of power pulses. As test, when he tries to do 30 power strokes per second (frequency tripling), he can't. The 600 reflexes per second noted indicated group pre-arrangement in which the passive frequency response of the chain is excited. Data[22] on brain wave autocorrelation shows a narrow band pass in the 8.5 - 9.1 cps. range. Also cited are closely defined central rhythms obtained by W. Grey Walter. From Caton, Beck, and Danielevsky (in the 1870's) directly in animal brains, through Berger (1929-1938) on the human, thousands of studies have demonstrated the reality of electric brain waves. Elementary brain wave characteristics[46] are frequencies in the range 1 - 30 cps. over moderate periods, or 0 - 50 cps. over more extended periods of time. The predominant frequency is a 10 cps. signal varying with age from about two cps. at one year, six cps. at two, eight cps. at five, to approximately 10 cps. above 10 years. With little mental activity there is a considerable amplitude. If a problem arises, the amplitude drops, then rises again, and drops again, if another problem arises. The same pattern is shown in learning. A small input doesn't change the amplitude, but a strong input does. If the large input always follows the small input, then the amplitude will drop off when the small input goes on. When awake, a common spectrum involves a small six cps. rhythm (theta), 10 cps. (alpha), and 20-25 cps. (beta); when asleep a strong 1-5 cps. (delta), and 13 cps. (sleep spindle). There is a possible 40-50 cps. wave (gamma). Brain waves of higher animals all look alike. Adrian's descriptions[47] of neurone activity exhibits more physiological complexity than any simple model could explain. While it is possible that the brain waves indicate some sore of regulation, in particular frequency regulation, Guyton states, "the synchronizing mechanisms responsible for the brain waves have never been elucidated".[70] The current status on brain waves was inspected in Gray.[48] Added details are that alpha rhythms are highly characteristic of each individual; there is abundance and variability with activity; the external response at remote electrodes is not an averaging from a vast aggregate of neural units, but a more coherent signal complex; alpha rhythms can be externally synchronized; and these brain rhythms are a different class of phenomena from the unitary propagated spike potentials found in the nerve. These conclusions point toward central oscillator coordination, but it is uncertain that all oscillator-using elements are tightly coupled by synchronization to the central oscillator.

(The oscillator still appears to be a frequency regulator poorly regulated as activity changes. The sharpest evidence for the nonlinear oscillator character is the ability to externally synchronize it. This property casts doubt on the previous hypothesis of a timing impulse fixed by transit time around a distributed line. This is not so conveniently used for synchronizing by phase shift. Nonlinear synchronization is far from an obvious characteristic, in spite of easy "explanations" for relaxation oscillators. Three hundred years of clock making have taught the designer that to play with the resonator or other element producing the timing phase spoils the timing purity. Biologically, a satisfactory nonlinear description of the operating chain in both the single neuron and the brain is lacking both for brain rhythms and aperiodic single spike. Thus, while Wiener's suggestion of binary type computation for the brain has general significance, and the logic of neural nets by McCulloch has specific merit for the transmission problem, the real autonomous nature of a main balancing chain in the brain has not been exposed.)

2. *The Cardiovascular System Oscillator* (*The Heartbeat*): Major references used were Rushmer[49] and Schaefer.[50] All myocardial fibers may exhibit sustained rhythmic contractions.[49] Under appropriate conditions, all muscle may exhibit myogenic excitation originating in the muscle itself. (Therefore, there are parametric changes capable of making any muscle a limit cycle oscillator.) The heart rate is determined normally by the frequency with which the sinoatrial node exhibits excitatory electrical impulses, but this is regulated by the activity of nerve fibers from the autonomic nervous system. It is believed that the heart rate is increased by change in level of chemical substance released from sympathetic nerves near the S-A node (Epinephrine released from smpathetic nerves to the heart increases the rate, suggesting a chemical parameter that influences the stability or frequency of the network), and decreased by substance released from the vagus nerve endings near the S-A node , acetylcholine.

These mechanisms lead to adjustments at a slow rate in minutes and are thus likely regulators. If too fast, they might spoil the time keeping). Since any portion of the myocardium can assume the role of pacemaker, it is believed that the pacemaker of the heart is that region with the fastest impulse rate, normally the S-A node. (This represents synchronization, and was recognized by a great contributor to nonlinear mechanics, Van der Pol.[51] He pointed out that the heart behaved like a nonlinear relaxation oscillation, and showed networks that could simulate a P, R, and S wave. His specific model was equivalent to a lumped network with three degrees of freedom, three relaxation oscillators, in which the S-A nodal coupling furnished the highest frequency mode.) The wave of excitation from the S-A node spreads. The effect, viewed as a network, is to show a variety of terminal electrical outputs that can be related to this atrial signal. In a number of electrode positions there are found pulse segments referred to as the P, Q, R, S, T, and sometimes U waves. The repetition rate of the P pulse is believed to be related to the S-A node signal. (There are approximately 13 parameters involved in such a wave — the P repetition rate, the P, Q, R, S, T, pulse widths, the P, Q, R, S, T, amplitudes, the P - R time delay, the P - T time delay. Considerable study has been devoted to these parameters. However, a complete model of the electrical characteristics of the heart requires the origin of all of them. For example, the Van der Pol model exhibited seven characteristics. It is not so difficult to model any parameter number as to obtain a model that fits all disturbances. This is the vexing nonlinear problem with no superposition principle. As elementary summary, the autonomous character of a particular high frequency electrical oscillator, of near relaxation oscillator form, is the governing frequency regulated oscillator for the heart as an electromechanical system.)

Schaefer[50] expresses a more restrictive point of view. The heart electromechanical problem is the causal relation between mechanical and electrical events, between specific electric element characteristics, membrane potentials, and mechanical changes. There appears to be a mechanical delay. However, short 0.1 msec. delays found in skeletal muscles are not observed. Latency starts with the Q pulse. The end of the QRS complex is not precisely reflected in the mechanical events, but may be related to pressure changes. Doubtless the action potential is the first step toward contraction. There is no action potential without a mechanical contraction. However, it is not possible to explain fully this apparently simple relationship. The spread of mechanical events even seems to imitate the paths taken by electric excitation. The electromechanical chain is complicated, and at times a correlation appears completely absent. A number of correlates such as the chemical effect of acetylcholine, depress both action potential and contraction in nearly proportional amounts. In general, these correlations are overruled by complete separability. (E. Schutz [1936] is referenced for lack of proportionality or even correlation.) A normal ECG may be found in hearts with almost no mechanical contraction although the reverse is never found. At low temperature the two are dissociated. These observations indicate that in spite of unquestionable relationships between membrane potentials and contraction, secondary events may interfere with and make the electromechanical coupling complex. (Thus the electrochemical-mechanical heart chain is not fully clear. Chemical mediators influence frequency. With nerve clocks of higher frequency, 10 cps. or higher, chemical regulation cannot be excluded. No specific explanation exists for the electric frequency governing the heart. Mechanical muscle actions may sometimes be independent and sometimes not. The nature of the nonlinear coupling is not explained.)

3. *The Respiration Rate Oscillator:* Useful background references were Adrian[47] (a 1932 view) and Campbell[52] (a 1958 view). A chief function of the central nervous system is to send messages to the muscles which will make the body move effectively as a whole.[47] Citing Sherrington (1931), each muscle must be capable of delicate adjustment. However, contractions occur as "motor units" of fibers. While incremental gradations in response might possess as many steps as there are units (or driving nerve fibers), in sustained contraction there is another possibility of using motor impulse frequency. If produced by variation in stimulating impulse frequency, the tension will vary with the frequency as well as the number of units. If the impulses fuse, the contraction is smooth and the tension just varies with the harmonic frequency. If all the motor units act together, the muscle will not give a steady contraction until the stimulation frequency is high enough to saturate. If the different units act independently, the tension may be essentially steady, even though each unit is jerky. This is the state in reflex or voluntary contractions. These are the general results on muscle units. Studies date from Wedensky (1883) and Piper (1912). In weak contractions, small irregular waves of no frequency were found. In strong contractions, the same result was obtained with one regular large wave in a 35-50 cps. range. The explanation offered is that in weak contraction, the impulses come at very low frequency, each motor unit may aperiodically twitch (i.e. twinkle) giving rise to a smooth overall contraction and rapid irregular electric response. In a stronger contraction, the impulse frequency increases and the different nerve cells work more and more in unison. As a frequency of 50 cps. is approached, each motor unit is supplying maximum (saturation) tension, and a coordinated rhythm appears in the output. (These phenomenological descriptions of behavior have complicated electrochemical-mechanical underlying mechanisms and processes. They do not make the mechanisms or processes clear. Yet, the correlation of events in running and coordinating of muscle sets, as the important actuator elements in the system, is one of the most important elements to understand.

The problem is introduced here in its involvement in a major oscillator, the respiratory cycle.) Studies directly into the muscles from Wachholder (1932) through others like Adrian and Bronk, offer more detail. In a weak contraction there is a succession of small brief repeated waves with a frequency as low as 5 cps. (never lower than 5-10 cps.). During a slow contraction, the frequency rises, but soon a confused medley of large irregular waves ("noise") occur. This is the common electromyogram. The small coherent signal is swamped, until it appeared again in the relaxing portion of the contraction. It finally appeared that the regular wave was the effect of the motor unit nearest the electrode, while the incoherent time varying signals were due to other motor units in play, or coming into play. In the motor nerve fiber itself, rates in the range 10 to 80-90 cps. are found, varying with contraction force. The connected outputs from several nerve fibers show irregular twinkling. In the single muscle motor unit, many begin at 10 cps. or less, but go up to 45-50 cps. For example, in a motor unit involved in the respiratory muscles one finds a large repetitive impulse synchronized with heartbeat but uncorrelated with respiratory rhythm, an impulse frequency of near 30 cps. that changes with drugs down to six cps. uncorrelated with inspiration or heartbeat.

(As general physical guidance, one notes that nerve elements involve Van der Pol relaxation oscillator type of elements, as opposed to continuous sinusoidal oscillators. The transform elements as Wiener concluded are communications elements; i.e. exhibiting abstract logic type of "signals," rather than obvious dynamic characteristics of various "engine" or mechanistic elements. However, by abstracting a communications theory without reference to the physical power theory, the limitations that are still placed by mechanistic elements do not appear. There is a descriptive level in which they are not needed. However, a knowledge of the underlying mechanisms, gives a better understanding of the type of logic, and its limitations. These points become significant in treating the coherence of the information, both in space and time. For example, it is quite complex that on one hand such rhythms as in the heart are synchronized, while in the motor elements there seems to be an incoherent twinkling, or worse, an organization from a regular rhythm per unit of a random twinkling per group of units only governed in statistical properties, and a superior rhythmicity as the number of units "saturate." While it is possible to invent electrical network analogues, it is more difficult to come up with precise operating elements and energy transformations in the body. It is not analogues that are needed, but accurate representations of mechanisms. Otherwise, one is misled on each succeeding or higher integration. Also, it must be noted that the heartbeat, although regular and large in the region of respiratory muscles, such as the intercostals, does not synchronize with respiration, or muscle frequency; that the muscle frequency level, also of relaxation nature, changes with drug level. Another point emerges that beyond chemical messenger signals at nerve endings widely regularizing information through the system, a major chemical effect is likely to be change in the stability of networks. A tentative hypothesis, not apparent in Cannon, is that while the "long time" minutes to days response of chemical product is regulated, the "short" time chemical characteristic of tenth second to minutes is to "regulate" the electrical and mechanical network.)

At the high frequency end of nerve cell discharge, activity tends to be synchronized, and definite rhythms appear. This is seen in a powerful contraction such as the discharge of the phrenic nerve during inspiration. There is some difficulty in interpretating contraction results, in that the rhythm may be set by feedback discharges from the muscle (i.e., it is not clear whether the basic unstable system is purely electrical or electro-mechanical). However, there are examples in sympathetic nerves of persistent discharges. A grouping of sympathetic discharge can be demonstrated in phase with a respiration cycle in animals which all respiratory motion has been abolished just as a cardiac grouping has been found with only aortic and sinus nerves intact. However, it seems clear that the sympathetic neurones can't remain steadily excited for any length of time, since they are exposed to a fluctuating influence from the respiratory center. In the central nervous system, electrical analysis is not of as much value for the organized elements as each individual signal. They show something of the mechanism, but little of the way in which it is built up and controlled.

The automatic rhythm of respiration as controlled by the central nervous system is considered. The impulses to the muscles increase and decrease in frequency with each breath. A group of nerve cells in the brain stem is periodically involved. There are two possible loops, one the local respiratory nerve cells acting as an oscillator, like the heart; the other involving the muscles with a feedback signal. Both loops probably are involved. When the lung stretches, endings in the vagus nerve are excited, feeding back a sensory derived periodic discharge which cuts short inspiration. (A system becomes unstable, goes into oscillation, which is then used, in undisclosed fashion, as an automatic trigger for a particular phase of a high frequency controlled motor element — the extension muscle mechanism for the lung.) The frequency of respiration is so determined, at least in part. It may be regarded as "reflex controlled," but it is not quite clear what a reflex is. Respiration control is similar to walking or running control. It can occur without feedback from the muscles, though in the intact animal the sensory discharge doubtlessly helps control the rhythm. In the respiratory center, there is a continued periodic discharge at slow breathing frequencies even after the sensory feedback has been cut off. This was shown by Winterstein (1911), who cut the vagi and abolished respiratory motion. Though there is no sensory discharge, a motor rhythm can be recorded in the phrenic nerve. Buytendijk and Adrian (1931) showed clear evidence of respiratory activity in an isolated brain stem. (A rhythm in 1 - 2 cps. range). The potential changes are smooth and continuous and free from the irregularities of a wave formed by summing statistically varying impulses. However, if portions of the central ganglion chain are included, then the characteristic nerve type of discharge is found, superimposed on a characteristic respiration rhythm. (The existence of an isolated respiratory rhythm not generated out of a stretch receptor and CO_2 trigger, suggests a nonlinear synchronization. However, there certainly is no modelling basis for the system up to this point.) The slow type of potential waves in the regions which produce the respiratory discharges occur in other parts of the nervous system. It is not explained why the respiratory discharge is periodic. A periodic wave possibly similar to the respiratory type of wave is shown in groups of nerve fibers placed in abnormal chemical media. (Evidence again that stability may be affected by the chemical milieu). The discharge appears periodic, but structured out of a decreasing high frequence impulse repetition rate that cuts off for brief time (as below a threshold) and then starts up again at high frequency. One may only guess at the causes of these similar types of (nonlinear) mechanisms. "for those who wish to look at it from a more strictly physical point of view, Van der Pol (1929) has analyzed the properties of a particular type of oscillation which he calls a 'relaxation oscillation'. This occurs when the system is so arranged that it becomes periodically unstable and then rapidly changes until the oscillation is brought to an end by the building up of some inhibiting factor, . . . examples . . . are the periodic recurrence of epidemics and economic crises. So the respiratory neurones are in important if not very cheerful company. One interesting property of the relaxation oscillation is that it is easily synchronized with external periodic phenomena acting upon the system, and this is certainly true in the case of the respiratory center and the periodic discharges of the vagus." (It is obvious, as biological material has been digested, that much classic biological work shows good physical intuition. The same empathy is acknowledged for Adrian as was previously expressed for D'Arcy Thompson).

From Campbell,[52] the diaphragm is probably the principal, most important, but not essential muscle to inspiration. Other muscles can serve. The only motor nerve to the diaphragm is the phrenic. The fibers from the intercostal nerves are sensory. The action of the intercostal muscles in respiration is equivocal. Surface electrodes show bursts near the peak of inspiration, regardless of depth and frequency of breathing. Needle electrodes also show bursts on the steepest part of the inspiration, shifting toward the peak of inspiration. Thus their action probably is inspiratory. In the abdominal muscles, electrical activity increases during inspiration and decreases during expiration, increasing in pulse repetition frequency with depth and frequency of breathing. There are also electrical responses from the sternomastoid and scalene muscles, larynx, thyroid cartilage, and many others which in some circumstances participate in respiratory acts. In quiet and moderately increased breathing, the diaphragm and intercostals are most important. At high rates (above 100 lpm.) all muscles of abdominal wall come into play. Regarding the control and organization of the respiratory muscles, Pitts (1946) developed and Hoff and Breckenridge (1955) modified the generally accepted account of the respiratory center. Nerve cells identified as the respiratory center, which initiate the contraction of the muscles of breathing are localized in the medulla. With greater detail, its localization becomes less satisfactory. Liljestrand (1953) has doubted the value of retaining the term. Pitts' model describes an inspiratory and expiratory center, not quite discreet, but intermingled, with the inspiratory center dominant. Its discharge is basically not rhythmic. Events are a discharge from the center down the spinal cord, stimulating the motor neurons of the inspiration muscles, but also inhibiting the expiratory center, relaxing the expiration muscles. Lung distension stimulates stretch receptors discharging up the vagus to excite the expiratory center which then inhibits the inspiratory center, which relaxes the inspiration muscles, and expiration is then passively produced by an elastic spring rate. If impulses up the vagi are blocked, a slower rhythm takes place. (This neglects Adrian's comments on respiratory rhythms persisting in the brain stem.) Hoff and Breckenridge believe a fundamental rhythm is developed within the medulla, and modified and normally suppressed by nervous activity at higher brain levels (in pons, midbrain and forebrain) and other inputs such as from the vagi. Both agree on reciprocal innervation, in which there is increasing excitation in inspiration of inspiratory neurones and motor units, and increasing excitation in expiration, and corollary inhibition. Both models appear inconsistent with the pattern of muscle activity predominantly active in inspiration (bursts of contraction) against a background of passive relaxation. Others have thus stressed an inspiratory center with doubt as to the existence of an expiratory center that participates significantly in regulating pulmonary ventilation. It appears unlikely that the chemoreceptor-respiratory center regulating system adjusting ventilation includes neurones which activate expiration muscles. The level of activity of the respiratory center and the resulting force of contraction is modified by nervous and chemical influences. For ventilation regulation, the chemical factors, CO_2, O_2, and pH, are most important. The cells most sensitive to CO_2 concentration and pH are within the medulla. While these used to be considered the respiratory center, the work of von Euler and Soderberg (1952) and Liljestrand suggests that there are distinct chemically sensitive cells. (Though the detailed mechanisms are in controversy, there appears to be a local respiratory oscillator, as a limit cycle, in some higher nerve center. In one associated network, the stability of the network determining the limit cycle frequency is chemically determined by CO_2 and pH. A relaxation type oscillator is created in the larger electromechanical network that included the respiratory muscles.) Activity continues in the muscles of inspiration during the early part of expiration. The expiratory muscles are inactive during respiration in quiet and moderate breathing. The pattern of activity of motor units in the respiratory muscles is similar to other skeletal muscles, with no units in action in the relaxed muscle, more motor units coming into play successively as a contraction develops. Thus the force of contraction is regulated by varying the number of motor units in action, and the frequency of contraction of each unit. If there is any form of breathing resistance, there is a decrease in ventilation. This increases arterial CO_2 which stimulates the respiratory center. This leads to an increased force of contraction of the inspiratory muscles.

The two references show a large degree of consistency in description between 1930 and 1960. Another physically interesting study on the nonlinear respiratory regulator is by Grodins.[53] Two more recent reviews will be briefly discussed. From Dejours,[54] Volkmann (1841) postulated that breathing ventilation appears to be of a response nature; the transport element is CO_2; the sites of stimulation lie in every part of the body; the signal is ultimately determined by all nerves with central connection that can contribute signals, albeit delayed. The ventilation derives its impulse from the breathing requirement arising finally from the nutritional requirements of the entire body. Heymans and others (1927) demonstrated chemoreceptors in the aortic and sinocarotid areas, as well as in other areas. General requirements for significant chemoreceptors have been defined as sensitivity to low intensity, connection to a center, here a respiratory center, and connection to actuating motor units. Illustratively there exists dispute over chemoreceptors for oxygen partial pressure level in the blood. Present main concern will be with the CO_2 drive. Arterial blood can stimulate aortic and carotid chemoreceptors. Blood CO_2 can stimulate the respiratory centers directly. However, it is not clear whether the CO_2 chemoreflex plays a definitive role in normal breathing as opposed to emergency high CO_2 content breathing. It is believed that the activities of the chemoreceptors is normally significant. Cat studies indicate a chemoreceptor-mediated CO_2 drive of the respiratory centers with a CO_2 threshold of nerve activity of about 20-30 mm. Hg of P_{CO_2}. Also, there is dependence on the pH of the blood. However it has not yet been possible to evaluate the importance of the CO_2 or pH chemoreflex drive in normal breathing (due, among other things, to use of anesthetized animals). Reviewing evidence for chemoreceptors in other areas (e.g., ether paralyzing stretch receptors), most physiologists do not feel that the existence of diffuse chemoreceptors in tissue (Volkmann's hypothesis), say in muscle, has been demonstrated. (Thus a view still remains that local CO_2 in the vicinity of controlling receptors, — likely as a sampling system in a higher portion of the nervous system — acts as a phase modulating element for a local limit cycle by shifting a concentration level that controls the breathing rate. This again is the same type of nervous control, as in other coupled nervous-muscle systems.)

In a British source,[55] Lloyd, using Gray's data (1950), attempts a complex fit of ventilation rate to the P_{CO_2} and pH. However, such questions are unanswered as to whether arterial concentrations are the direct regulators of nervous activity, or whether the regulated device is only directly accessible to other fluid concentration levels. (This is a substantive paper from a physical point of view. It suggests need for breath to breath study of these factors to determine the chain in the chemical regulation. Papers that apply conventional servo control diagrams to the respiratory control are of little help in a physical analysis.) Widdicombe[55] reviews the respiratory response in the mean deep lung pressure level, the vagus nerve, and some other conditions. Breathing, viewed in esophageal pressure, resembles a relaxation oscillator. Increase in lung pressure inhibits the inspiration cycle if the vagus nerve is intact. Decrease in lung pressure (suction) on the other hand increases both depth and rate of respiration. Adrian had concluded that there was a pulmonary stretch receptor, possibly in the airways. Cooling the vagus nerve causes slower and deeper breathing. (This physically perplexing paper warns against casual analogue modelling of physiological mechanisms and recalls the dictum that to be sure of a model of a nonlinear process, the model and the real process must agree substantially for every major input type and network connection.) Cunningham,[55] on regulation during exercise, suggests increased respiratory rate is likely due to neural involvement at a fast rate of less than one breath, and a hormonal cycle involvement in a scale of minutes. It is widely held that changes in hormone level are minimal. Thus, there is some other unknown exercise factor. At the end of exercise, there is a rapid drop in ventilation rate in one breath, and then a slow decline. Gray and others have shown that the oxygen consumption rate and ventilation rate are proportional in work and exercise. Arterial P_{CO_2} rises a little, but not enough to account for the change in ventilation rate. The pH falls as the oxygen consumption rate increases, mainly due to a rise in blood lactate. A thesis is advanced that P_{CO_2} and pH changes observed may account for the slow hormonal component of the ventilation recovery rate. Thus, traditional static chemical stimuli in respiration can continue to account for ventilation during exercise. (These reviews enrich detail but do not extend a deterministic model of the respiratory oscillator. So far three oscillators, brain, heart and respiration rhythms, have been examined. They all have a neural local relaxation oscillator type characteristic. Their stability, as limit cycles, are adjusted by a variety of outside factors or loops, such as slow or transient changes in surrounding chemical concentration level.)

Iberall[56] examined the human as an energy transforming source both in rest and exercise, and found evidence for chemical engine dynamics in a time domain of minutes. Ventilation rate and oxygen consumption, and therefore metabolism, as computed from oxygen consumption measured at the mouth, were essentially proportional, as in Gray, so that changes in heat generated in the "engine" is reflected in changes in ventilation rate. Both in temperature rate changes, and ventilation rate changes, cycles of the order of two minutes, seven minutes, 35 minutes, and 3½ hours were found. In a quiescent subject changes in ventilation rate of the order to six to one exist in any five hour period. It was hypothesized that the high frequency (two minute) cycle involves a hormonal cycle, as the only possible mechanism that might fit the time scale. (Such studies suggest a second grouping of oscillator cycles, slower than the local neural timing oscillators, used for significant power actuator element controls. They pose a problem. If there is a coherent and a twinkling component in the primarily neuron derived oscillators, how would one organize fast power elements, the motor units with a "ten" cps. frequency response, into a slower rhythm at the minutes level? Such interrelation of the neural and hormonal systems is basic. In some undisclosed way there are follow-up characteristics in the hormonal system.)

In addition to an excellent older physical attempt at parts of the ventilation rhythm by Grodins[53] there are physically interesting automatic control views by Defares,[57] Defares and Visser (same volume), Clynes,[58] Horgan and Lange,[59] or Grodins (in press, New York Academy Conference on Regulation of Respiration – 1962). If the somewhat artificial transform techniques of automatic control theory were dropped in favor of the kind of analysis that Grodins or Defares and Visser give, the limitations, assumptions, and successes of the models would be made clearer. In a classical physical view, natural laws lie in the domain of differential relations involving physical state variables and time. Particular system characteristics may then be logically associated with properties of these equations, whether continuous, or only piece wise continuous. The physical science must select the mathematics, not the mathematics the physical science. The difficulties with nonlinear physical systems have only been partially exposed, and only by techniques that can be related to particular illustrative mathematical classes of differential equations. Techniques adopted from linear differential equations are of little fundamental aid. Applied mathematics does not end with the differential equation. It would be useful to have richer methods of solving these equations. The physical scientist is at present troubled at both steps of formulating valid wide-range physically founded, not correlation founded, equations and of solving these equations. As Defares and Visser point out, their modelling of dissociation and diffusion of CO_2 and O_2 in the blood, even though cast with considerable physical detail — as they put it, not a single known relationship was neglected for the sake of mathematical expedience — is not "isomorphic" with the real system, but an abstract scheme at a first, primitive stage of development. Such candor and understanding is refreshing. Thus, the type of static analysis of Lloyd's, even though of lesser ultimate significance in showing system operation, is more significant than correlative theories in forcing criteria for dynamic theories to fulfill.

4. *The Muscle "Engines"*: The muscle motor unit network was discussed.[47] Of added interest is Stuart, *et al.*[60] Shiver oscillations at 10 cps. seem identical to physiological tremor. In the literature, such "microvibration" is a regular oscillation dominantly in the 7-13 cps. range with 10 cps. mode. In a resting limb, tremor is seen as a composite of heartbeat pulse, as part of a high frequency ripple on postural change, and as muscle tone (i.e. as limit cycles). It changes with pulse rate or position change, and persists under drugs. Neural connection is shown during postural excitations of the body by bursts of electrical potential with the same tremor frequency. At rest the muscles show no electrical activity, perhaps involving too few motor units to detect. When chilled, activity of thermal muscle tone, or "preshivering tone", appears in resting muscles with vibrations similar to tremor, although a firing synchronization is not found. The frequency is 5-25 cps. Further cooling results in characteristic limb and muscle oscillations of shivering. There are potential bursts during contraction in each shivering cycle and complete silence in the relaxed phase. Each isolated motor unit fires once during the cycle, implying twinkling. The number of motor units per unit volume may change without change in tremor rate. During respiration, for example, a shivering tremor amplitude and the electric potential increases during inspiration and decreases between breaths, with a constant tremor rate. Shivering and physiological tremor seem to have a common underlying mechanism for a number of reasons. Antagonistic muscles are involved respectively in contraction and relation. The shivering is produced by contractions in opposing muscles with limited excursions. (Physically they act as a degenerate thermodynamic engine, doing no external work.) Tremors to give a few fold increase in oxygen consumption would require violent excitation. Descending inputs inducing shivering are not rhythmic. For example, a 50 cps. electrical brain stimulation is an optimal frequency to induce shivering, yet there is synchronization with lower frequency shivering rhythms. Further discussion attempts to elucidate the mechanisms underlying the shivering oscillation, in biological and in network terms, without satisfactory resolution. Many properties require accounting. Shivering is preceded by increased contrac-

tion, has a nearly constant frequency in all muscles, the frequency doesn't change as amplitude changes, is synchronized in antagonistic muscles, deafferation disrupts the rhythm but not the occurrence of shivering contractions, shivering resembles tremor. (The paper is suggestive. One surmises limit cycles, mediated by frequency signals representing communications information from thermal receptors. There also seems to be some loose coupling from the nervous system that tends to coordinate the oscillators.)

The experimental nature of muscle tremor is given by Rohracher.[61] All through life the body shows small vibrations, mainly with amplitudes in the range of 0.5-3 microns, and with frequencies in the 7-15 cps. range. They are an unbroken series of larger and smaller waves that change in an irregular manner; there seldom are long series of regular frequencies; most show a second frequency of different size. The frequencies are not stationary, nor purely sinusoidal. Typical records show a strong varying fundamental, and waxing and waning. If near arteries, the pulse rhythm will also be found in the vibration. In a large sample of people, vibrations are found throughout life with very little deviations, and in sleep and under drugs. In animals, even in death or with separation of the medulla or extirpation of the heart, the rhythm persisted 50-70 minutes. On a large sample of people, the composite frequency range of the fundamental was 6-18 cps. (the major band is 8-12 cps.). Coherence or synchronization with the alpha rhythm is not clear. The frequencies vary somewhat with animals, illustratively higher in birds. There are temperature effects, moderate psychological effects. During work, the amplitude is largely increased, but returns to normal within 10 minutes after cessation. The microvibration is thus inferred to be muscle contraction. Whether voluntary or not, or from drugs, change in the muscle extension is accompanied by a change in microvibration amplitude. By innervation of the motor nerve the vibration disappears. The frequency lies in the action potential frequency range of 5-14 cps. Apparently the microvibration is a more sensitive indicator of muscle activity than the action potentials. Even when electrical activity is not found, as in sleep, the microvibration continues. Possible functions of the vibration are discussed. For example, one is assigned in temperature regulation. Microvibration changes with temperature. It is suggested that at 10 cps., 650 gr. of muscle could produce 1700 Kcal per day of heat, i.e., by only 2½ per cent of the 27 kg. of muscle of a 70 kg. man, and this could be regulated through frequency changes. (These two papers are significant in showing the reality of muscle oscillators, that all muscles are generally in the same frequency domain as the brain waves, that a persistent limit cycle oscillation exists likely as precursor to power control of muscles both for external work and heating.)

Returning to an earlier discussion,[56] in seeking explanation for temperature regulation a limit cycle engine was required. An approximate two zone temperature distribution in the body (nearly "constant" core temperature and nearly linear peripheral drop to skin temperature) suggested that the active power source had to be located at the juncture of these distributions, basically in the muscle sheath plus re-entrant pockets of other "muscle" elements. Thus metabolic variations of these elements should be the major regulating heat source, and yet must be available also to do external work. The microvibrations show a reality of high frequency, neurally mediated, oscillations (likely localized). Thus a high frequency electrochemical-mechanical domain (in which the chemicals are either fast internal or synaptic traces in or near the nerves) is secured. Experimental data, at much lower frequency, show a muscle engine at the minutes level, suggesting that this must be under hormonal control. (Grodins' work suggests careful review of this reasoning.) Other slower frequencies are also found, as limit cycle oscillators, with increasing vagueness in function. A 3½ hour limit cycle is interpreted as being a thermodynamic cycle, whose closure source is not clear. (For longer time, the likelihood of circadian rhythms exist. Thus there is a rich frequency spectrum of just oscillators in this main actuator mechanism, the muscles. Each frequency domain has different functions. The highest frequency, 10 cps., is likely a primary A.C. frequency used at near communication levels. It is unlikely that there are local electrochemical-mechanical oscillators in the body higher than 100 cps., although time delays down to millisecond levels may be used. The two minute muscle cycle seems to be a major engine cycle. A difficult problem as in the motor unit coordination is how to coordinate the entire body muscle system to produce long cycles. This likely requires cooperative effort from the hormonal system and higher nervous centers. The body may act quickly on sensory inputs and electrically connect up motor elements using chemical messages dropped along the network. If significant power is demanded, this hormonal system comes into play to furnish longer time adjustments and regulation. The information state may be known by the chemical messages left at each synaptic point. For power elements, the hormonal system stays in operation. If the task becomes trivial or routine, as shown by unnecessary loading of the power or communications channel, a subchannel, a "conditioned" reflex, is assigned the temporary duty. While crude, this model binds bits of "information" about the system into a cohesive picture of a central computer control system. Control functions may not be an intrinsic portion of the system, while regulating functions may be. When the system wants a particular control function, it can be set up from its available networks. Thus, the characteristic property of the system may be that it can operate in control modes, rather than own many controllers, and that most of these control modes are likely learned.)

5. *Eating, Resting, Voiding Oscillators:* The previous oscillators all had a fast component involving a localized neural-chemical-mechanical chain. Transition to slower rhythms seems to involve more direct chemical level mediation of longer chain relaxation oscillators. Finally, a longer, less direct, chemical mediation from the hormonal system appeared. Involvement of even longer chains is apparent in a very first examination of the whole system. Suppose one wants to do a static test of the system. It is immediately clear that it can't be done. The system doesn't operate in a static 'steady state.' It intermittently wakes and rests, eats and drinks and stops, it voids and stops. The previous oscillators were not affected, to the point of stopping, by such intermittencies. Thus, they were viewed as essentially autonomous limit cycles. The present cases do not permit such easy escape. A common imperfect technique is to observe the entire behavioral response of lower animals including incidental self-actuation. If there is no frequency entrainment by group behavior, and each animal is isolated, behavior rhythms and a large variability emerges. In physical terms, both coherent signal and noise are considerable. In many phenomena the signal is weak or poorly coherent, but clearly rest-activity; eating-drinking and stopping; voiding and nonvoiding are all relaxation oscillators. (It is implicit in a theory of oscillators, that resonant element oscillators tend to be quite rigid in time metering, whence their accuracy, but it is easier to vary the time keeping of relaxation oscillators. This may account for the considerable frequency jitter.)

Regarding triggering eating, voiding, and drinking Alvarez[62] adds more detail on chemically mediated hunger pang oscillations. The small bowel is the most important part of the digestive tract. There appear rhythmic segmentation movements, slower tonus waves, and peristaltic rushes, in which the latter is trigger-excited immediately upon taking food. There is a frequency difference along the intestine varying with distance from the pylorus (20 cpm. in the duodenum to 10 cpm. in the lower ileum). In examining rhythmic contractions in the gut, the question arises of distinguishing rhythmic oscillations in the muscle itself and in the nerve. Though there generally is cooperative endeavor, in the face of overwhelming evidence that individual muscle cells show rhythmic contraction, it is presumptuous to insist that every rhythm is of nervous origin. (The local oscillator theme continues to arise.) He has a final summary on hunger, appetite, and thirst. There are sensations both general and specific associated with hunger. Some believe that emptiness of the stomach results in hunger contractions, others that signals reach the brain from all over the body, others that there is a lowering of food material in the blood, or that there are changes in the brain. Contractions may be an alarm, but not the sole symptom. People get hungry for specific foods. The very thin, who should be hungry, are not. It does not increase during fasting, but lets up after a number of days. A few mouthfuls of food can then make the sensation disappear. Blood sugar does not always influence it. Appetite and hunger are different. Thirst has been thought to be due to dryness of membranes, but this is not essential. It can be produced by intravenous high salt solutions, or if dehydrated, it can be relieved by injection of physiologic salt solution. Water intake corresponds to metabolic needs, i.e., is closely regulated. (While this points to gastrointestinal mechanisms, no connection has been shown to eating and drinking rhythms.)

Anand[63] indicates that hunger, appetite, and satiety were formerly considered in digestion physiology, now more a function of the central nervous system. The regulation of food intake, his review topic, thus becomes a problem in the regulation of the interior. Theories of the origin of hunger sensation which determines food intake, were a peripheral theory of hunger pangs and rhythmic contractions of the stomach (evidence against this was that various degrees of eliminating the stomach or its nerves did not change the food ingestion rate. It appeared that a calorie level was being sought by the animal. Stomach sensations tend to be an alarm signal for hunger, not a control); a central theory with a hunger center in the brain; and a theory in which hunger is a sensation of general origin. Gradually the hypothalamic region emerged as a likely regulator of food intake. (Slow regulation is being discussed.) A feeding and satiety center are proposed. Electrical stimulation in the region increases daily food intake. While these centers act to facilitate or inhibit, there may be more basic mechanisms of feeding behavior involving the brain stem and spinal cord (Brobeck, 1957). An urge to eat, stemming from the nervous system, increases self-actuated activity in the animal. The mechanisms for regulation of feeding and self-actuating locomotion, a prerequisite to feeding, are integrated in the hypothalamic region. On a lower level, sensory components serve as inputs. In a hungry state with its decrease of blood sugar level, the circulating adrenalin rises, produces intense reticular stimulation, leading to random locomotor activity. The hypothalamus functions in a qualitative fashion on a higher level. Brobeck (1957, 1960) has stressed the similarities between the regulation of feeding and of respiration. They are both rhythmic, subject to reflex control, with integration and motivation from the brain stem. All levels of the nervous system, including the cortex, take part. Their rates consist of an intermittent quantity multipled by a frequency. While possessing central mechanisms, they are affected by specific reflexes from organs or sensory sources. Sensations of hunger are so strong that they must be included in any explanation of feeding, but with explanation in physiological terms. A large portion of the early neural development of the brain is referred to as the limbic system. This appears to regulate internal activities, whereas the neocortex regulates reactions of the body to the external environment. The internal regulation is achieved through the regulation of autonomic outflows, secretions of the endocrine glands through changes in the secretion of hormones from the anterior pituitary, and through regulation of affectively determined behavior. It appears that the calorie level is what is ultimately regulated, but in shorter time food intake may be adjusted to the water intake. It is unclear how the hypothalamus might determine the dehydration of specific tissues. The specific effect of hormones in affecting food intake regulation is suspected, but not determined. (This review points up many common problems. As physical argument, if an approximate equilibrium situation exists such as humans or rats in some kind of standard averaged daily situation might show, then a nominal standard activity and equilibrium weight level exists. Thus essentially constant mean calorie requirement, standard oxygen consumption, standard water consumption, and an essentially standard ventilation rate exists. The different mechanisms or organs involved in each element can require a different time scale, thus likely requiring storage elements to achieve coordination among these correlated parameters. If one of them exhibits limit cycles, they all must, and it is likely that related instabilities might exist. Furthermore, if there is an appreciable power cycle — as in the muscles — then the materials scheduling, done by limit cycles, must come off very well or systems tend to queue up. In order not to be tied down to tight scheduling, the limit cycles seem to be of a relaxation oscillator nature, so as to permit large degrees of delay in individual cycles without sacrificing the long time integrity of the oscillator. Consider the following suggestive parallel. In such common activity as talking, individual breaths can be delayed or speeded up one or two. However, "noise" tends to drop out over five to seven breath averages. On the other hand, as extreme, the breath can be held for 30 to 60 breaths. In eating, individual meals can be delayed or speeded up one or two. However, "noise" tends to drop out over five to seven meal averages. On the other hand, as extreme, meals can be delayed for 30 to 60 meals. Components that create a cycle in a physical engine need not have similar mechanisms or schematics, but it would not be surprising if the body tends to use a similar organizing logic over and over again. Thus this paper, particularly Brobeck's ideas, illuminate active elements in the body. It would be most revealing, if just as primary oscillator signals were shown in the S-A node for the heart, and by Adrian in brain stem for ventilation, one could be found for the food intake, and water.) A recent example on electrogram responses of the stomach is shown by Sobakin *et al.*[64] Potentials from the stomach are recorded on the skin with a three cpm. rhythm. These are strongest ½ to 2 hours after eating. The same rhythm is found at the mucous membrane of the stomach when free from food.

In a symposium[65] on food intake regulation, Anderson indicates that water balance is maintained by mechanisms controlling water losses via the kidney and by those concerned with regulating water intake, with the hypothalamus playing an integrating role. Knowledge of central water intake regulation, obtained by lesions, is piecemeal, so that the thirst mechanism is still puzzling, but it remains reasonable that both food and water intake regulation are located in the hypothalamic region. Various inputs seem to influence these mechanisms. The preoptic region also seems to be connected with the drinking urge, but not the eating urge. The pallidofugal fiber system in the lateral hypothalamus seems to be essential for both. (The hypothalamic region has been involved in a large number of local oscillator engine elements both in short signals up to the 10 cps. range, as well as many suggested regulation functions in longer time domains. The region appears well endowed with local areas capable of producing mediating electrical signals which may be direct stimuli, as in the case of muscles, or may act by frequency conversion. This thus tends to be an "alarm" switchboard to produce regulation at all time domains. An idea arises that there may be a major key input such as its local temperature. This may add importance to Benzinger's thesis. He has shown a very sensitive response in the hypothalamus. A shortcoming is that the regulation dynamics of the region has not yet been exposed, for if the area as a whole is an alarm switchboard, involving a very sensitive temperature key, it is essential that the full static and dynamic behavior of the connected mechanisms be traced. Explanations of system operation await this primary step.) Comments by Cort make an added point that the control of water balance is linked with the Na balance in the body. Morgane strikes a more mechanistic note. Between the rhinencephalon and hypothalamus, on-off mechanisms — say for feeding — are to be found. These seem to provide the regulator of caloric balance, by which energy intake is adjusted to energy expenditure. Some anatomical evidences are reviewed. (This paper may be oversimplified. However, it focuses the previous hypothesis. These brain stem level systems that appear to help regulate interior parameters seem to act in a coordinating switchboard as on-off switches. If there is some motor network, in the present context a wide aggregate of coordinated oscillators, and an alarm is received, then a new network loop may be switched in. These are not necessarily switched in one at a time, or even absolutely specifically. Any alarm signal may switch particular complexes of networks, and thus influence local oscillator stability. A continuous flow of alarm signals is then constantly readjusting the oscillator complexes according to some undisclosed scheduling. All of this does not have to involve higher brain activity, except in a twinkling mode. The higher brain may occasionally or regularly — its algorithm is not known — sample the lower system through electrical or even chemical feedback to take interference action. It is also possible that a master signal — such as temperature or excitations of the anterior pituitary — may key these brain stem on-off switches, say by changing their set points, so that constantly shifting switch levels exist, with constant receipt of input alarm signals, and a continued shifting of networks that change the stability of the motor oscillators removed from the center.)

Soulairac[65] adds another element of complexity. While the hypothalamo-rhinencephalic elements may perform the on-off switch function, certain neocortical regions may mediate, say hunger or food intake. In particular, the importance of wakefulness state regulation is emphasized. Metabolic variations, basically used to regulate food intake, central temperature, and intestinal absorption, finally inform the H - R - C systems of neurohormonal messages that affect degrees of wakefulness. It is known that a certain fundamental wakefulness exists that essentially regulates waking and sleeping, and that the element responsible is the mesencephalic reticular formulation with an adrenergic hormonal function (apparently by a restlessness type of function). A second type of specific wakefulness, with the thalamic and rhinencephic structure responsible, exists. A lack of balance between these two degrees of wakefulness causes important disturbances in the regulation of food intake. (These ideas seem to point to one or two frequencies in sleep-wakefulness, with coupling through the alarm system to the food intake system.)

In another review, Anand[65] notes that the pattern of nervous regulation of food and water intake is similar to most other visceral and autonomic activities such as the cardiovascular, respiratory, gastrointestinal, or body temperature; that these, with the hormonal systems, are ultimately responsible for the regulation of the interior. (Thus the path of disentanglement chosen here for physical orientation is supported.) Rapid messages from the organs involved are received. This is not discussed. Slower information from the interior, such as the effect of feeding, is transmitted to the nervous regulating mechanism. It is likely sugar level that is noted at the hypothalamus. Brobeck suggested that day to day regulation of food intake might be temperature sensitivity in the hypothalamus, but not longer time effects. Hervey[65] comments on the signal that informs the hypothalamus about the state of energy balance, and a short and long term response. However, no theory of the regulation of calorie balance explains how the balance state of the body is actually measured. (Disturbing in these discussions is that no satisfactory data are shown of the steady state of the system.) Janowitz[65] eliminates hunger contractions and epigastic pang as a regulating element or even cue for food intake, and gastrointestinal elements as cue for cessation of feeding. Yet determinants of the food volume per feeding are needed. They are, speculatively, neural and nonspecific, and likely multiple factored. LeMagnen's[65] remarks are complementary. Individual intake per meal is computed in advance of the eating to correspond to a metabolic requirement. Action of the food on mouth and stomach receptors then mediate the short term regulation of food intake. There are time delays before the system catches up with its metabolic requirements. Teitelbaum[65] accepts the hypothalamus as an on-off switch to excite and inhibit feeding for both single meals and longer time. The food urge also involves the hypothalamus. A symposium summary is by de Ruiter.[65] A key thought is that in food intake regulation, one is dealing with a vast and intricate network of information channels. (While cycles exist in food and water intake, it appears that the experts have not viewed this as an important facet of their problem, but it is also clear that they have not provided any real mechanistic picture of how the food intake rate is regulated. From a physical point of view, the lack of view of both the static and dynamic characteristics of the elements that must lead to an oscillator cycle is damaging.)

Shapiro[66] on rest-wake notes that while daily sleep is familiar, and there are obvious and contradictory theories of function and mechanism, not known is why or how much sleep is necessary, what happens that is biologically useful, and why some sleep periods are more useful than others. Until recently mechanical, electrical, chemical or psychological analogues were naively put forth. With no sleep, people feel tired and sleepy, but perform motivated tasks with usual strength and skill, and experience periodic variations in alertness, following the 24 hour body temperature curve, even with no sleep. Aserinsky and Kleitman (1953) started a new phase in examining physiological events in sleep. Four stages are found. There are recurring episodes in which states of arousal like waking appear. Ultimately a 90 minutes cycle is established. As time goes on, the proportion of time spent in a lighter stage of sleep increases with succeeding periods and the cycles become increasingly shallow until 7½ to 9 hours after going to bed the subject awakes. The prominent 90 minute cycle was first shown by Ohlmeyer, *et al.* (1944). Hypothetically this is a periodic oscillation in the brain, and sleep is an aperiodic modulation of this cycle organized into a sleep segment. (Presumably these sleep segments are then periodically recurrent. Only a limited amount of information may likely be cited as to the precise mechanisms of these oscillators.)

6. *Hormonal Rhythms:* (It emerges that the major interior oscillator mechanisms and autonomous systems so far viewed as immersed in the regulation of a portion of the brain associated with the hypothalamus, more inclusively the limbic system, and that the chemical signalling system, the hormones, may be similarly coordinated. Also, nervous signals to hypothalamic centers in mammals produce hormonal correlates, illustratively hypothalamic regulation of anterior pituitary function. A current idea is that the pituitary stalk is the final common pathway between the central

nervous system and the endocrine system. Oscillator mechanisms will now be sought. Animal "heat", menstruation, are examples of hormonal mediated cycles. The estral cycle of the rat is repeated every four to five days, if there is no coitus. Yet Desclin (1954) notes that rats submitted to continuous illumination show a state of constant estrus. Light level has abolished the rhythm. Again evidence points to level mediated instabilities, now on a time scale long compared to 10 cps. rhythms.)

A 1950 treatise[67] points out that the cyclic nature of ovarian activity — estrus and menstrual cycles — is well known. It includes a follicle growth phase under hormone influence and a "spontaneous" luteal development and discharge phase from ruptured follicles with hormone secretion. Nervous stimulation in mating in some animals, starting at the hypothalamus and acting on the anterior pituitary, releases hormone to trigger rupture. (How long time delays for long period relaxation oscillators may arise is answered plausibly, though vaguely. Hormones can regulate a growth process, under the secondary supervision of a hypothalamus on-off regulator center — possibly connected as yet undisclosed to a central hormonal regulation center, also on-off, likely the pituitary — to help regulate a slow growth, which at some phase "spontaneously" discharges, and as a result of discharge produces new hormonal signal.) The essential role of acetylcholine in conduction at the nerve junction is stressed in illustration of chemical control of nervous activity. (One notes little attention to the dynamic or cyclic nature of hormones in conceiving their biological action, likely because of the measuring difficulties.)

In a 1959 pituitary symposium[68] the only oscillator actions cited are by Ikkos and Luft on metabolic action of human growth hormone. When administered, there are possible cycles, of the order of five days, shown in creatin secretion and its level; there may be some weight rate cycles, but certainly weight rate changes, and a relaxation time of the order of 10 days with cessation; there may be similar cycles in excretion of ketones. (Metabolic associations here on a longer time scale are thus quite real.) Loraine[68] on pituitary gonadotropic assays in human urine, shows hormonal excretions during menstrual cycles. The work reported is more meaningful quantitatively than any previous. Gonadotropic and oestrogen peaks occur at midcycle and are presumed to be associated with ovulation. The gonadotropic peak was either simultaneous or delayed by one to four days behind the oestrogen. A result of insemination was a rise in gonadotropin after nine days, and a rise and maintenance of a high luteal phase level of pregnandiol and marked delayed rise in oestrogen excretion. In its discussion there is an interesting short exchange in which de la Balze asks whether the relative time of peaking of oestrogens and gonadotropins in urine means that the pituitary is not the master gland, and Loraine replies that further work assaying directly in the blood in menstruating women demonstrated gonadotropic activity at midcycle, but in no case was activity detected in the follicular or luteal phase of the cycle, that postulating "ovarian autonomy" during the cycle is fascinating but only hypothetical. (This excellent work touches on the fact that dynamic assays of hormones is in its infancy. Seeking to expose hormonal mechanisms of dynamic chains or oscillators, except by inference is not yet too practical. It is likely a measure of prominence, rather than uniqueness, that hormonal oscillations are detected in menstrual and sexual cycles rather than in many, many other hormonal loops. In this connection, the Kinsey studies showed a considerable degree of rhythmicity in sexual "appetite" on a behavioral level in humans that varies with factors such as age. Frequencies were of the order of a few "feedings" per week. It is valid to point toward a hunger analogue, here at a very low frequency.) Bottari[68] alludes to the significant work of G. W. Harris (1948, 1955) in indicating that the thyroid function is influenced by the hypothalamus and the pituitary stalk.

Beach[69] looks at relations between endocrine secretions and overt behavior. Ovarian secretions exert a profound effect upon spontaneous activity of the female mammal; during estrus they become restless; activity increases during the period of greatest follicular development. A study by Farris (1944) in women indicated that activity (miles per day walked) was maximum at the midpoint of the menstrual cycle, and that in both women and female rats activity had a hormonal basis with a maximum occurring at the time of ovulation. (This firmly shows that the reality of longer time "hunger" is shown in creating an instability that brings a lower frequency limit cycle oscillation into play. In rats, this was shown in a four to five day estrous cycle. Now it appears that activity level, and metabolic level — at least in females — can have long time oscillator cycles, obviously hormonal, with long time delay elements now obtained by growth, a spatially distributed active process, rather than from passive inertias, or relaxations.) Beach reviews a large number of indirect ways in which hormones can condition behavior reactions. (In general, physical analysis avoids "abnormal" operation, such as opening chains by lesions, or artificial or "nonphysiological" levels of drug excitation, etc. However, this luxury is not always possible. Hormone operations at low concentrations are difficult to find directly. One may still seek plausible effects.) A few cited were temperature regulation, nest building activity, water and food intake, selection of dietary elements, salt intake, metabolic rate, heart rate, sexual response, calcium deposition, locomotor activity, oxygen consumption, cell division, growth, blood volume and composition, milk secretion, etc. (It is obvious that so many functions can be named for which evidence exists for hormonal components, that it would be foolhardy to deny likelihood of regulation or control or involvement in the dynamic chain. It is only real, specific details of mechanisms, and proof of the nature of the response, that is lacking. It is foolhardly for the nonendocrinologist to do little more than read and note. However, a cursory search may be made for rhythms.) Illustrative of endocrine control in cyclic processes, the normal one-year larval period of the bullfrog and salamander can be reduced to one month by thyroid feeding. Anterior pituitary extract can induce molting, likely through activation of the thyroid. These processes may be synchronized. Secondary sex characteristics in frogs may vary with a seasonal sex cycle. There are hormonal rhythms in seasonal breeding species, particularly pituitary. Some animals are believed to exhibit an inherent pituitary rhythm; others may be dominated by environmental stimuli. However, in most species it is inherently cyclic, and most commonly, synchronized. It is likely that day-night, seasonal, and temperature, synchronization exists. An example is the ovarian cycle in the sand smelt of about 14-15 days, likely, synochronized by two week tides. Domestication of some animals almost completely obliterates seasonal effects. Normally, mice outdoors may not breed from November to February, whereas indoors they reproduce all months of the year. Light level can control mating rate activity. Lizards maintained in darkness show marked diurnal color rhythms. A provocative thought was developed by Coghill and Watkins (1943) of an inherent periodicity in the responsiveness of organic systems to stimulation, and more specialized functions may depend upon these embedded basic periodicities of general and primitive processes on which these newer functions have arisen, illustratively the complex of locomotor activities. The lactation cycle in a female rat can be prolonged for many months by supplying her newborn young every few weeks. Bissonnette (1935) developed a theory of pituitary periodicity and an inherent rhythm of secretory activity which affects the gonad, thyroid, adrenal, and possibly other glands. In a final interpretation of hormonal effects, Beach stresses that little is known about the effecting mechanisms for endocrine substances. Real difficulties exist to assure connectivity between the endocrinological elements and the behavioral responses which are often neglected by experimenters or theories. Illustrative of poor practices are correlating gland weights and behavior, assuming a hormonal factor when psychological factors exist, isolation of one hormone and a single behavioral response, or of one stimulus aspect in the environment, or broad generalization from narrow experiments. Some guiding generalizations are that no behavioral responses investigated depend on only one hormone. Hormonal control of a complete behavior pattern is mediated by a number of mechanisms rather than a critical one. Different behavior patterns may vary in degree of dependence on endocrine products. Every behavioral response is by a complex of mechanisms to internal and external inputs. The mechanisms are neuromuscular, and neurohormonal, with characteristics determined genetically, by previous excitation, and by the chemical nature of the internal medium.

Hormones may influence behavior through their effects upon the organism as a whole; on specific morphological structures employed in particular response patterns; through their efforts on peripheral receptor mechanisms; or their effects on integrative functions of the central nervous system. They may also control nervous organization development; periodic growth or inhibition of nervous elements; and control of sensitivity to stimulation. The latter is believed by many as existing, and taking place by altering the conductivity of nervous tissue. Alternately, there is Danforth's statement (1939) that in general, cells utilize hormones rather than hormones actively stimulating cells. (No clear-cut summary emerges. In some respects the hormonal system appears to be a system parallel in function to the nervous system, and involving a local neurochemical oscillator; in some respects there appears to be a similar or tied in "on-off" chemical regulator switchboard, whose action is somewhat more diffuse than the "on-off" centers in the hypothalamus. The signalling elements, the endocrine glands, are spread out through the system for not completely explained reasons. The signals seem of lower level, more diffuse, generally slower, and don't involve as much higher computer control intervention. On the other hand, at the communications level, there seems to be intimate connection between the nervous system conduction and the hormonal regulating state. At the distribution level, it is not clear which system keys which. However, the fast action existing at times suggests that the nervous system makes distributed chemical signals available to key the entire interior chemical system, and thus furnish interior sensing information for the endocrine system to ultimately act upon. Outside of the fact that there are likely hormonal oscillators, both slow and fast, that there is evidence for broad synchronization of some cycles — possibly indicating relaxation oscillators — and that there is considerable hormonal regulation of interior and overt self-actuated behavior, the system still remains msyterious.)

Two short symposia,[65] on brain-gonad relationships, and on mechanisms governing luteotropin release were examined. Van der Werff Ten Bosch states that the significance of the hypothalamus in the physiology of reproduction is well accepted. The pituitary gland's secretion of ovarian stimulating hormones does not occur appreciably without a hypothalamus. Hypothalamic action is involved in sexual differentiation early after birth (in rats), in sexual maturation, in the adult female cycle, and likely in the adult male in gonadotrophin secretions. It provides the pituitary with appropriate stimuli for the release of gonadotrophin. After puberty, hypothalamic sensitivity greatly diminishes. Lundberg[65] discusses extrahypothalamic regions in the central nervous system that may be involved in gonadotrophin secretion. A discussion by de Groot emphasizes "limbic" brain components. There is an on-off regulation system produced as a higher order or organization, consisting of the hypothalamus, the pituitary and target-organs. (Further endocrine complexity in these papers are left to experts.) Harris' summary[65] is that a vague general view of brain-gonad relations has formed. In autonomous fashion, the hypothalamus is capable of regulating gonadotrophic secretion in localized areas, with more peripheral areas of the central nervous system showing their effects through the hypothalamus. The function of the pituitary stalk, the "final common pathway", is now established as the hormonal link between the central nervous system and the endocrine. Reciprocally, how the gonadal hormones return signals to the central nervous system to complete the regulating chain of the rate of secretion of gonadotrophic hormone, and how behavior characteristics of the animals are adjusted in accordance with the endocrine balance are being experimentally demonstrated. Remaining unknowns are hypothalamic site and function localization; extrahypothalamic areas involved, amygdaloid nuclei, piriform cortex, hippocampus, others; if the pituitary stalk through its hypophysial portal vessels is an anatomical and functional link between the hypothalamus and anterior pituitary gland, and there is evidence that the rate of secretion of luteinizing hormone is controlled by hormone released from the hypothalamic nerve fibers into the portal vessels, there is a problem of the number of humoral agents from the hypothalamus in relation to the number of anterior pituitary hormones; assay of gonadotrophic hormones in blood would be of great value in analyzing gonadotrophic secretion; the feedback of gonadal hormone to the central nervous system requires work. (W. Masters comment [1955] that the endocrine system is intact and capable of effective functioning at any age if the failing effects of the gonads at later age are neglected, and in this defection they may well be the "Achilles Heel" of the endocrine system, physically highlights this attention to the gonadal system. Harris' ample summary assigns a near central role to the anterior pituitary hormones, linked in a parallel regulating system to the hypothalamus with undetermined connections back from hormones out in the "field" to the central nervous system.) There is preliminary evidence from Wolthuis that the hypothalamus acts to inhibit secretion of prolactin from the hypophysis. A summary by Desclin[65] reviews the various facts and ideas about the release of prolactin.

To insure that the accepted foundations of current teaching were not lost, Guyton,[70] Ruch and Fulton,[71] and Best and Taylor[72] were reviewed in conclusion. In Guyton,[70] hormones control chemical reaction rates, transport of substances through cell membranes, and secretion. Secretions are controlled in part or whole by effects from the nervous system. Glands tend to under and oversecrate. Information is fed back to check further secretion. (These are more likely regulating chains, but with no certainty that even more than balances exist. Dynamic stability of the action is an open question. The description is only literary.) Illustration of speedy hormone action is given in a bone break in a rat. A nervous signal is transmitted to the hypothalamus, a hormone secretes into the hypophyseal portal system and is then carried to the adenohypophysis where corticotropin secretion is excited in the glandular cells, in turn causing adrenocortical secretion of cortisol to show up with a time delay of about five to six minutes. A rat with normal growth hormone holds constant weight over a substantial portion of his life span of a number of years with a few per cent ripple, perhaps involving a 20 - 30 day cycle. A thyroid extract injection shows two time constant effects of about six days and 20 days on metabolic rate. Other time delays are illustrated. In modelling cyclic relations in the hormonal and gonadotropic hormones in menstruation, varying frequency of estrogen excretion during the human female life is shown from puberty to menopause. (An excellent example of an oscillator in which some parameter, likely chemical, has changed the stability and frequency.) Body temperature cycle is illustrated during the menstrual cycle. A uterine contraction rhythm during birth is discussed. The likelihood of increased rhythm stability is shown in body temperature where its daily value settles down in amplitude within 10-15 days after birth. In Ruch and Fulton,[71] hormone action controls development and growth (aperiodic and periodic); integration of autonomic function and "instinctual" behavior patterns; and internal environment regulation. They regulate, but do not initiate processes. The mechanisms of their effects is unknown. Likely they affect specific enzyme systems, not as catalysts, but by altering the organization of enzyme systems. It seem probable that endocrines each have a basal secretion rate which is acted upon by humoral or nervous signals to change the rate, generally to restore the organism to the state before the signal. This principle of regulation is a current useful, though imperfect framework for viewing the hormones. Examples are that an increase of blood sugar level stimulates insulin secretion to hasten removal of blood sugar; deficiency of gonadal, thyroid, or adrenocortical hormones cause increase of pituitary hormones controlling these organs, and excess of hormones depressing secretion of respective trophic hormones of the pituitary body. Ingestion of glucose produces a two time constant effect on blood glucose, a rise time constant of about an hour, and a second time constant of about two hours. Some adrenal hormone and thyroid hormone time constants are shown. Uterine musculature shows rhythmic contractions strongest under the influence of estrogens, and relatively quiescent during the progestational state. Pituitrin increases the contractions if the uterine muscles are subjcted to estrogens. A response from humoral elements alone can be shown in isolated uteri. In Best and Taylor[72] rapid action of adrenaline is illustrated. (Exhibiting balancing or regulating chains, let alone oscillator chains, in the hormones still awaits techniques for detecting them dynamically in action, in order to ascribe connectivity in the temporal events of the chains. Physical causality requires strict association in the time and the order both in presence and absence of elements or responses, in order to assign order. It is such long causal chains that are really still lacking in the hormones. Thus, it may be surmised that cycles exist, but only a few from direct evidence.)

7. *Circadian Rhythms and Oscillators:* (While considerable data on near 24 hour cycles exist, it is difficult to separate them from the daily cycle and a possible frequency synchronization. There is impatience with the fussy methodology to establish ultimate steady state performance. Consider a physical illustration. A linear system, say mass-spring, will show oscillations, but it ultimately dies down because thermodynamic laws applied to macroscopic systems require degradation of a passive system. Thus, this is not an oscillator. The requirement for autonomous oscillation is that it be an active system forming sustained limit cycles. Does a limit cycle exist if some cycles are noted? The only test is to repeat with further observations or systems, and see if data similar in harmonic content is obtained. Thermodynamics enters again in a more subtle form. Ultimately all macroscopic isolated systems degrade. In a long time context there are no macroscopic oscillators. Thus an oscillator has a more limited meaning. Over a long observation period, comparable to its "life," one must find serial time segments with corresponding harmonic content. As illustrated in skipping breaths, neither 6 nor 60 cycles is necessarily sufficient. "Proof" likely begins in the hundreds of cycles. Illustrating, there is belief in a menstrual cycle because it may be noted monthly for periods up to 40 years. This must be the elementary background in examining circadian rhythms.)

In a symposium on biological clocks,[73] Bunning cites DeMairan (1729) and Pfeffer (1875) for early strong evidence of a daily plant leaf motion with constant light and temperature. Infra-red commonly may be the drive; but an autonomous rhythm exists that is not quite 24 hours, and synchronized by light-dark alternation. Other near 24 hours rhythms were found in plants and insects. He exposed Drosophila to constant conditions for 15 consecutive generations (1935) without eliminating a diurnal rhythm. A single 10 hour pulse of "light" stimulus evoked the rhythm in living forms raised in constant "light" conditions (1931). A relaxation oscillator is indicated and dealt with. (Actually a hard type of nonlinear limit cycle,[26] judging from the illustrations.) Periods can be changed by some environmental parameters, red light wave length, alcohol, or alkaloids. Aschoff,[73] discussing rhythms, stresses constant conditions to exclude environmental synchronizing, but accepts five to seven periods as adequate ground for limit cycles. A bird raised in constant conditions of temperature, feeding, noise isolation, at different light intensity levels, shows circadian activity frequencies that vary with intensity, and entrain with a light rhythm, of 12 hours light and dark. Previous work on other plants and animals showing circadian oscillation is summarized. The length of the period varies linearly with log illumination. A rule is offered that light-active animals increase frequency with illumination, dark-active animals decrease. (These data lend conviction to circadian rhythms, except for the limited length of runs. However, attempts to infer detailed results on time structure and noise from few cycles is not warranted.) Lizards raised from birth in constant illumination or artificial time cycles showed periods similar to normal growing animals. However, animals raised in constant conditions for several generations may not be autonomous oscillators but synchronized if the period remains 24 hours. Besides activity some organisms show circadian rhythms in luminescense, space formation, and growth rate. Attempts are made to assess the accuracy of the bird oscillator frequencies. (There exists a need for spectral analysis, or correlation techniques to assess sharpness, stability, and noise levels.) Useful references are given. The work of Halberg (who proposed the term circadian rhythm) is alluded to. Bruce[73] (adding more useful references) allows any periodic oscillation, even if damped, to be a circadian rhythm. (Transient responses are not acceptable within the domain of truly periodic phenomena. A linear damped mathematical fiction is permitted because it decays "forever.") Various cyclic entrainments by light and temperature are discussed. Examples of subharmonic resonance are shown. (These papers suggest that light-dark and temperature are two sensitive parameters which trigger the limit cycle. Sensitivity to these inputs is further shown by the ease with which they can be cyclically used to synochronize oscillators in the body. There seems to be a common circadian oscillator. Its sensitivity makes it unlikely that it is a continuous sine wave resonator as in precision clocks, but of a general Van der Pol relaxation oscillator nature. Similar ideas about relaxation oscillators in biological systems was expressed by A. Hill (1933). Credit accrues to Halberg to stress the significance of near 24 hour oscillations. However, the papers do not discuss mechanisms for such oscillators. That it is adapted to need, as a wake-sleep cycle would appear to require, is self-evident.) In discussing a DeCoursey paper, Barlow[73] calls attention to a possible nonlinear entrainment in an ensemble of coupled nonlinear oscillators as described by Wiener (1958) on nonlinear processes. From this he draws conclusions about the precision of the frequency of entrainment of a group of fireflies. (Minorsky[28] illustrates potentially greater complexities in viewing entrainment.) Brown[73] attempts a case that many, if not all, circadian rhythms may involve subtle geophysical entrainment by factors such as pressure, atmospheric variables, lunar cycles, magnetic fields, radiation fields, and electrostatic fields. Pittendrigh's remark[73] that "the applied mathematicians and physicists from whom we are seeking models and analogs wish to know not all the facts but the significant facts", has physical flavor. His empirical generalizations about circadian rhythms are a refreshing summary. However, point seven, that the limit cycle period displays remarkable precision is one that makes the scheme less than physically acceptable. (Examine Lewis,[74] books[39] or a study on oscillators.[75] Precision is obtained in timing systems by the use of resonator oscillators, with pure timing phases. It is difficult to visualize an electrochemical-mechanical complex, operating as a relaxation oscillator, that can give precision. The inclusion of this one point, if true, makes the entire circadian scheme suspect. What a physical scientist might expect, and evidence in this review suggests, is a rather dense, not too stationary, spectrum of limit cycles with entrainment possibilities and frequency shifting mainly by chemical level in a poorly regulated interior. That the system might develop a near 24 hour oscillator is not a surprise. On the other hand, Brown validly asks that its components be demonstrated.) Schmitt,[73] more realistically, points up some of the known properties of nearly linear and nonlinear electrical networks with regard to oscillator performance. He shows a few elementary models. Harker[73] attempts to relate light sensitivity and some endocrine factors in insects to light-dark entrainment. (However, difficulties appear such as it being dubious that the very sensitivity generally invoked, by Harker as a rhythm resetting, would result in any functional use for the circadian rhythm. This is a first elementary probing at stability, but it begins to entangle the circadian problem.) Halberg[73] reviews much of the work in which he has been involved. Hellbrugge[73] attempts a case for infant rhythms becoming synchronized toward 24 hour periodicity by maturing processes. (While interesting, it appears equally possible that a 25 hour daily routine synchronization took place.) Lobban[73] offers a very reasonable review of circadian rhythms in man. (Her references are apt starting points for viewing this subject, particularly beginning with Kleitman's work on sleep and wakefulness.) Specific results or field studies in Arctic environments on artificial day schedules of 21-27 hour "days" show entrainment of certain functions, such as water elimination, but a persistent 24 hour cycle in potassium excretion and body temperature. Controlling mechanisms may lie in the hypothalamic-hypophyseal axis for water and salt, and in the adrenal cortex for potassium. (This thesis begins theoretical conversation.) In indigenous Arctic inhabitants, a 24 hour urinary rhythm, including potassium excretion, disappears. However, there are social pattern organization, and other environmental cues. (The arguments end weakly in that a suitable test situation has not been devised yet to test the full problem.) Further review of rhythms may be found.[76, 77, 78, 79, 80] (In summary there are long time cycles and cues. However, mechanisms have not been discussed.)

8. *Other Illustrative Oscillator:* Many major mechanisms and associated oscillators have been touched on. A few more increase the scope. Uterine contractions, as example of a local muscle oscillator, hormonal mediated, was already mentioned.[71] Oscillatory complexes in conditioned reflexes are illustrated in Russian work.[65] Krogh demonstrated active capillary twinkling as a response to oxygen concentration in the tissue in response to neural and hormonal factors.[81] Randall demonstrated sweat gland twinkling as the mechanism for producing an effective wetted area in thermoregulation.[82] (This reference complements a previous source.[56] It establishes a cycle in the evaporate loss corresponding to the two minute cycle found in temperature, ventilation and metabolism. A conclusion emerges that the body can produce twinkling phenomena at the higher frequency neural level, at the chemical - mechanical muscle level, at the chemical level, at the mechanism level, and can then quantitatively coordinate it. A mechanistic model could be built, but this constitutes no proof as to how the body does it.) Deman[83] indicates nonlinear oscillations in epilepsy. An ecological example is given by Krebs.[84] Periodic fluctuations in small mammal populations have not been explained. As illustration there is the three to four year lemming cycle in the tundra, a classic example of such cycles in rodent populations. (Nonlinear limit cycles are real in biological systems. They cover a wide frequency spectrum. There is obviously an equally rich rich time delay spectra of aperiodic phenomena. A variety of mechanisms are likely, commonly bistable elements as was classically illustrated by Poincaré in exposing instability problems, as was used by Van der Pol in a classic quantitative illustration of such limit cycles, and as has crept into the electronic literature on nonlinear instabilities. The basic systems are electrical-chemical-mechanical. The physical scientist is not so accustomed to chemically mediated dynamic systems; thus some strangeness. Parallel systems of regulation, on-off regulators, and control modes seem to exist.)

C. *Regulation and Control*

Limit cycles are sought to determine some of the necessary degrees of freedom of the system. Each oscillator represents one or two degrees of freedom, one if an exterior degree (as in mechanical or electrical equations of motion), and two if an internal degree (thermodynamic relations come from first integrals of the mechanical motion of molecules, requiring two first order equations to produce an oscillator). There are other degrees of freedom that can decay. For these, one excites the system by step, pulse, periodically, or with a noise input. Maximal information may be obtained most rapidly from pulses, but it may be the most difficult technique to use diagnostically. There are still other unstable degrees (i.e., the system can destroy itself). These will not be considered. The human is so rich in degrees of freedom, it would be impossible to examine all its known transient behavior. A physical limitation generally put on examining a complex system is to count only main power transforming elements, or systems that transmit significant information content. In this section concern is only with system elements that show significant regulating or control functions, and not with general transient behavior. Their relation to the limit cycles must be considered. If accustomed to complex physical processes and plants, most disconcerting in the body "chemical" plant is the large number of unstable oscillator cycles that exist with chemical mediation. Most chemical plant processes show very little dynamics, except for storage lags and in the dynamics of electrical or mechanical equipment. In the body the oscillators are active electrochemical-mechanical elements, novel because of their small size. Common at all time domains are local and remotely mediated relaxation elements, not only at the highest frequency level, but even at the frequency level of the life reproducing cycle; in broader scale in social behavior, and even in longer biological adaptions. (The senior author began a model of social behavior with this important element in mind in 1947. The general idea cannot be regarded as original. This review commends major credit to Van der Pol. It appears that the biological system, for adaptability, utilizes the "cheap and dirty" relaxation oscillator for process regularization and for an ability to quickly modify a response from cycle to cycle. To discover many resonator elements in the biological system would be surprising. Circulation elements like delay lines seem to be much more common. Corollary is that the general regulator and control action likely stems from similar elements, mainly static regulators, and on-off dynamic regulators, both with time delays. A question arises about the controllers. During the course of this review, a particular hypothesis developed. The body appears adaptive. Through "conditioned reflexes" or other means, it strings temporary or more permanent networks as are required by an internal computer controlled hierarchial logic. In general, instead of building permanent controllers, it operates elements in control modes. If a game is proposed, the body may go along until it doesn't want to play. Some have long been conditioned. Eye habits, activity habits, sleep habits, etc. are conditioned, though retraining is possible. Thus, it is not clear what constitutes controller mechanism if the mechanism, though not the functional necessity, can be rearranged. On the other hand, there may be limiting physical performance that the system cannot exceed. It is difficult to determine what is the "normal" or "steady-state" behavior of a self-actuated nonlinear system. A few important regulators and controllers will be examined, somewhat discursively.)

1. *Body Activity Regulation:* To get at regulation or control, one must average over the limit cycles. One "reason" for oscillator cycles may be to furnish transmissible power. The average of steady state oscillator cycles

presents mean performance of the system. The quality of regulation can be examined by the characteristics of such means. A wake-sleep cycle has been discussed which is initiated at the 90 minute level, may be aperiodic for seven to nine hours, and may be circadian or adaptively synchronized at a geophysical day. To examine body performance, one wishes to average over these cycles, but one should first note human behavior. In addition to such "definite" cycles, there is a large degree of randomness or other non-scheduled purpose in human activity that is implied by "self-actuation". However, one recognizes a twinkling performance. Thus, in assessing activity the experimenter can use statistical averages over population samples indicative of near monochromatic individual behavior. Circadian references are replete with examples. This is not only true for lower animals, but also man. Thus, it is fair to average over the circadian or the synchronous day, or over a population sample. (The ergodic hypothesis creeps in on usual physical grounds as a useful approximation.) What results is the average activity level. Average activity level is a function of temperature. This is demonstrated in metabolism by Herrington[1] on guinea pig, rat and mouse with normal caged activity for temperatures over the 10-35° C. range. A linear fall of metabolism by about a factor of two is shown from 10° C. to near 30° C., and an approximate linear rise to 35° C. These changes are accompanied in the experiment by no external work. Since it varies with temperature rather than being constant, it is not a controlled function, but somewhat poorly regulated. Observed in time there may be maxima and minima. Activity level variations with the menstrual cycle in rats and humans were cited as cycles longer than circadian. With less filtered data, performance similar to that shown in ventilation may be expected, of maximum to minimum peaks of the order of 6 - 8 to 1 and average cycles of closer to 1.5 - 2 to 1. Such ranges may be the nature of power systems that are not completely stationary in time. Beside regulation with respect to temperature, it appears with regard to other factors. A message of Bernard, Cannon, Smith, Darwin, etc. was that the development of regulators was the adaption to environmental conditions. Activity level may be a regulated function with organism age. There is an activity change to available food supply, again probably a regulated function. On the other hand, there is obviously controller type activity in the humans, but likely in specific actions. The concept has to be developed carefully.

2. *Regulation or Control in Power Production:* Distinct from a "normal" activity regulation curve dealing with power consumption schedules, there is the power production; in engineering terms, the prime mover characteristics. Examining its temperature variation, what one finds at various activity levels, in particular a quiescent level, is not quite level metabolic characteristic[1, 85, 86] with a regulating "droop" af about 20 per cent from 10° C. to 30° C. and about a 10 per cent rise to 40° C. Some sources [1, 85]

show storage of heat at temperatures below 30° C., thus describing a nonequilibrium situation, and state that when cooler, temperature regulation must take place by metabolic increase, which is not found however. This confusion casts doubt on the metabolic data. The ASHVE results[86] validate a heat balance. Systematic data at other objective activity levels are hard to come by,[87] but one may estimate that the mean power production at quiescence or other levels of overt activity, objectively evaluated, are also regulated curves. (Some comments are in order. In a mechanical system, the power consumption curves would be superimposed on the power production curves, here objective activity levels, and the activity level assessed. A common "objective activity" level is output horsepower, i.e. work done in the external world. However, one is dealing here with a system that does not have a unique association between activity and power. Activity results depend partly on learning, practice, and computer control. The physiologist commonly deals with the issue by using a standard task — walk on a treadmill, use a bicycle, etc. References are given by Carlson[87] covering the work of Scholander and others on men and a variety of other animals. Part of the difficulty is that the engine can operate in a degenerate thermodynamic engine mode in which internal power is degraded to heat. The next reference is illustrative.)

Karpovich[88] shows the energy expenditure for various tasks, such as swimming at a certain rate. (Assume that the external work necessary to drag the body through the water is essentially fixed.) A rise in heat production with speed is shown. Power production and external work consumption are not perfectly proportional. This efficiency is not constant. At slow speed a power production is up to four to five greater for a poor swimmer than for a competent one. (The example suggests that even the engine performance seems to be made up of regulator modes, rather than fixed regulators. It appears that most networks are wired up by conditioned reflexes rather than by permanent circuits. Frequent intervention by the central computer determines whether to keep a circuit, be it regulator or controller. A scheme for this will be mentioned later. A "proof" is that habits, such as playing an instrument, swimming, even reading, or movements are matters of practice. Stop practicing and the performance changes; even for the expert, changes or moderate decisions occur at each performance; athletes find ways to improve records that are not just instances of better equipment; the amateur shows high variability and even more volitionally, if the computer system does not want to, it can balk in very sophisticated ways at anyone who has carried a heavy load with another "loafer" can testify. To speak of a regulated or controlled power production is not determinate. There is a broad range of computer control function entering between power consumption, external work, and power production. Instances of practice show that it is even necessary to talk carefully about a limiting performance of the system. With style change and practice, a range can increase enormously. There certainly is limiting performance, a point well made by D'Arcy Thompson, but it may not be invoked so easily except in extremes. While such extremes are invoked in destructive testing, humans generally operate far removed from such limits. The system likely becomes habituated to a level of performance, not only for the individual but even society. Common practiced conditioned reflex circuits are not matters for constant intervention of the computer controller. Instead, one may visualize a verbally plausible scheme. The controller prepares algorithms for the hypothalamus switchboard. It has connections to the pituitary. The guiding algorithm for the switchboard permits the use of the hypothalamus as an on-off regulator of a large number of local circuits, using various electrochemical signals for switching. Intermittently, perhaps timed, perhaps not, the higher computer circuits, "consciously" inspect the hypothalamus switchboard and change the algorithm. Thus an intermittent system is in operation that is partially "volitional" and partly "automatic". Many of the volitional, i.e. self-actuating functions, are also of course routine.)

3. *Temperature Regulation or Control:* Having discussed prime mover characteristics of the muscle engine system, it is useful to comment on another salient characteristic of homeothermic animals, core temperature regulation. Earlier, an active muscle sheath engine was proposed. Integrating over the engine cycles, physically about 3½ hours long, and over the refueling rhythms and rest-activity level circadian rhythms, what remains is the power production, the heat losses, and some external work levels. It appears that the metabolic production at various temperature levels is moderately regulated, and that the averaged core temperature is nearly regulated. If the power production remains essentially regulated and the losses tend to increase with lowered temperature, how does the core stay regulated? Noting that the amount of core that is regulated diminishes removes the paradox.[56] It is only the losses per unit area in regulated regions that have increased. Other areas reduce their losses. This is not a learned regulation. (However, the adaption of the system to activity level or to an unsatisfactory environmental condition by self-actuation is likely a control mode. If the system is forced to respond, where it can neither loaf nor avoid, and in particular if called upon rapidly, then a partly learned power production controller mode action is invoked. For slower cases the system may put itself into a controller mode.) Although his thesis has met with objections, Benzinger[41] has uncovered probably a central idea in temperature regulation and control, ultrasensitivity of the hypothalamus to its local temperature. (Physical objections center around questions of systems stability. Benzinger has viewed the hypothalamus as an ultrasensitive thermostat. However, the hypothalamus action in itself does not

represent the system control dynamics, which still has to be shown. Its properties partly emerge. A region is sensitive to temperature; a difference of 0.01° C. is sufficient to scan its potential signalling region. Sensing at this level is sufficient for the hypothalamus to initiate corrective on-off regulator action. It may cause a muscle to shiver with large amplitude and produce heat, etc. The instantaneous algorithm that the switchboard is working on is computer controlled. The computer takes into account the sensed hypothalamus temperature and may let the extremities freeze, run, go find a warmer place, etc.) The hypothalamus temperature itself, because of its sensitivity, may always be used as a controlled temperature in a permanent controller system. However, the core temperature is achieved by regulator and control modes. (It is not clear what instantaneous overall system algorithm is used.) By operating the body in specific activity modes one may get some idea of the time scale of the controller action. First, Burton-Bronk experiments[60] tie the 10 cps. muscle oscillator to action potentials to the muscle from the hypothalamus and show an amplitude modulation with breathing. It may be that this modulation results from thermal proximity of the hypothalamus to the breathing channels. If true, then the time constant for controller action is at the one to a few tenths of a second level. Second, a two minute coordinated power cycle of the muscle sheath seems to be a regulated function, since there are likely steady state errors in the broad regulated central zone. Next, a seven minute cycle is also likely representative of a poor regulation mode, speculatively involving vasomotor activity in the fluid system. Beyond that are uncertain thermal regulated modes. Finally circadian temperature cycles are commonly reported. (This suggested frequency spectrum is a scheme of frequencies rather than precise frequency parameters.)

4. *Muscular Task Control or Regulation:* Specific elements of control modes, is shown in detailed muscular tasks. In modern view, the subject opens with Tustin.[89] (This is the source from which the view of the authors as well as many engineers toward biological systems control begins.) Basically Tustin shows the nature of an eye-muscular system coordination as predominantly that of a linear error-actuated automatic servocontroller, but with additional irregular variation, partly random and partly nearly unstable oscillations; and the interrelation between this system and the operation of a larger man-machine loop in tracking problems. (A good nonlinear background is evident, not shown in many subsequent engineering efforts.) Later illustration in more conventional control theory terms is the pupil response and a tracking response of the eye by Stark and coworkers Young, et al.[90,91] (Although these papers indicate controller action, they are most likely controller modes. However, this is a controversial statement.) Another likely even more fundamental, but later paper than Tustin's, is by Cacioppo.[92] In studying an operation complex, piloting an

airplane, he found three different types of response: in untrained subjects, a high frequency noisy controller response wobbling over the track; in a subject trained in the general problem but experienced to slower response, tracking with considerable overdamped slow response, cautiously approaching the track; in a competently trained subject, a high frequency lively controller response was indicated that could follow a track with purposeful command. (It is possible that the major control modes that the human systems can approach through the conditioned reflex learning process are revealed here characteristically.)

5. *Regulation or Control in Interior Elements:* Having mentioned the exterior responses, mainly regulation and control of external modes of behavior, rather than intrinsic regulators and controllers, the review approaches an end by touching again on the interior elements. Cannon's concept of intrinsic regulators of interior parameters still stands up. What doesn't come into clear perspective in the literature is the action of the high speed trace chemicals acting in regulation, control, communications, power transformations, or as network passive elements. No brief review here will improve the picture. Thus, only a few examples will be given. A mathematical attempt at a hormonal problem[93] develops a model of the thyroid — pituitary chain by which thyroid hormone is controlled. (The effort is substantial. However, the equations are more nearly equations of convention rather than mathematical — physical equations that describe specific physical mechanisms. Kleitman in another context in refuting universal biological law points out that such ideas do not touch on the mechanism. While there is sympathy for the ends, such equations can only have limited utility.) A paper by Gerritzen[76] on rhythmic function of liver is interesting. With "continuous" water supply and feeding, an experimental circadian rhythm is shown in humans in water, chloride, and urea excretion. A conclusion is that the kidney functions rhythmically. Increase in the meat intake leads to greater amplitude in urea excretion. Since urea is formed from meat, the liver is the only organ that can make urea out of meat, and determination of urea in the blood showed hardly any variation at all, it is clear that the liver functions rhythmically. (This is a rather direct demonstration of a regulating function achieved by an oscillator cycle.)

The cardiovascular system is a major complex system in the body. A common summary is that its basic function is as pump for pressurizing and circulating fluids and other salient elements throughout the body. There are mechanisms that provide many regulated and controlled functions in the system. A satisfactory elementary survey for a physical view of the system is certainly given in the circulation section by Gregg in Best and Taylor,[72] Rushmer,[49] and MacDonald.[94] (Clearly indicated is the need for detailed review of each system. In general modern physiological summary books, the Physiological Reviews, and the growing Handbbook of Physiology can and will represent excellent source material with growing physical references. At present, fully systematic static or more difficult dynamic data do not exist in this literature in satisfactory form. The physical scientist can help suggest the form that some of these data must take if physical modeling and explanation is required. Framed by the purpose of this review to get a physical view of the status of regulation and control in the biological system, existing data are insufficient for mechanistic explanations of these functions in most biological systems. Adding a section on waste product regulation and control would invoke similar remarks, and is therefore omitted.)

6. *Central Coordination Control:* A summary of Denny-Brown's review[95] on the general principles of motor integration points up that most of the motor-sensory reactions are fairly organized up to the midbrain - subthalamic - cerebellum - brain stem level, that the hypothalamus adds the interior regulating functions, but that it is the cerebral cortex that dominates the whole system, with only slender clues to the mechanism of cortical domination. Final ideas come from Bremer's summary[95] on central regulatory mechanisms. The nervous system as a whole complex machine is regulatory and may be considered to parallel the sensor and motor systems, and thus to modify their activity. There are also completely internal regulatory effects. However, there is need for clearer understanding of the information exchange that is postulated between the cortex and connected thalamic nuclei. He then continues to trace further relations to the cerebellum, the reticular formation, cortex, hippocampus. Subsequent authors take up each of the parts. (Great difficulties still exist in the system integration.)

SUMMARY

Regulation and control in biological systems from a physical point of view has been examined. A background of physical ideas useful for such analysis include:

(a) Static regulator performance — near static performance of physical elements that are affected by, but are quite insensitive through design to specific physical parameters. (It includes compensators and governors.)

(b) Dynamic systems performance — the classical physics program of equations of motion for both internal and external degrees of freedom, and mass and energy balances, all leading to a differential equation set to be solved for particular boundary conditions. The solutions characterize the dynamic systems performance.

(c) Control performance — the program of investigation of a subclass of dynamic systems in which the static solutions — known in nonlinear mechanics as the singular states of motion of the system — have prescribed characteristics (typically that an "output" variable should be constant, or should follow a particular law), and concerned with limiting the transient disturbed performance around the desired static solution.

(d) Linear control performance — a limited control program in which the dynamic equations are linear differential equations with constant coefficients.

(e) Nonlinear mechanics — the very difficult program associated with formulating and solving the dynamic system performance for nonlinear systems.

This view of systems dynamics analyzed by nonlinear mechanics is partly at variance with some common views that analyze systems performance by linear control theory, electrical network theory, a theory of stationary time series, or a communications theory. The differences would involve considerable controversy between classical physicists, modern physicists, engineers, and mathematicians.

The main biological line of description of regulation and control seems to be: Bernard's identification and isolation of the watery interior of the body, as a physical field in which biological materials, mechanisms, and processes operate and exhibit their performance; Cannon's thesis that major material constituents of the interior and many of the processes and mechanisms are regulated; identification of the salient role of the kidney in regulating the material constituents of the watery interior; Wiener's identification of the computer control nature of the brain, operating through a digital computer-like communications net complex; McCulloch and colleagues Pitts and Lettvin's sustained effort to find a communications logic for the neural nets.

To begin dynamic systems analysis, salient active mechanisms in the watery interior were reviewed. (In network theory, an active network is one that contains its own power sources. In engineering and physical views, a supply of energy stored in potential form requires a prime mover for availability in active form.) As a first step one seeks sustained system oscillations when immersed in a constant potential external environment of temperature and other factors. The periodic components are viewed individually as oscillator outputs, D.C.-A.C. converters, engines, prime mover cycles, rhythms, and clock cycles. In the language of nonlinear mechanics, they are all nonlinear limit cycles of Poincaré. Their presence indicates necessary degrees of freedom in the system. Examination of systems in the body showed a fundamental mechanistic characteristic of being based on local oscillators. The basic units are small electric-chemical-mechanical power packs with a fundamental oscillator frequency of the order of 10 cps. The primary type of limit cycle used is likely of a relaxation nature. Much of the basic knowledge about these units was systematized by Adrian. Van der Pol systematically developed the quantitative exposition of the relaxation oscillator, and pointed out its biological applicability at the same time. It is pertinent that nonlinear oscillating systems can be shifted in operating point, or show frequency entrainment either as synchronization or subharmonic resonance. This may be plausibly understood in relaxation oscillators. (There exists a useful elementary view of bistable elements and their development into aperiodic and periodic circuits in electronic circuit analysis.) This property makes it possible to change oscillator characteristics by chemical level or signal in the vicinity of the oscillator, or by electrical signal to the oscillator. Such phenomena were illustrated in brain wave rhythms, heartbeat, respiration cycle, muscle engines, and digestive tract rhythms. These thus indicate systems immersed in the watery interior that have at least some primary local oscillator determinant of the basic rhythms that permit them to perform their functions. At lower frequencies, many other major oscillator cycles were found, illustratively eating, drinking, rest-waking, the estral cycle, menstruation, temperature cycles, metamorphosis, and circadian rhythms.

A salient fact emerged that many of them were under the mediation of the hypothalamic center in the brain. As a plausible description of the hypothalamus, it may be described as a central switchboard that receives information signals, including alarms, from many remote and adjacent mechanisms, and in accordance with a mechanistic algorithm — a rule — routes signals to other elements. The existing algorithm may or may not be able to clear the alarm signals. An important part of the algorithm thus likely includes instructions that are the equivalent of the hypothalamus acting as an on-off regulator (e,g., parallel networks may be switched). A central computer at cortical levels likely in synchronous computation fashion, intermittently attends to the switchboard and modifies the algorithm as it desires. The higher algorithm that the central computer uses is more subject for psychological investigation. It likely involves at least one element of behavior that is required to put out hypothalamic fires. Thus, if true, most interior elements are regulated, as Cannon proposed, in which active circuit elements instead of passive circuit elements are used.

The chemical regulation or control system involves the endocrine glands which act in antagonistic pairs. The overall nature of the interrelation among the various hormones does not emerge clearly except in the idea that the chemical signalling products are more specific. The pituitary gland is considered to be a master regularizing gland for the hormones. G. Harris is credited with having established the pituitary stalk as the pathway link between the central nervous system of the hypothalamus and the endocrine system.

Having superficially examined the oscillators and at least gotten some idea of how central electrical and chemical mediation tends to modify the oscillations, generally for regulating functions of the interior, the question arises as to where the more conventional ideas of control in the system reside. The idea of looking for control functions in the biological system most likely may be best attributed to Tustin.

The systems analysis is further continued by averaging over the cycles — at least the faster circles through the circadian — to obtain the quasistatic steady state responses of the system. One may then examine the system in a mechanical engineering power sense. This inquiry was conducted in turn into the items of power production, power consumption, temperature regulation, motor activity, energy intake, waste disposal, and central regulation and control.

Mean power production is a function of a number of variables; illustratively, temperature and activity level. For given activity levels, power production appears to be a regulated function of temperature. In examining power consumption, on the other hand, it is necessary to examine the activity level and its associated external work performance. Averaged over population samples in animal studies, activity level, as shown by power production, appears to have a standard form with temperature. The activity level pattern, however, is a much poorer regulated function of temperature than is the metabolism. The next problem derives from the physiological fact that a significant portion of the core has constant temperature, and thus whether this is regulated, or controlled, for temperature and activity level disturbances. The likely answer is that the hypothalamus, operating as an on-off regulator, develops a control function for temperature using the body fluids in the fraction of core that is regulated as a control element. However, with activity level the hypothalamus acts only as a regulator of power production.

While paradoxical, such analysis led to the concept that the body acts in control modes rather than by permanent controllers. For example, it is postulated that the "current" power production associated with a given activity level is under the control of the "instantaneously current" algorithm that the hypothalamus is operating under, which depends on cortical computer control. In examining other detailed motor activities that deviate from standard activity patterns, that may be regarded as volitional, or the response to specific environmental stimuli, the same general theme seemed to emerge even when the motor activity is very old and very practiced — such as eye response, reading habits, swimming, music playing, etc. The system tends to act in control modes, and if the computer controller changes its "mind" the system just won't control any more. Its algorithm has been changed. The conditioned reflex thus becomes a primary "temporary" hookup that the system uses for all sorts of regulation, control, and communications purposes. Postulating that the cortex operates on a higher type of algorithm, including putting out hypothalamus fires, would seem to correspond to the psychologist's thesis that the system attempts to reduce its nervous activity level. It is likely that networks cannot be hooked up in times faster than approximately 0.1 second. This suggests that the individual cycles of local oscillators are used in the connections.

The chemical communications net still does not emerge clearly. One can only point suggestively that not only does the chemical signal interact as a regulator of local oscillator instability, and on through its master center to the hypothalamus, but that the electrical signals also drop a line of chemical signal at the nerve junctions. One may suspect that the latter function continues to bind the system together by leaving a temporary memory spread out through the entire system. It is currently considered in neurophysiology that the permanent memory is stored electrochemically at the nerve synapse. Every intake seems to be a regulated function. However, the regulation source is not established. This leads back to the interior elements, where it then turns out in conclusion that Cannon's idea of internal regulators seems to be essentially correct.

To model the body by dynamic networks begins to be currently plausible. However, only a most rudimentary Model T model can emerge. Having noted many models develop, original crudeness is not a significant defect. Key ideas and central hypotheses count. Details can improve with time. The biological system specifically faces the problem of achieving a structural, but mobile system, without the use of solid materials such as metal, essentially using water. In a recent study[96] on particle measurements, it appeared as a hypothesis that particle systems at colloidal levels, whether living or so derived, had the major characteristic of organizing their vicinity by electrical control. One might say that they had developed techniques of controlling water aggregation to nearly rigid states. One might even look at the process as a reversible "polymerization" of water into a structural form. The mediating element used for the structuring is protein. (Oparin[97] discusses an even more primitive process of liquid coacervates.) To achieve freedom to control the state, the elementary system had to be self-powered, and thus it became a primitive oscillator. To be adaptable to its surroundings it is likely that a relaxation oscillator was necessary. Thus the basic cellular element with its surrounding milieu, comes into focus. Conceptually, the surround is not yet a sophisticated electrically controlled membrane with some "rigid" properties, but is a sol-gel state that can be electrically controlled to "polymerize" water. (The cell and other elements of molecular biology are not the issue in this review. What is useful is that the unit element in the system is probably an engine oscillator, of relaxation type, a prime mover of electrical-chemical-mechanical form, that mediates a water structure so as not to lose its identity or its viability in water.) That such a system or group can be organized into a cooperative local oscillator is no wonder. If there arises an arrangement of electrical networks to regularize the oscillator function, this is no surprise. If the system in maintaining a self-actuated characteristic — the system started out in water, so that self-actuation had the meaning of movement in water — has to deal with auxiliary requirements of ingestion, waste, etc., obviously it has to have a more complex chemistry than that just necessary to "sol" or "gel" water. It is clear that a high polymer type of organization, with many signal capabilities, has to be created, likely capable of responding to chemical signalling at low concentration levels. Why response at such very small concentration levels? The general type of answer may lie in the metabolic power oscillator cycle within the cell. It cannot be a passive oxidation, whether with or without catalyst. Without going too far afield, one must postulate enzyme (inside) — hormone (outside) triggering, with electrical interactions from polarizations, as creating or at least involved in the fundamental engine cycle of the cell (Oparin suggests illustratively that even the "droplet" is in "dynamic" equilibrium with regard to its controlled surround of water. This is different from a passive — say surface tension — type of barrier). It is then possible that oscillator stability, etc. can be influenced or mediated by very small environmental chemical signals. Again conditions are correct for a relaxation type of behavior at this multicell level with mediation possible either electrically, or chemically, but not necessarily at the same time scale. (The authors allow themselves a bit of poetic fancy. With regard to the property of relaxation oscillation, in a hierarchy of systems the general type of nonlinear limit cycle continues to repeat — in the individual behavioral level, the group level, and the culture and civilization level. One might say that the mechanics and organization of external behavior mimics the internal biological behavior. Similar evidence likely impressed scientists of different backgrounds with the same conclusion. This time it impresses the authors from a physical point of view.)

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