First Quarterly Report

A Study on Dynamic Systems Response of the Performance Characteristics of Some Major Biophysical Systems

prepared by
Rand Development Corporation
Cleveland, Ohio

for
National Aeronautics and Space Administration

July, 1963

Reference: Contract No. NASw-678 (sc-4077)
Dated April 1, 1963
First Quarterly Report due July 1, 1963

Technical Authors

A. S. Iberall

S. Z. Cardon

CONTROL IN BIOLOGICAL SYSTEMS - A PHYSICAL REVIEW

A. S. Iberall, S. Z. Cardon, Rand Development Corp., Cleveland, Ohio.

As a first quarterly report on this contract a general review of control in biological systems was prepared. This furnishes an apt framework for all of the subsequent work. It has two major parts, a summary of regulation and control ideas from a physical point of view, and a review and parenthetical commentary on such ideas in the biological literature. Such interdisciplinary exposition is not new. Burton (1) in a 1939 Temperature Symposium, a significant attempt to bring biologists and physical scientists together, proposed to use a comprehensive theory of temperature control to illuminate and separate physical and physiological factors of control for the physiologist, and control system complexity for the physicist. More recent examples are a review on physiological regulation by Adolph (2), and a survey on biological control system by Jury and Pavlidis (3). The success of such efforts can only be judged by the extent to which they are illuminating to both disciplines involved.

I. SUMMARY OF IDEAS IN PHYSICAL CONTROL

Ideas about governors, compensators, and regulators were an outcome of the Industrial Revolution and took form through such devices as the steam engine with need for speed governors, in development of instruments with need for such properties as temperature compensation, and in development of a number of slow control devices such as temperature or pressure regulators. Discontinuous regulation begins with the on-off temperature regulator.

Continuous feedback control began with attempts to control properties of the active electric network through 1925. It achieved continuity with mechanical feedback control in the 1930's, and by the 1940's emerged as a full fledged linear or small amplitude control theory in the electromechanical field, as servomechanism theory. Linear control theory was considerably generalized in the 1950's, and gradually became enriched by discontinuous automatic control. At the present, means are being sought for a broad generalization of control theory.

Some background bibliography is the following: A brief introduction to automatic control in mechanical engineering practice (mainly industrial) is in Considine (4), or more simply in the Chemical Engineers Handbook (5). A current elementary electrical engineering view is in Cosgriff (6).

The electromechanical view is in excellent older books by James, Nichols, Phillips (7), Brown and Campbell (8), or Chestnut and Mayer (9).

A good introduction to important elements of modern non-linear control theory is a fundamental book by Flügge-Lotz (10). A brief, useful paper in this subject was given by Loeb (11). In its currently used state, one may refer to Thaler and Pastel (12).

Broad engineering views of control theory are found in Truxal (13) and Smith (14). Some other modern control books include Seifert and Steeg (15), Horowitz (16), and Gibson (17). A few European references include Oldenbourg and Sartorius (18), Macmillan (19), and Letov (20). A fairly modern view of the broader aspect of computer control theory is in Leondes (21). Other complex synthetic views of control, as part of systems engineering, general cybernetics, computer control systems, or as adaptive control theory will not be mentioned, except for Wiener's book on cybernetics (22), because of its biological significance. The present state of the automatic control field can be viewed in the preprints of the 1962 Joint Automatic Control Conference (23).

At another extreme as a background to dynamic analysis as viewed by the physicist one might include books like denHartog (24), Cunningham (25), Andronow and Chaikin (26), Whittaker (27), and Minorsky (28).

Briefly then, what are the fundamental ideas that underlie this

this material? While the literature is a little careless, a primary distinction exists between regulation and control.

A. Regulation

A regulator makes one variable respond uniquely to another variable independent of disturbances, when all quantities vary slowly. Upsets that occur quickly create transient disturbances that die out, if the regulator is dynamically stable. The regulator then continues to adjust slowly to the ever changing input variables.

Mathematically, an ideal relation is sought

$$z = f_0\ (x)$$

Instead, what is available is

$$z = f\ (x,\ y_1,\ \ldots y_n)$$

x = an input variable

z = a desired regulated output variable

$y_{1,\ \ldots n}$ = disturbance variables.

For example, a variation of pressure x is transmitted into a Bourdon tube to cause it to bulge, unwind, and ultimately, through a sector and pinion, to cause an output angular rotation z of a shaft. There are temperature disturbances y that upset all of the elements. A temperature compensating linkage is included in the array to compensate for the slow disturbance variable. As another example, an adjustment of the displacement position x of the flat end 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 is designed to compensate for such changes.

The design art for regulators or compensators deals primarily with static characteristics; (29), (30), or a review by Newman (31). These references illustrate a number of details about regulators.

(a) The compensation is not perfect. There remain "static" errors. If

$$z = f(x, y_1, .. y_n)$$

$$dz = \left(\frac{\partial z}{\partial x}\right)dx + \left(\frac{\partial z}{\partial y_1}\right)dy_1 + .. + \left(\frac{\partial z}{\partial y_n}\right)dy_n$$

The quantities $\left(\frac{\partial z}{\partial y_1}\right)$ .... $\left(\frac{\partial z}{\partial y_n}\right)$ are not zero.

(b) If the quality requirements are high, considerable complex design study is required to make the design approach the ideal law.

When then does one have a regulator? Generally this requires that a change over the entire design range of the disturbance variables should not cause more change in the output variable than some small change permitted in the output. . In fact in good regulators, full scale disturbance variable changes do not create errors more significant than the desired overall output accuracy. The problem can arise in biological systems as to what the desired overall accuracy is. Without understanding fully the function of the design, it is especially difficult to assess regulation as a minor loop effect in an overall complex dynamic system.

Thus in regulation some sort of expected response is achieved in a slow time scale which shows only small errors to a variety of slow disturbance sources. Transient disturbances will not set the regulating system into uncontrolled oscillation (i.e., ones which grow without end or do not die out to negligible oscillatory amplitude). The method of testing for regulation consists of exploring the system at a variety of constant input variable states x, at selected fixed values of the disturbance variables y_i. This determines a family of curves that demonstrate the regulation.

Stability is noted by causing a variety of dynamic upsets, illustratively step functions from state to state, 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 the difficulty in designing regulators, led to use of on-off regulation. This is commonly absorbed within the control literature as a control technique. Chestnut and Mayer (9) state, illustratively, that the non-linear characteristics of this type of system precluded the use of linear servo design techniques, but that Kochenburger's describing function approach has led to design methods for such discontinuous type systems. However, the common foundation established is more descriptive mathematical than of a fundamental physical nature. One may note in (24) the similarities in response of a simple second order linear system with linear "viscous" damping and with discontinuous "dry friction" damping. The differences ultimately are also mathematical. However for a moderate amplitude range, the two have similar elementary response characteristics.

For conceptually significant physical reasons it is preferable to regard the on-off system as a type of regulator that works discontinuously. (The introduction in (10) is quite explicit in recognizing the discontinuous on-off regulator as a regulator.) It is here proposed that it is desirable to regard the previous class of regulator as static regulators, and the present type as examples of dynamic regulators.

In the on-off regulator, there exists a physical system in two or more distinct physical states. There may be more states, but only two in prototype. The two states are distinct and essentially not related to each other. In one state, there is generally an active element capable of delivering power in the system network. In the other state, there may be a lesser, even zero, power source in the network. The working concept is that the first state may be "switched on", or "switched off" to the second state. The effect of the switching is to cause the system to change the state of the output "regulated" variable. This may be expressed as

$$z = f(x, y_i, p)$$

Previously, the parametric variable p might have been one of the disturbance sources of an internal nature. Now it is isolated, essentially, as a two state variable $p = p_1$, or $p = p_2$ which changes z. Alternately there may be two different system functions in the two states

$$z = f_1 (x, y_i, p_1) , z = f_2 (x, y_i, p_2)$$

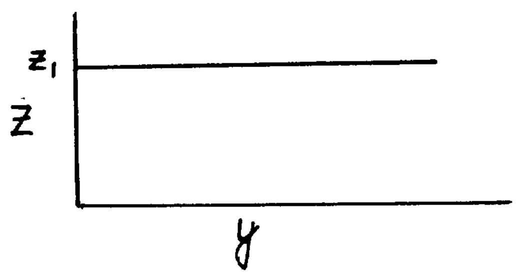
Up to this point, very little regulating function has been accomplished. However, a few more details of regulator design theory are useful. These are illustrated in Figure 1.

Suppose a regulator is desired with the property of a constant output z_1 independent of some disturbance y.. A very poor regulator is illustrated, which may be referred to as a one point regulator, for at some value of y in the range, z will be right. A better two point regulator will be right twice in the range. A still better, "three point" regulator will be right three times, etc. The designer's problem is, for a given number of points to stretch a tolerable regulating band over as wide a range of disturbance value as possible.

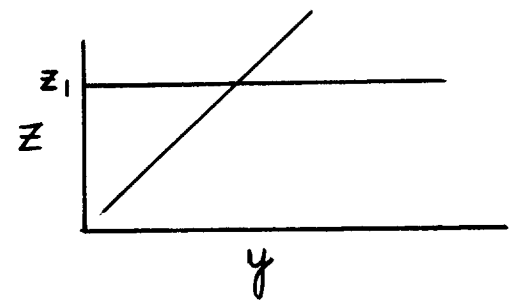
On-off switch states create two one-point regulators, one that will rise through the desired constant level and the other that will fall through the desired constant level. The elementary on-off regulator provides two levels of detection, a lower level at which the upper state is switched on and an upper level at which the lower state is switched on. This system really provides no response that is significantly different from a static regulator.

(a) It has a steady state error similar to a regulator; namely its performance will lie within a design or adjustment band for slow variations of disturbance levels.

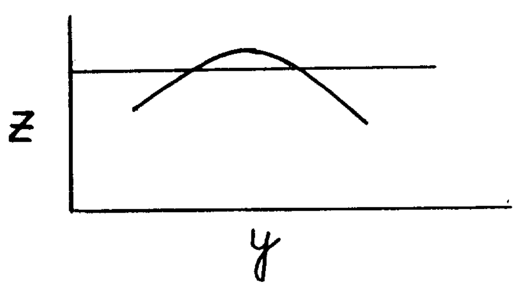
(b) The dynamics of the system will cause over-shoot outside of the regulation band for more rapid transient disturbances.



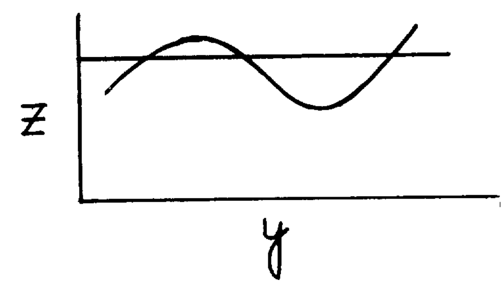
a. A desired regulator property



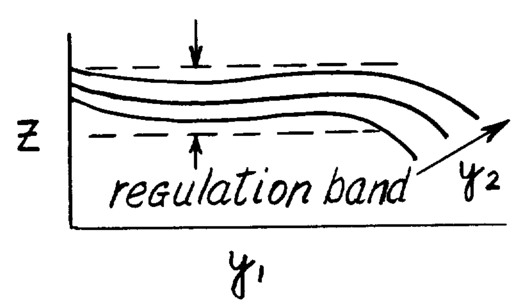
b. A poor 'one point' regulator



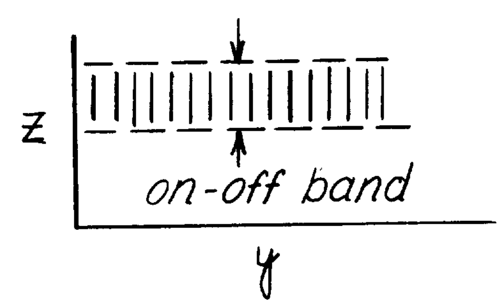
c. A better 'two point' regulator



d. A 'three point' regulator



e. Static regulator characteristics



f. Dynamic regulator characteristics

Figure 1. Illustration of regulator performance.

(c) The system may or may not be dynamically stable. In a good dynamic regulator, the system will be stable.

The difference between the static regulator and the dynamic regulator is that in the static regulator, the system is confined within a design band, for slow disturbance variations, to fixed performance curves, whereas in the dynamic regulator, there tends to be a time-describable cycle, with repetition rate and duty cycle, that depend both on the system dynamics and disturbance levels. This has commonly led to some sort of time or frequency spectrum description. However, 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 latter description demonstrates a large degree of formal equivalence with the static regulator.

The dynamic regulator thus also possesses mean steady state errors. Transient disturbances may not set the regulating system into uncontrolled oscillation. The method of testing for regulation consists of exploring the duty cycle performances of the system to a variety of constant input variable states x, at selected fixed values of the disturbance variables y_i. This determines a family of curves that demonstrate the regulation. Stability is noted by causing a variety of dynamic upsets; step functions, pulse functions, etc., and noting the nature of the transient response before the system settles down to equilibrium.

C. Continuous Automatic Control.

Control Theory represents a particular aspect of the dynamics of physical systems. In a control system, there is a referent input state x, established by some physical element associated with the system. A correlated output variable, in common measure with the input state, is noted by means of the difference between it and the input variable. This difference is referred to as the error, or its measure, as the error signal. This measure difference is operated on by a mathematical operator that involves 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 toward zero. This act of driving the error toward zero is one that finally results in no static errors.

Control may be illustrated as follows: Given an operational relation of the form

$$O_1 (z) = O_2 (x, y_1, y_2, \ldots, y_n, t)$$

Can the underlying system be designed or modified to produce some desired control relation, say

$$z = f (x)$$

z = an output controlled variable

x = an input signal variable

$z - f(x)$ = an "error" variable

$y_1, \ldots y_n$ = input disturbance variables

O_1 = a differential operator that transforms the output into some other time dependent variable.

O_2 = an operator that transforms the right hand into a time dependent function of input, of disturbance variables, and of arbitrary, usually stochastic, functions of time.

Typically, if the operators were linear, independent, and of some particular limited order, one might have

$$A_1\ddot{z} + B_1\dot{z} + C_1 z = A_2\ddot{x} + B_2\dot{x} + C_2 x + O_3 (y_2) + O_4 (y_3) + \ldots f_1(t)$$

A Type 1 control system (taking the clue from servo classifications), ultimately has no static error, if the inputs are held constant. This requires that the arbitrary stochastic inputs $f_1(t)$ are indifferently small, that the steady state parts $C_i\ y_i$ of the disturbance variable operators are indifferently small, and that the system ultimately settles down to a steady state $C_1 z = C_2 x$. It is also required that the system be at least locally stable in the vicinity of this singular steady state, i.e. stable against moderate disturbances from the steady state. The same sort of ideas may be used for the broader generalization to non-linear control systems.

A Type 2 control system ultimately has no static error and ultimately no velocity error, if the inputs are changing at most by a constant rate. This would mean that the arbitrary stochastic inputs $f_1(t)$ are indifferently small, that the disturbance variable operators have indifferently small steady state parts $C_i y_i$, that first derivative parts $B_i \dot{y}_i$ are such that the input and output operators are proportional to the order of their first derivatives, and that the system can settle down to $C_1 z = C_2 x$ for inputs as variable as

$$x = x_0 + \dot{x}_0 \, t$$

Generally, the design problem in control systems involves attempting to satisfy the prime requirement for the type system, investigating the stability of the system over a range of the feasibly adjustable parameters (some parameters such as the mass of the system, etc. may be physically fixed), and then selecting those values of parameters that minimize the dynamic errors, i.e., errors that arise from non-quasistatic input changes. Excellent illustrations of such a process are in papers by S. Lees (32). However, as in the case of regulation, such optimalization determines the quality of the controller, rather than defining it.

In continuous automatic control, these control functions are performed with continuous, not necessarily linear, operations. The testing and exposition of the characteristics of a continuous automatic control system is made by subjecting the system to a number of constant input variable states x, at selected fixed values of the disturbance variables y_i. A lack of steady state error characterizes the likelihood of a control system. Stability may then be noted by causing a variety of dynamic upsets, and noting the nature of the transient response before the system settles down to its static value. The system may then be subjected to a series of constant rate of change inputs, to note whether it settles down to zero error or a non-zero error with constant rate inputs, at selected fixed values of the disturbance variables. In the latter case, the system is a Type 1 controller; in the former case a Type 2 controller, etc.

D. Discontinuous Automatic Control.

At present, discontinuous automatic control refers to systems that are piece-wise continuous but with different switch states, i.e. the elements are physical elements, but there are certain "low-mass" switch elements capable of distinct or nearly distinct multistable states. Except in some very ideal physically non-realizable cases, the systems do not have zero steady state error. Thus they really are part of a rather sophisticated dynamic regulator art. In this regard one must study the non-linear control references with considerable care.

E. Some Underlying Physics Preliminary to Regulation and Control.

It is useful to characterize some of the primitive concepts of physical systems, of statics and dynamics, that lie at the foundations of regulation and control theory.

There is a fundamental idea of a static chain of elements that is interconnected by mathematical-physical relationships, link by link. In some quasi-static fashion one can verbally or mathematically describe the relations from element to element. Causality or reciprocity determines the nature of the response chain in one direction or another.

In addition the links may have certain dynamic characteristics, creating dynamic chains of elements. They may respond or be interconnected by operational relations such as time rates of change, by integrated values, threshold levels, or even more complex connections. In instrument terminology, the linking elements are transducers, since they transform one physical quantity to another. In prototype, they are regarded as two terminal passive elements (i.e., elements containing no internal power sources). Two conjugate quantities y and x, are interrelated by an operator O,

$$y = O(x)$$

when the application of x to the "terminals" results in a conjugate response variable.

In order to produce change, either external power must be applied to disturb the chain, or there are also power elements (active elements) that can be connected into the chain as two terminal elements. A one or more dimensional chain can be thus produced. The links in the chain are in an indeterminate state unless the chain is closed in one or more loops to form a network. In principle, the description of these physical chains lead to mathematical expressions in the form of differential equation sets. In order to proceed with an analysis of the chain, one must conceptually remove any time varying active power elements and replace them by a stationary or quasi-static sequence of potential sources of power. One may then determine that there exists a sequence of stationary states of the network. If so, these states, which may be described as singular states (of motion) of the system, can be considered to describe a state of balance of the chain.

These singular states of balance can 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 case represents catastrophic transient behavior, and is thus not generally the subject of balanced states, or regulation and control system. It is one subject of dynamic transient analysis. The second case represents the behavior of a bounded system, which obviously has some sort of dynamic balance. However the analysis of this sort of system (non-linear limit cycles) is very difficult, and is subject, at least as yet, to some arbitrary concepts of its stability, its balance, and of regulation and control concepts to be associated with this type of system.

In the case that either the state of oscillation becomes very small or indifferent, then the ideas of a static balanced chain became useful. Thus the analysis procedure tends to be one of setting up a conceptual chain, and finding out whether small disturbances will leave the chain stationary. These closed loops of a balanced stable chain do not make a regulated or controlled system. They make a balanced system (Named in favor of the concept of a mechanical force balance system). Electrically, the 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 has been defined with regard to stable chains. One may attempt to use analogous concepts for systems that are not absolutely stable. However one must examine each case carefully and see what objectives are achieved. This is the problem with regard to discontinuous regulation or control, and with many more complex frequency modulated, or pulse modulated systems, and other fragmentations of the time domain.

In examining biological systems, both physical and biological scientist will have to accept a foundation in understanding that is far from perfect and often enormously over-simplified.

II. REVIEW OF CONTROL IN BIOLOGICAL SYSTEMS

A. A System Outline

One quickly surmises that the human biological system is a physical-chemical system with complex information, communications, and power net characteristics. Noting in a quiescent state, indicates that there are a variety of sustained dynamic phenomena going on internally. Various electrical, thermal, chemical, mechanical measurements indicate periodic phenomena in a range Kc/sec. to a cycle per century. Many of these are sustained non-linear limit cycles. This is sufficient evidence for an active network that contains internal power sources. The requirement that it only has to be intermittently recharged is sufficient evidence of storage elements. The "random" nature of its detailed actuation, i.e., imperfecting correlation with any 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.

Illustrative limit cycles (or clocks, engines, oscillators, and rhythms) are electrical wave activity in the brain, sustained neural activity, continued body awareness, muscle tremor, heart beat, capillary twinkling, eye blink, respiration rate, blood circulation rate, hormonal dynamics, intestinal peristalsis, muscle engine cycles, vasomotor pulsing cycles, sweat gland twinkling, thermal control cycles, water retention cycles, food injestion cycles, circadian cycles, menstrual cycles, seasonal cycles, and others. It is this active type of sustained dynamics of the biological system that can furnish a common point of departure of both the physical and the biological sciences.

Examined from a physical point of view, such characteristics imply non-linear system dynamics, which may or may not have anything to do with regulation and control. As an elementary example, the pacemaker cells of the heart form an autonomous system. As long as nutrient is provided, the pacemaker remains an approximately constant frequency oscillator. It is likely that a variety of disturbances, such as activity level or chemical environment, may change its frequency, but within limits, only moderately. Thus the pacemaker cells may be best considered a frequency regulator (whether static or dynamic depends on detailed nature of its operation). On the other hand, an eye blink cycle might be a device run by small, near noise level, signals in the eye field. The device might still be nearly a non-linear oscillator or it might approach the limit of an aperiodic network that requires input signal to trigger it.

Thus a dynamic control analysis of a complex active system starts by delimiting its exterior boundaries, visualizing a "isothermal" ambient environment (In passive systems, testing may be done by prescribing either an adiabatic or isothermal environment. In active systems, to prevent overheating, only an isothermal environment can be used), and then by observation of variables, determining the degree of constancy of their various temporal means, and the number of active limit cycle oscillators that exist. These oscillators may be simply autonomous, or used as internal regulators or controllers. The oscillators require exposition before basic treatment of the internal operation, regulation, and control is possible. It would be most difficult, with current physical methodology, to justify any fundamentally sound attack on complex systems other than by attack on its autonomic oscillations.

How is the systems analysis to be discussed from a biological point of view? This requires casting a framework for the system. The main line of biological development of regulation and control is the physiological-biochemical one that begins with Bernard (33,34,35), and stretches to Cannon (36). Smith (20) illustrates further advance in the main biochemical line. Wiener (15) developed the physiological-mechanistic offshoot, which has been extended by McCullough and his coworkers Pitts and Lettvin (38).

Bernard identified the system field in the human and its boundaries, his classic internal medium. By this masterly delimitation, the field in which the materials, processes, and mechanisms interact becomes significantly defined. Further, he advanced the case most forcefully of the physical-chemical nature within this biological envelope. Thus the system can be attacked by current physical science.

Bernard also characterized a state of balance of physical-chemical conditions in this interior field. The internal environment preserves the necessary relations of exchange and equilibrium with the external environment, but this interior environment has become specialized and isolated from the surroundings. This is an improvement biologically in the protecting mechanisms.

Beyond this, Bernard discloses 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". Such a thought can only delight the reviewers.

As his fourth contribution, it is clear that Bernard devoted himself to biochemical chains. Thus he brought to the field both the materials and processes end of systems analysis. (Thus Bernard expressed a point of view of physical-chemical plant organized to perform external functions, and involving internal chains without explicitly defining the regulating and control functions).

From a systems point of view, the introduction to dynamic chains in the internal system and the likelihood of regulation begins with Cannon's pursuit of the concept of homeostatis. His basic point (36) is that in spite of extremely unstable mechanisms, there is an essential constancy that is maintained in the internal field in the face of static and dynamic disturbances in the external environment. This would suggest that he was calling attention to both regulation and control in the internal system. However, more precisely Cannon states 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 is certainly a perfect definition of regulation, whether static or dynamic. Moderate steady state errors, within bounded limits are tolerated. To have written in these terms in the biological sciences indicated a primary comprehension of regulation. (Cannon attributes the recognition of "regulation" to Bernard. He states: "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 the chain of background that stretches from Bernard to Cannon covers quite well an understanding of regulation in the internal system. Reference (36) will be used to trace Cannon's outline of the interior biochemical regulation.

In Chapter 1, he describes some of the elements in the chain of mechanisms and processes that create balances, regulators, or controllers in the interior. In general this is concerned with the elements that handle the fluid matrix.

In Chapter 2, he discusses some response elements that tend to restore blood pressure, basically only if the disturbance is the amount of fluid in the system. Changes discussed are cataclysmic rather than the systematic changes within a normal operating range that one requires to characterize regulation. He points toward sensing at "some sensitive nerve endings in the blood vessels high in the neck near the brain". (This is a common weakness in which the discovery of a sensing or transducing element with some involvement in a process is often confused as the end in itself of characterizing the chain or the regulator).

In Chapter 3, he discusses one sensor element, thirst, that tends to assure a water supply for the fluid matrix. (This is not an apt element to involve in the direct chain in which the magnitude of body water is regulated. In an operation normal for this system, one might have a description like: "recharging phase--note this system has a reservoir storage. Recharging is initiated by an alarm sensor, which when actuated sets the entire system into self motion in space to seek out a supply of water. This actuation mechanism is not to be confused with the water level regulator - ..." The difference in point of view must be appreciated. A regulator is a specific mechanism that achieves a certain performance band for particular ranges and types of disturbances. To test the water level regulation requires a constant potential environment within narrow limits, supplying at various constant water rate inputs, and a determination of the steady state water level response. It appears that the results of a variety of such simple regulation type experiments are lacking. Instead more difficult experimental situations of the self actuated system engaged in a variety of complex tasks is viewed for evidence of its regulation; or, as previously cited, the response of the system to such drastic steps as tearing out its walls is investigated. These are certainly valid biological questions. They are not valid physical questions, at least not for a beginning of understanding of regulation and control.)

The second problem discussed in Chapter 3 is a sensor, stomach hunger pangs, to assure an energy supply for the fluid matrix. Cannon suggests and investigated a chemical level trigger for this process, possibly sugar, but says that it requires more work. He finds that the stomach pangs form a repetitive periodic cycle.

(The previous remarks are pertinent. This is not a regulating mechanism, but an aperiodic alarm mechanism. The alarm itself is an oscillator. It is tied into the system in a fashion that is usual for alarm systems. This oscillating network has adjustable parameters that may put it into stable or unstable states. Illustration of explicit stability design may be found in Reich (1961), Sec. 45 (39). If certain threshold elements have certain parameter ranges, the circuit is stable. If a threshold or stability boundary is passed, then the circuit is unstable. As an alarm, the network itself is a limit cycle oscillator, but is being used in an aperiodic mode. If by other means a larger chain is closed, then this on-off alarm chacteristic may be used as part of a dynamic regulator, or even controller. However, without complete specification of the chain, its function is not known. Thus this second problem has brought forth an oscillator mechanism, and some unexplored ideas on the stability of the network.)

Chapter 4 returns to the constancy of water content in the organism. After briefly touching on the chain of elements in which water is involved, Cannon points to the kidney as the excess regulator, i.e. an "overflow", or peak quantity regulator. (The combination of a storage element and an on-off resistance element, like a flush valve, does not of itself create a regulator. It creates an aperiodic relaxation network which may be used in a more complete chain for balancing, regulation, or control.)

The chapter then shifts to the suggestion that the desired effect is to be considered more precisely maintenance of the consistency of the blood. The problem is how the blood consistency is kept "uniform" when water is taken into the body in excess, or when no water is supplied. In the latter case, water stored in the muscles and skin may be drawn upon. It is suggested that the pH may shift the storage level offered. (It appears more likely that water, whatever way or organ it is regulated or controlled in, is controlled as a large chain zero water rate regulator, i.e., within its control range, against steady state disturbances, the net steady state water rate is almost zero. The rate at which water enters some regulating zone is the rate at which water leaves. The unbalance may not be measured directly as a rate, but by some parameter that is proportional to the rate, such as pressure, distension, or concentration changes of fluids in a reference volume).

Chapter 5 relates to the constancy of salt content. The same type of regulator arrangement is proposed as for water. Excess is gotten rid of through the kidneys. In deficit, there is withdrawal from the storage. (However it is more likely that a zero rate regulator, or on-off regulator is actually involved.)

Chapter 6 relates to regulation of blood sugar. Normal regulation is implied in the vicinity of 100 mg of blood sugar per 100 cc of blood. Two "force balance" elements, adrenin from the sympathico-adrenal apparatus brings forth sugar from storage in the liver, and insulin from the insular apparatus leads to depression in blood sugar concentration, possibly by being involved in the storage of sugar in the liver and muscles. While this combination furnishes a "restoring force" toward a balance, it is not clear whether this is a tendency to regulate by a continuous restoring force, or by a two position on-off dynamic regulator.

(Another element of physical regulator theory may be pertinent. It is common that a "spring" element is used to create a force balance near a desired regulating point. A considerable amount of regulating design may go into attempting to design a very high spring rate so that the deviations from the regulating point may be quite small. The two position band-determining on-off switch generally is designed to be a non-linear restoring spring that does not quite have any "exact" balance point. In this context, the reference of on-off control as a dynamic regulating system may be better understood).

Below the 70 mg per 100 cc. sugar level, possibly down to 45 mg, low sugar reactions take place, among whose symptoms are hunger pangs. (This is not a regulating or control function, but an alarm function. An alarm is turned on which is partially a limit cycle, and partially other D.C. signals. It may or may not be used in a larger regulating or control chain. It is reasonable that there must be 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 the much more localized regulating or control chains that have an operating range, and that only signal alarm when they are not able to continue their function.

At this point, a rather significant overall view of the complex biological system must begin 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 is a panel board in the central nervous system - a figure of speech, but the function suggested is not any figure - in which various alarm states are indicated. Now 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. It is not clear whether this is a new concept or not. It certainly would not be considered new within the scope of physical control theory. However, it is proposed as one that may be palatable to both physical and biological scientist. The details of the processes and mechanisms are biological -- namely physiological, biochemical, etc.; the abstracted characteristics of processes and mechanisms are physical).

There is likely an overflow level at 170 mg into the liver since large charges of sugar into the system appear to stop at this level, below the kidney threshold. There is likely a second overflow level at 180 mg into the kidney, indicating serious malfunctioning of the system. Whether a regulating chain is really involved in the former level is not indicated.

Chapter 7 deals with regulation of blood proteins. Nitrogen as protein is stored in the system, to a considerable extent in the liver. Protein in the plasma is maintained constant. If a step function of decrease of plasma proteins is made, there is a nominal relaxational rise with a time constant of the order of a day in which material is likely restored from the liver. Possibly the thyroid gland is important in controlling both storage and release.

Chapter 8 deals with the regulation of blood fat. Fat is increased in the blood after eating, and is stored in the system. The regulation of fat storage and its release is obscure.

Chapter 9 deals with the regulation of blood calcium. Refering to the precision of regulation of calcium in the blood, Cannon talks about 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. However, how the regulation takes place has not been fully determined. Storage may be depleted by secretions from the thyroid gland or from the pituitary gland. Secretions from the parathyroid glands seem to be the main associated agent. Deficient secretion reduces blood calcium (raises phosphorus). With excess secretion blood calcium is increased and phosphorus decreased. If the glands are lacking, there is defective calcium deposition. Neither the balancing nor the regulating chain is described. Yet, it appears quite reasonable that regulation functions must exist. For example, Cannon points out that the blood osmotic pressure, dependent in the main on the concentrations of glucose, salt, protein, and calcium - largely on the salt concentration - after a few minutes of relaxation of subjects toward steady state, only showed a half percent deviation in statistical variation from a fixed level for a considerable experimental group.

Chapter 10 deals with an oxygen supply. While food and water are stored in the body and can be drawn upon for days, storage of oxygen is essentially not provided for. Activity of the organism requires continuous delivery of oxygen "to permit the burning of the waste products of those activities" (this latter phrase seems surprising). Regulation is achieved by speeding up the continuous process.

Oxygen requirements may vary from 250 - 300 cc. per min. quiescent, to 15 lpm with severe effort. Four lpm is the likely maximal sustained amount. As a result of high muscle activity, lactic acid, which develops, accumulates in the muscles. This must either be burned or transformed back into glycogen. The organism borrows the ability to go on working beyond the limit set by available oxygen with the proviso that it will take up enough oxygen later to burn the accumulated waste. This is Hill's oxygen debt. The regulation of oxygen supply to remote cells is only provided during moderate activity. The respiratory and circulatory system adjustments are not adequate to prevent acid development. Other devices, in the next chapter on blood neutrality, are brought into play to maintain neutrality. To supply the need for extra oxygen, a variety of mechanisms are brought into play. For example, the respiration becomes deeper and more frequent. However the main triggering element is more rapid elimination of carbon dioxide. An increased carbon dioxide partial pressure in the arterial blood, as it passes the respiratory center, sends signals to the respiratory muscles so that their action becomes more vigorous. This pumps out the extra carbon dioxide in the lung space. A small percentage increase in the carbon dioxide level, say as measured in the lung space, causes large changes in ventilation, suggesting a carbon dioxide regulation.

Vigorous muscle activity involves the sympathico-adrenal system which likely leads to secretions that increase rate. Thus a duality of increased depth of breathing and breathing rate is brought about. In the deep lung spaces, the exchange oxygen partial pressure is thus maintained even in the face of 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, predominantly by increase in blood rate. The pumping action of limb muscles, the diaphragm, and the heart all change both rate and stroke to increase the blood rate. For example, to get a ten-fold increase of oxygen delivery, the heart can double its stroke volume, and more than double its rate. In addition there is an increase in arterial blood pressure by constriction of blood vessels to the abdominal organs, which expands the capillaries where the greater oxygen supply is needed. This also tends to make added oxygen delivery available.

Increase of carbon dioxide and temperature in the muscles also 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 3 - 4 cc. in outlying capillaries in a quiet state; but only return 5 cc. in active regions.

(In this chapter a complex dynamic problem is discussed in outline. The authors are not competent to judge the validity of the outline. However it is not adequate from a dynamic analysis point of view. Beside the problem of regulation and control, it would be impossible to create a sequence of mechanisms, whether mathematical or physical doesn't matter, that would duplicate major characteristics of those systems, which in whole or part are involved in deciding on the adequacy or level of the oxygen supply. It would be particularly misleading to encourage engineering efforts to quickly model by analogue techniques, various aspects of the system. While physiologists may self police and determine the content, language, and areas that they investigate with reasonable confidence, the exchanges and feedbacks with other disciplines must be observed with caution. It would be 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.

Specifically, one can point out a few reactions that arise physically. Muscles must be considered to be mechanisms that can do either external work or internal work. In fact the self actuation of the system as a whole depends on the ability to quickly shift from one state to another as required. The self actuation of the muscles requires that they be an active engine, or oscillator cycle. While other cells in the body have to be fed, and are likely tied into some rhythmic oscillator cycle, they all do not have the requirement of transforming energy both for their own function and some other function. Thus one might expect, in general, a somewhat different cycle or power level for these cells, but one would expect a specific engine cycle for the muscle cells. At such a point, engineering thought would be concerned with the prime mover engine cycle to "explain" oxygen demand, since the basic cycle implied is a "combustion" cycle.

With regard to another point, since there is no oxygen storage for the combustion process, while storage has been pointed to of the sugar fuel -- whether drawn from the general "inundation" mass of the body or the liver -- there would first seem to be a needed proportioning of fuel to oxygen, or oxygen to fuel. How is the fuel metered to the muscle engine cells, particularly if drawn from the liver? Assuming that the self-actuated muscle range, the swing of the arm, or lift of foot, etc., is determined by the central nervous system, or by conditioned reflex, or whatever it may be, it is not completely clear what loads the body may have to overcome during that stroke. It is thus not clear what external work the body will have to perform in that period. For these short strokes, does the body draw on storage? In an automobile, for example, flywheels, or multiple firing cycles, are used to carry the power over the rotational cycle. For a longer period, is there an essential fuel -- oxygen equilibrium? In an auto, you can't get very many cycles out of balance without backfiring. Does a hormonal signal -- say adrenalin -- shove part or all of the muscle system into "high gear", capable of supplying high external demand power if needed? If so, is it not possible that sustained transients have to occur before the supplied power subsides? Thus isn't the concept of oxygen debt misleading? It may be perfectly valid that fatigue products are stored, and require another power level adjustment to bring about a new quiescent equilibrium. Again the point is, not that these questions are necessarily valid, but that a much greater complex dynamic chain is needed to describe even the steady state chain of a given activity level in which some external and some internal work is being done and some heat is flowing.)

Chapter 11 deals with the regulation of blood neutrality. Work, resulting in lactic acid and carbon dioxide, acidifies the blood. Base radicals in food can render the blood alkali. Blood is slightly basic at pH 7.4. At pH 6.95 coma and death ensue. At pH 7.7 tetonic convulsions ensue. If too acid, the heart relaxes and ceases to beat; if too alkali the heart contracts and ceases. Complex physico-chemical processes are involved. Roughly, acid reacts with sodium bicarbonate to form more carbon dioxide which stimulates the respiratory center, which pumps out the carbon dioxide. Another buffer is alkaline sodium phosphate, which reacts with acid to give acid sodium phosphate. Both forms are almost neutral. However the acid form is slightly acid and may not be permitted to accumulate. It is gotten rid of in the kidney tubules, where by absorption and concentration much of the acid is excreted. If the blood becomes alkali, the respiratory stimulus is lacking and the carbon dioxide percentage, supplied by the persistent active organs, cumulates in the blood.

Thus alterations in the chemical reaction of the blood are quite dangerous, so that regulation of the very delicate balance is quite urgent. The combination of sensitive respiratory center, blood buffers, and kidney act as sentinels, continuously on the alert to prevent swings away from the normal state.

(Here again, it is precisely because many of the correct mechanisms that are needed for the regulating or control chain have been identified, and because their function is likely basic, that the need is greatest for a completely valid description first of the experimental nature of regulation or control, and second of the entire mechanistic chain needed to account for the characteristics found.

Chapter 12 discusses the constancy of body temperature. Deep body temperature is maintained in the vicinity of 37°C. Drugs, fever interfere. Above 42°C. brain disturbances occur. Below 24°C. deep lethargy prevails. Internal processes tend to obey an Arrhenius type law of doubling the chemical process rate per 10°C. change.

Heat is continuously produced by activities involving the organs, and is transfered through the body. Heat production is under control and is remarkably constant in normal people at standard conditions. From the consumption of oxygen and production of carbon dioxide during a series of short periods, a basal metabolism representing the heat produced by burning fuel can be computed. Small variations of a few percent 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 kept the thyroid gland constantly active was not known.

The regulation of body temperature, like the oxygen supply rate, is achieved by modifying the speed of a process. 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. With warm temperatures there is also a pouring out of sweat through skin glands and 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 the rise of body temperature, sweating and even panting take place. If constriction doesn't prevent a fall in temperature, 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, in short for the automatic reactions which govern the production and loss of heat. This theremostat may be affected by the blood temperature, or by nerve impulses from the surface.

(Except for some moderate changes in details, this picture of temperature regulation is essentially the same as is accepted today. See for example Hardy (40), or articles by Benziger, of which (41) is representative. The question arises again as to whether this picture models the temperature dependent, or temperature regulating chain. In this instance, the authors can argue from fact because of work done by one of the authors. The question must be raised, as before, that if energy is actively required to satisfy both temperature regulation and external work on rapid demand, there must be an engine cycle. The constancy of temperature precludes the cycle from being active through all body cells, unless there is a hormone cycle mechanism that constantly coordinates the cells into metabolic activity. Under quiescent conditions, for example, the data such as Cannon discusses does not make this likely. Thus it is more likely that the engine cycle must be isolated. Physical reasons, particularly the body temperature distribution, suggests that the engine must be localized, in particular at the site of muscles, and possibly other active organs. Thus one would expect active oscillator type engine cycles rather than the astonishing uniformity of basal metabolism that Cannon discusses, or that even Benziger implies.

This was the physical expectation. Experiments in fact uncovered a coordinated type of power cycle with a frequency of about 1 cycle per two minutes. This is the system's engine cycle. The fact that the mean metabolism is "constant" or nearly so, is only evidence that the power cycle is regulated in some as yet undisclosed fashion, although one may be suggested. It is possible, that the anterior hypothalamus temperature, as a term for a localization of mechanism, controls the amplitude of an action potential carrier wave at about 10 cps that stimulates a sustained muscle tremor as one basic element in temperature regulation. Again, it must be emphasized that the latter statement, while it may suggest considerably greater complexity or enriched possibilities in construction to the engineer, 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. However various regulation defects show themselves.). These are not too pertinent in the present review.

In Chapters 15, 18 and the Epilogue there is some attempt at general assessment.

In Chapter 15 on the margin of safety in the system, the ideas of a 1907 paper by Meltzer are touched on as to whether the body is organized in a generous or limited plan. This question either appears to be whether the system operates with poor or high quality regulation. The answer seems to be that the system operates with "sloppy" regulation, copious material, and a considerable amount of redundancy.

(This is a very valuable message. It represents a view that is much more comprehensible in an old-fashioned chemical plant or production line.

A remarkably 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 sloppiness and redundancy. At greater through put requirements, problems of stability, and of critical regulation and control of sub-elements arise, and such systems are inoperative.)

Chapter 18 discusses general features of body stabilization. The body elements are naturally unstable; it is regulation in the body fluid that stabilizes the system; the system has alarms; there are automatic regulators with instrument measure sensors; materials and processes are regulated; an important element in material regulation is storage of both short time and long time nature; overflow is an important element in regulation in the fluid field; many process regulators, such as temperature regulation in the fluid field; many process regulators, such as temperature regulation, oxygen supply, pH, are automatic; and that the sympathico-adrenal apparatus automatically makes many of the adjustments to preserve normal internal conditions both for various individual conditions and as a unitary system. Cannon further reviews a number of tentative regulation propositions that he laid down in a 1926 paper. These include:

(a) In the open loop body response, there are many regulating functions, as exhibited by their steady state constancy.

(b) The constancy, i.e., quality of regulation, exists because of large restoring forces to the disturbance sources.

(c) The regulating mechanisms may be multiple to increase the effectiveness of regulation.

(d) The restoring mechanisms occur in pair, i.e., since they tend to be unidirectional chemical reactions, it requires a pair to create a restoring "spring" force, instead of a balance force.

The higher animals tend to have the more complex or complete regulation mechanisms. In summary, 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. In the final chapter there is a philosophic discussion of whether the same principles of regulation exist or could be brought to bear on the social system.

(To physical scientists, occupied with regulation and control, this book is tremendous, and contains great, friendly and familiar thoughts. It is clear that if Bernard isolated the important physical-chemical field, Cannon understood the primacy and need for regulation, and even likely identified the systematic elements of the regulation. However, the missing ingredient is the systematic exposition of the system characteristics of each proposed regulator under a large variety of steady state input environmental conditions. There exists further need for an exposition of control functions under conditions of dynamic or transient response.

The validating kinds of experiments, according to intrinsic ideas about regulation, are measurement 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 it is argued that it is not pertinent to hold all of the input variables constant, the burden of proof, in each particular case, is on the investigator. In non-linear systems, the lack of a principle of superposition will not permit

<u>an automatic correlation between one type of signal and another</u>. For example, it is not common to run physiological experiments with constant rate of food input. It is quite clear that the clock-like nature of hunger pangs, as a system that arises from a concentration induced instability, will be different for constant rate food inputs and intermittent rate food inputs. The burden of proof is on the investigator as to whether he can relate these two conditions, if his interest, say, were in the stomach pang response. In fact many of the interesting details of regulation or control can very likely result from such experiments).

Proceeding along the main biochemical chain of regulation or control, as embodied in H. W. Smith (37), the kidneys are the master chemical engineers of the internal environment. It is their balancing function that keeps the internal environment regulated. Other organs tend to perform one function; the kidney has an innumerable variety of tasks. (This summary is so elegant, that it was adopted as a thread of continuity pursuing the main biochemical line of Bernard and Cannon. The one exception that must be taken to the generalization is the likely need to embed certain major mechanisms in this milieu that is purported to be so well regulated by the kidneys).

In (37) Smith chooses to trace the evolutionary story of the kidney. For present elementary purposes this will suffice. For greater detail his other publications may be examined. The fact that early vertebraes evolved in fresh water, and that an internal milieu of salt was necessary for the elaboration of complex organs and mechanisms required tenacious conservation of salt as a most primitive function of the kidney. A second development problem that arose when they left the water was conservation of water.

He depicts the evolution of the kidney 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 in 1842 showed evidence that the tuft acts as a filter. In 1917 Cushing published the first definitive work on urine formation. Experimental work then demônstrated the reality of filtration theory. Later studies by Marshall and Edwards exhibited the nature of tubular excretion in vertebrates without glomeruli.

Later amphibia, in order to serve the ends of water balance, have a mechanism for reducing the rate of glomerular filtration (and thus water excretion) when out of water, and also a mechanism for varying skin permeability to water. These mechanisms are governed by the pituitary gland.

The studies on aglomerular forms proved that the tubule could excrete all the important constituents of urine. These include such materials as creatinine, creatine, uric acid, magnesium, calcium, potassium, sulfate, iodide, nitrate, many dyes and synthetic compounds. They cannot secrete carbohydrates or protein.

In the reptiles, a change in protein metabolism leads to uric acid which requires only half as much water for the same amount of protein metabolized, conserving water. However, uric acid is insoluble in water. Thus reptiles deposit uric acid by tubular excretion in the urine in very high concentrations, such as 3000 times the blood concentration.

Mammals also void a urine that is more concentrated than the blood. The consequence of a temperature regulated system required an increased blood circulation and blood pressure, and thus increased glomerular filtration, which then required tubular reabsorption of valuable constituents from the filtrate, with a capacity to conserve water by making a super concentrated urine, even with urea. This unique functional ability was accompanied by two anatomical changes, the bending into a hairpin loop, and the disappearance of a venous blood supply to the tubules.

The function of the mammalian kidney is described with reference to man. The individual nephron consists of a ball of capillaries from the renal artery, balled into an elastic membrane capsule to form the glomerulus; 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 filtering surface of 3/4 sq. meter and filter about 50 gallons per day. For this quantity of filtrate, the kidneys receive a supply of about 500 gallons per day of blood. The 50 gallons of filtrate per day contains 2-1/2 pounds of salt of which only 5% is excreted in the urine, and 95% reabsorbed by the tubules. A pound of sodium bicarbonate and 1/3 pound of glucose are also filtered, and more than 99% 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 1-1/2 quarts of final wastes, water and waste material which may have been concentrated a hundredfold or more, is excreted. The total circulating fluids, which amount to about 3 gallons, have thus been filtered approximately 16 times per day. Once the filtrate enters the capsule, it is effectively outside of the body. The main ingredients that are filtered and reabsorbed, one must keep in mind, are salt and water. (It is obvious that there is a physically intriguing problem as to how these rather complex functions are achieved by what appears to be nearly an essentially passive mechanism. Thus there is interest in a functional mechanistic description of the chain.)

Smith says that 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 osmotically from the tubule in the presence of an anti-diuretic 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 latter 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 latter segment of tubule under control of ADH.

Osmotically sensitive receptors in the midbrain and the pituitary gland are affected by osmotic pressure in the blood via ADH to increase or decrease the excretion of water, resulting in osmotic pressure changes in the blood of not more than 1 or 2 percent. 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 the 85% reabsorption in the early part of the tubule, urine flow cannot exceed 15% of the glomerular filtrate, or 7 gallons per day. (It is not quite clear whether the system is thus regulated against input water rates or controlled. If controlled, i.e., if the osmotic pressure is what is controlled, there would be negligible change in osmotic pressure at any input rate up to 7 gallons per day of water, possibly with some lower limit otherwise set. If regulated there would be modest shifts in the osmotic pressure).

While this completes Smith's discussion on the kidney, there are a few more comments that are interesting. First, in discussing man, he points up Bernard's later thoughts, and those of Frederica's, that the higher organisms are so constituted that when disturbed they react to restore a balance, and the higher the organism the more numerous and complex do the regulatory mechanisms become. The heart of the problem is thus not in the essentially passive but regulated fluid, but in the end, the functions of the "living" mechanisms, the protoplasmic unit, the cell. (To a classical physicist, 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 considerable taste for the views of a D'Arcy Thompson. This is not meant to object to molecularized, atomized, or quantized problem solving, but is a caution that science cannot go only to one extreme or another).

Smith briefly discusses the nervous system. The nervous system 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 of the body activities - circulation, digestion, excretion, temperature control - are taken care of by an autonomic nervous system which is organized to handle a very great number of details. In the higher animals the nervous system is the most adaptable organ in the body.

(One gets the impression that this represents a great variety of patching networks in which all sorts of chains -- balancing, regulatory, control, oscillator, alarm chains -- are locally created to coordinate desired functions. Viewed from a background of large networks, plants, or systems, it suggests a loose coupling so that these minor loops cannot transmit very much that will upset the overall system stability. It is this sort of property that enlarges the scope of the problem to more modern and abstract automatic control theory. However there appears to be so clearly a number of major systems that must be relatively simply conceived in order to obtain stability of the main system. These could be a major physical controversy for a long time. That a considerable amount of the patching, as learning, constitutes a part of adaptive control mechanisms is clear).

In a final chapter on consciousness, the concept of "mind" is replaced by "consciousness", as 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, <u>many involving power</u>, can be executed. For example, 20 power strokes (playing notes) per second have been observed. This is under control, because at 30 notes per second the play becomes ragged. (These are levels of 400-600 motor actions per second). Thus 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.

Consciousness is thus more fully 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. Consciousness 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 are more or less specifically involved in sensory or motor activity, and to specific parts of the body. This localization is more a functional pattern than anatomical regions. For example, during changes in growth in an infant, the cortex acts as if it were in control of a big sucking mouth, a tongue, a big nose, and hands. Later hands and mouth regions shrink as eyes, ears, feet, etc. come in. At the beginning there is also little localization. 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 of this point,

(a) The significance of the kidney has been stressed.

(b) An adequate description has not been given either for the balancing chain or the regulating function of the kidney.

(c) That this is still an area for disagreement is apparent in Zinsser (42), who states, in part, that the analysis of the kidney as a process has just barely begun and that warring generations of physiologists have still not validated any hydrodynamic analysis of the nephron. He and others indicate some models. For example he shows a set of equations for a mechanical analogue. (The equations shown in both referenced papers are not essentially correct. They represent linear, or near so, general process representations, rather than specific functional models. They are common and conventional in engineering analogue studies. Their philosophy is given to some extent in Karplus and Soroka (43). However their main type of defect is that they miss having sufficient wide range applicability to account validly for all of the singular states of motion, and the nature of the stability near the singularities).

(d) Thus the nature of the physical system, the regulation or control is still not completely exhibited either theoretically or experimentally.

(e) It is likely that such general efforts as Smith's completes the main biochemical materials regulation line of description.

Having illustrated a chemically regulated fluid matrix is not satisfactory as a complete system model, even if it is a main regulation line. There is need for a few major operating mechanisms that are essentially regulated or controlled. It is likely that they are engine or oscillator cycles because of self-actuation. Since oscillator cycles will be discussed later, discussion of these mechanisms will be deferred. However, it is appropriate that Smith ended with notes on the nervous system, for there are coordinating, regularizing, communications, or computing functions that have to be performed. These, in some fashion, must fall into the automatic control line. There are likely two systems (and two main lines) that require consideration - the nervous "communications" system, and the signalling hormonal system.

The primary exposition of the communications system may be attributed to Wiener (22), although the detailed foundations are due to neurophysiologists. Steps leading to synthesis involved the fact that as physical-mathematical scientist, Wiener was involved in an informal interdisciplinary study program with Rosenblueth (Cannon's collaborator) in contact with the differential analyzer development, and involved in electric network analysis. In part in common with a number of others, Wiener visualized high speed computation, using digital (i.e. arithmetic rather than continuous 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. From a tracking problem involving prediction of path for a network involving a human, the suggestion arose that the element of feedback (i.e. servomechanism theory) is essential to human operation. (Illustrated was picking up a pencil in which the hand acts as a follow up mechanism to the tracking eye, i.e. as a servo, which may show oscillations. Wiener chose to look at loop instability. In answer to a specific question 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 inputs (sensory) and discharging outputs. There must be active circulating loops (presumably oscillatory 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 of electrical engineering, but a communications theory for "signals" (i.e. time series) as a statistical science. An attempt at unity was made of the problems of communications, control, and statistical mechanics for both machine and biological system. Included is 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 spread to neurophysiologists, mathematicians, logicians, biophysicists, engineers, computer designers, physiologists, psychologists, sociologists, anthropologists, economists, and philosophers. A typical example of work attempted was the dynamics of an isolated muscle-nervous system reflex in a living animal, analyzed as a control system (1946).

Entering the text, Chapter 1 makes the point of the need of a communications theory, low power point of view, rather than the power net point of view.

Chapter 2 presents formalism on the nature of the ergodic hypothesis (briefly, the reason by which averages in phase space and averages in time are equal). The formalism of Gibbs is questioned. (Actually, in a classical physical sense, it is generally only the physical result that is desired, not the formalism. For many degrees of freedom systems, it is the Helmholz, Boltzmann results that are used to ascertain the nature of the approach to equilibrium. More particularly, phenomenological equations are really used to replace the non-equilibrium Boltzmann equations. Now it is true that a standoff is reached in systems with large statistical fluctuations. However, it will always continue to be a race whether the statistical or continum descriptions succeed to a greater extent when there is only moderate fluctuations. Chapter 3 on time series theory furnishes apt illustrations. Wiener proposes that such problems as the turbulent or the weather field are to be thus most hopefully treated. It is for this type of problem that a most definite challenge is made).

Chapter 4 is on feedback and oscillation. From illustrations of biological control instability (ataxia), he proceeds to illustrations of 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 the point of view of feedback. Whether regulation or control is implied is not discussed. Instead the follower type characteristic (i.e. linear servo theory) is generally discussed with some attention to stability. (It is surprising that the available servo theory books are not referenced). It is implied that similar follower action by feedback takes place in biological mechanisms (in hand motion, or more generally in physiological cybernetic systems) but with greater complexity. (Up to this point, no distinction has been made between regulation and control, nor between linear or non-linear systems. Differences between linear and nonlinear dynamics are indicated. (It is not clear whether in general non-linear limit cycle oscillations are being discussed. However appropriate to previous comments, one remark must be rebutted. With regard to an organ pipe driven by a "D.C." source of air, there is no cruder linear theory as opposed to a more precise non-linear theory. At most plausibility arguments - testimonials - may be advanced. After disputing Gibbs' formalism, such imprecision is not permissable, particularly, since what can easily be involved are stability questions). "In general, non-linear systems of equations are hard to solve." (They are also hard to formulate when no "exact" science exists). Nearly linear systems are mentioned. It is suggested that physiological tremors may be treated roughly as perturbed linear systems. (The authors question this except for moderately trivial tremors. Most real tremors in the biological system are likely to arise from considerably non-linear mechanisms). In nearing the end of discussion, Wiener states that the feedback systems of control discussed (the linear ones?) and the compensation schemes discussed previously (the regulators?) are competitive. (The double 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. The relative usefulness of the two control methods depends on the constancy of characteristics of controller element. (While these statements indicate acceptance of clear distinction between regulators and controllers, they repeat a belief that is common in automatic control theory, namely that constancy of the characteristic 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. Such an example is regulating an input, or staging regulators. Feedback loops thus become bigger, and have more complex possibilities. (Actually it is most significant to recognize that 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 the 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 what is a very complicated and yet imperfect theory, which should get more attention.

(The subject has gotten more attention. It is incidentally pertinent to suggest that it was likely H. Ziebolz, then of Askania Regulator Company, who was the 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. It is such efforts that have led to computer control and adaptive control. It is also incidentally obvious that complex combinations of regulators and controllers are controllers. This stems simply from the fact that the mathematical description must continue to lie in the dynamics of differential relations or equations involving time).

In conclusion, important application of feedback is to physiological homeostatic mechanisms. However these homeostatic mechanisms tend to be to be slower than, say, the feedbacks involving the nervous system. (Here arises a basic point. It is possible, but not really useful, to involve a concept of "feedback" in regulator design. The designer is concerned generally only with force balance links 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, i.e. to identify a Type 0 system as a linear servos is fine. However in general non-linear networks or systems, the term "feedback" stuffed into regulator design is a concept unwanted by the designer, who is more occupied with the broader problem of coupling. Cannon clearly defined homeostatic mechanisms as regulators, and 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 that controllers are in action. The problem is to find them. It serves no purpose to put mechanisms with two intrinsically different classes of behavior under one roof. There is of course, one common roof. Both regulators and controllers do have dynamic behavior, but this arises from the basic presence of "masses" and inertias, and not from "feedback" but from "coupling").

Chapter 6 on computing machines and the nervous system points out the element of the digital computer - its elementary Boolean algebraic character, the equivalence of this to switching, and to logical addition and multiplication. He points to the neurons as being ideally suited to act as relays, with two states of firing or resting. With a little more detail he characterizes the nerve action, the function of both a temporary and permanent memory in the nervous system (by temporary 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 that the chief changes, representing memory, are increases in thresholds). He considers the brain, as the computer, to be a logical machine. Based on the work of Turing, he then believes that the study of logic, and the logical machine, whether nervous or mechanical are equivalent.

Discussion continues on the relation of logical characteristics and psychological characteristics of the mind, some of the logical difficulties, an implied 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, etc. could be accomplished in computers. The problem is tackled of assigning a neural mechanism to the principle of similarity; namely, how does the system identify an object specifically from incomplete or distorted information? The sense of vision is used as an example. It is likely that there is a visual - muscular feedback system. For example in worms a negative phototropism drives the animal into the darkest region accessible. With regard to the human system, there are some regulators, such as the 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. This likely involves enhanced sensitivity at boundaries. There is likely comparison between an outline and a standard stored in memory. However the aspects of the object image seems to constitute a complex that involves permanent subassemblies. The nature of some feasible subassembly is visualized in one mathematical form of group theory, in terms of group transformations. In some complex of this sort may lie the Gestalt of the object image. An illustration is given of a reading mechanism for a blind person, in which the letter forms are standard but the size of type may vary, requiring identification of both form of specific letters 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 such as the alpha rhythm of the brain. This represented a beginning of talking 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 logic. One finds further development of the logic in subsequent works of von Neumann and Ashby).

Chapter 7 on the possible relation between computer malfunctions and psychopathology is not of present concern except to note that there is moderate evidence that the prefrontal lobes may have control over the circulating memory, and to note the reliability in performance required by the long neural chains in man.

Chapter 8 touches on higher cell, group, race organizations, on chemical-hormonal-communication, on the lack of stability in political and social organizations, on a theory of games in which only limited regulation exists, regulation in the social past, on the nature of society, etc.

Chapter 9 (a 1961 supplement) deals with learning and self-reproducing machines, the former from the point of view of a theory of games, the latter from the point of view of a non-linear mathematical theory.

The final chapter 10 deals with the electric signals of the brain wave, and some aspects of correlation theory. (It is somewhat surprising that the thorough earlier application of correlation theory to such processes as turbulence is dismissed so briefly. It is in fact through these studies that the use of correlation techniques in physical fields has commonly reached physics. It is also in this field that the use of correlation techniques for non-linear fields is found to produce results that are considerably less than perfect). 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. Thus some general discussion is given about synchronization in non-linear networks. It is suggested that such non-linear synchronization can generate a self organizing system as in brain waves, and that this contains the idea of a dynamic template. (These later remarks of Wiener's are in line with a great deal of modern thinking. However the authors have certain reservations. They have had considerable experience with problems involving time series, to mention a few diverse ones, ranging from thermal 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. Viewed always from physical training, there has been a great reluctance to consider the problem as one in stationary time series. Thus the statistical correlation analysis that Wiener has popularized has little appeal. Their approach to the problem tends to remain a deterministic mechanics to certain indeterministic elements in inputs. With finite samples of data, it appears very difficult to determine, a priori, which philosophy will give better answers. Such authors as Munk and MacDonald (44) with reference to the Chandler wobble, of the earth take note of the problem. It is difficult to distinguish between a monochromatic response with a wide stationary dispersion, and a monochromatic response that wanders around, particularly from limited data. They allude to discussions in 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). In particular the problem becomes somewhat chaotic when dealing with non-linear systems. Jeffries cites much earlier discussion in Goudny Yule (1927). The same criticism is susceptable to documentation in turbulence. For example, with regard to synchronization or to non-linear resonance, it is most appropriate to spend time with the material and references in Minorsky (28) in chapters 18 and 19. The only quantitative discussions have taken place around electrical network illustrations because they can be formulated mathematically. Actually, more generally, it is only very simple non-linear problems that have been treated quantitatively and with any degree of system.)

In summary, Wiener brought to the biological system a mathematical-physical-logical view of organization of the nervous system, and response complexes involving the nervous system, similar autonomic ideas as in the digital computer, and he brought in the ideas of communications theory. These great contributions brought the possibility of interpreting the functioning, the regulation, and the control of the complex biological system one step closer.

It remained for Warren McCulloch and his colleagues Pitts and Lettvin (38), acting at least partially under the impact of Wiener and von Neumann, to attempt the detailed attack on neurophysiological problems from a communications point of view. The importance of their work is in the philosophy of the details of their reasoning, their errors and accomplishments, and is thus not within the present purposes to comment on.

With the view of a regulated interior, with emphasis on materials regulation, and a guiding mechanism with an emphasis on self actuated and autonomic processes of a mechanistic-logical nature, there remains the entire array of physiologically significant mechanisms and organs.

B. Oscillator Mechanisms

The basic problem in a dynamic analysis of an unknown system is to separate out analyzable phenomena with measurement techniques that create negligible interference, without disconnecting. Physically one may only start by some steady fixing of the system. If it contains internal prime movers which convert stored energy to energy in flux, then the system will ultimately degrade its energy to heat. Therefore the only plausible steady test state is a sequence of isothermal states (in which all potentials and fluxes in the environment are kept constant, or at constant rate). It becomes necessary to keep track of all fluxes in and out of the isothermal boundary. One then notes periodic, significant power transformating cycles. If found in a quiescent environment, they are sufficient indications of unstable steady states. They are the limit cycles of Poincare. 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 non-linear non-conservative systems, such as physical-chemical, including biological, systems. (These phenomena are also denoted as clocks, engines, oscillators, rhythems, D.C.-A.C. converters. Distinctions among these more literary terms for limit cycles are that a clock has a very pure timing phase; an engine involves considerable transformation of power, generally into 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 of a limit cycle nature). One must uncover elements of this type to expose what goes on beneath.

1. The Nervous System Clock (The Brain Wave)

An orienting physical hypothesis for nervous system waves is the following. In the development of electrical transmission, DC transmission was given up for an AC transmission, and a suitable choice of frequency had to be made in the face of various conflicting requirements. In the U.S. 60 cps was ultimately chosen. The household, plant, etc. all run from 60 cps, generated and monitored by prime movers at power sources. Local equipment may or may not be synchronous with 60 cps. Ordinary AC motors are not. Quality hi-fi has demanded the synchronous motor. Most equipment may show effects partially correlated to the 60 cps frequency. Some equipment may even show subharmonic resonance, or frequency division. However there is a general pervasiveness of 60 cps noise. Similarly it is likely that the body has a 10 cps or near 10 cps "fundamental" embedded into its structure. The timing function is possibly accurately established, and if so, by the general theory of "clocks" (26). The primary timing impulse may be obtained from the time delay of a signal running around a distributed line. It is then necessary that the return of the impulsive signal trigger another one. Thus timing accuracy here might depend on the propagation velocity along the line. Since such quantities tend to be temperature dependent, it would not be surprising that the interior, in particular near the clock, needs to be carefully temperature controlled.

The physical conviction for such an idea is not based on the brain waves themselves. This type of evidence is reminiscent of black box analysis, (e.g. as with a stethoscope), in which a hash of noise, equipment, etc. are all intermingled. One attends to such signals for predominant harmonic and transient behavior, but it is difficult to get all the process details by standing outside, particularly if the signals are small communications type signals rather than power signals. With power signals, however, it is possible to obtain significant prime mover informations. The prevalence of the 10 cps in and about the brain waves can only suggest prime significance without detailing functions. The action potentials tend to a 10 cps frequency. The muscle tremor tends to the 10 cps frequency. (Here at least an actuator power element is involved). Burton and Bronk clearly showed connection with action potential discharges. The 0.1 second (i.e. 0.1 - 0.2 second) character of reflex suggests a single pulse selection by non-linear synchronization rather than a general propagation time that holds for many body paths. Apt illustration of this is Smith's musical examples. He says 10 independent power strokes can be done by well trained amateurs. This is a near 1 - 1 correspondence of the primary impulse rate. The very gifted can do 20 strokes per second. The authors would interpret that the player has learned to sequence pairs of power pulses. The test is that <u>when he tries to do 30 power strokes per second</u> (frequency tripling) <u>he can't</u>. The fact that 600 reflexes per second are done, indicates that these have been pre-arranged in groups so that the passive frequency response of the chain is being excited. The task now exists to seek out autonomic nervous system data in search of the

the waves.

The data in Wiener (22) on brain wave autocorrelation shows a narrow band pass in the 8.5 - 9.1 cps range. He states that W. Grey Walter has obtained closely defined central rhythms. Starting from the studies of Caton, Beck, and Danielevsky in the 1870's directly in animal brains, on through Berger who published many studies on the human in the period 1929-1938, thousands of studies have demonstrated the reality of electric brain waves.

Some of the elementary characteristics of brain waves are given in Galambos (37). One finds brain wave frequencies in the range 1-30 cps over moderate periods of time (0 - 50 cps over more extended periods of time). The predominant frequency tends to be a 10 cps signal. This varies with age from about 2 cps at 1 year, 6 cps at 2 years, 8 cps at 5 years, to approximately 10 cps from 10 years on up. With concentrated effort, the wave amplitude drops; with no activity the wave amplitude rises. Illustratively, with little mental activity there is a fair amplitude. If a problem arises, the amplitude drops. Then the amplitude rises again, and drops again if another problem rises. The same pattern is shown in learning. A small signal doesn't change the amplitude, but a strong signal does. If, in learning, the large signal always follows the small signal, then the amplitude will drop off when the small signal goes on. When awake, a common spectrum involves a small 6 cps rhythm (theta), the 10 cps (alpha), and a 20-25 cps (beta). When asleep, there is a strong 1-5 cps (delta), and a 13 cps (sleep spindle). There is a possible 40-50 cps wave (gamma). The brain waves of higher animals all look alike.

However inspecting Adrian (47) on activity of the neurone, there is much greater complex of physiological phenomena than any simple model could explain. Thus it is not likely that the entire oscillator mechanism has been exposed. (It is possible that the brain waves are representative of some sort of regulation, say in particular, frequency regulation.) Guyton, Medical Physiology, 1961, for example says "the synchronizing mechanisms responsible for the brain waves have never yet been elucidated". The current status on brain waves was inspected in a section of the Handbook of Physiology (48). Added details are that alpha rhythms are highly characteristic of each individual; there is abundance and variability of rhythms with activity; the external response by remote electrodes is not an averaging from a vast aggregate of neural units, but is a more coherent signal complex; alpha rhythms can be externally synchronized; and that these brain rhythms are a different class of phenomena from the unitary propagated spike potentials which are found in the nerve. These conclusions point toward central oscillator coordination. However it is not certain that all the oscillator-using elements are tightly coupled by synchronization to the central oscillator. The oscillator still appears to be a frequency regulator poorly regulated with activity. The sharpest evidence for the oscillator - and its non-linear character - is the ability to externally synchronize it. Incidentally this characteristic tends to cast some doubt on the previously suggested hypothesis of using a fixed transit time around a distributed line as a timing impulse. This is not the most convenient element whose phase shift can be used for synchronizing purposes.

Non-linear synchronization is far from an obvious characteristic, in spite of the fact that elementary discussions can "explain" the property very easily for relaxation oscillators. On the other hand, while some clocks have elements marked "regulator", or one can advance or retard the spark in an engine, three hundred years of clock making have left a "practical" conclusion for the designer. Don't monkey with the resonator or whatever element produces the timing phase. It spoils the timing purity. More generally the source of such rhythms, or even the aperiodic nature of the single spike is still not adequately explained, although it obviously requires a satisfactory non-linear description of the operating chain in both the single neuron and the brain. 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 autonomic nature of a main balancing chain in the brain has not been exposed.

2. The Cardiovascular System Oscillator (The Heart Beat)

Major references that have been used for this section are Rushmer (49) and Schaefer (41) in the Handbook of Physiology.

Selecting from Rushmer, all myocardial fibers may exhibit sustained rhythmic contractions. Under appropriate conditions, all forms of muscle may exhibit myogenic excitation originating within 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 sino-atrial node exhibits excitatory electrical impulses. However this frequency is governed or regulated by the activity of nerve fibers from the autonomic nervous system. For example, 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 sympathetic nerves to the heart increases the rate. This suggests a 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 best described as 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 obviously represents a synchronization idea. It is thus appropriate to note a recognition of this by one of the great workers in non-linear mechanics, B. Van Der Pol (42). He correctly pointed out that the heart behavior was like a non-linear relaxation oscillation, and showed networks that could simulate a P, R, and S wave. His specific model of the heart was equivalent to a lumped network with three degrees of freedom, i.e. 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 (which has an approximate relaxation oscillator type of appearance). In a number of standard electrode positions there are found pulse segments in the wave that are 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 cannot be claimed until the origin of all the response elements can be explained. For example, the Van Der Pol model exhibited 7 characteristics. Thus it is not difficult to model any number of characteristics as to obtain a model that fits all disturbances. This is the vexing nonlinear problem of no principle of superposition). Implied in this simple abstract is that 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 expresses a more restrictive point of view. The electromechanical problem in the heart is the relation between the mechanical and electrical events, and the causal relations between specific electric element characteristics, membrane potentials, and mechanical changes. There appears to be a mechanical delay. However short 0.1 m sec. 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. However it is not possible to explain fully this apparently simple relationship. There is no action potential without a mechanical contraction. 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, depresses 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 an unquestionable relationship between action (membrane) potentials and contraction, secondary events may interfere with and make the electromechanical coupling complicated.

(The latter expresses the current status of the heart oscillator. The electro-chemical-mechanical heart oscillator chain is not clear yet as a physiological mechanism. It seems likely that there are chemical mediators acting as frequency regulators. Since nerve clocks may have higher frequency rhythms, 10 cps or higher, if may be necessary to suppress high frequency instabilities by definite means, such as by chemical regulation. Thus chemical regulation, even if slow, can not be excluded from the chain. For reasons that are not clear, a much lower electric frequency governs the heart. However the nature of the non-linear coupling is not explained. The mechanical muscle actions may sometimes be independent and sometimes not.)

3. The Respiration Rate Oscillator

Two useful background references were Adrian (47) and Campbell (43). The former presents a 1932 view; the latter a 1958 view.

First from Adrian. The chief function of the central nervous system is to send messages to the muscles which will make the body move effectively as a whole. For this, each muscle must be capable of delicate adjustment. Sherrington (1931) is cited as a source on such adjustments. 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. The studies date from Wedensky (1883) and Piper (1912). In weak contraction, 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 are phenomenological descriptions of behavior that have complicated electro-chemical-mechanical underlying mechanisms and processes. These descriptions do not make the mechanisms or processes clear. Yet the correlation of events in the running and coordination of muscle sets, as the important actuator elements in the system, is one of the most important elements to understand. The problem has been here introduced in its involvement in a major oscillator, the respiratory cycle).

In more detail, studies directly into the muscles from Wachholder (1923) through others like Adrain and Bronk, showed the following complexities. In a weak contraction there is a succession of small brief repeated waves with a frequency as low as 5 cps (never lower than a 5-10 cps range). 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 from the heart beat synchronized to heart beat, but uncorrelated with respiratory rhythm, an impulse frequency of near 30 cps, that changes with drugs down to 6 cps uncorrelated with inspiration or heart beat.

(For physical guidance at this point, one notes Van der Pol tried to make clear that nerve elements involve relaxation oscillator type of elements, as opposed to continuous sinusoidal oscillators. The transform elements, Wiener tried to make clear, are communications elements; i.e. containing abstract logic type of "signals", rather than obvious dynamic characteristics of various "engine" or mechanistic elements. However by abstracting the communications theory without reference to the physical power theory, the limitations that are still placed by mechanistic elements do not appear. That there is a descriptive level in which they are not needed is true. However a reasonable knowledge of the underlying mechanisms, i.e., can give a better understanding of the type of logic, and its likely limitations. These points become significant in treating the coherence of the information, both in space and time. For example, it is somewhat disturbing mechanistically that on one hand such rhythms as in the heart are synchronized, whereas in the motor elements there seems to be an incoherent twinkling, or worse yet, an organization from a regular rhythm per unit of the random twinkling per grouping or units, which are only governed in their statistical properties, and a superior rhythmicity as the number of units "saturate". It is not impossible to invent electrical network analogues. It is more difficult to come up with precise elements of operation in the body, and precise energy transformations. It is not analogues that are needed, but accurate representations of mechanisms. Otherwise it becomes misleading on how to perform each succeeding or higher integration. Finally it must be noted that the heart beat, 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 a relaxation nature, changes with drug level. The conclusion thus emerges that just as nerve endings developed chemical messenger signals and thus regularized information widely through the system, a major effect of chemicals is likely to be changes in the stability of networks. A tentative conclusion, not apparent in Cannon, is that, whereas the "long time" minutes to days response of chemical product is to be regulated, the "short" time characteristic of tenth second to minutes of the chemicals, 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. Such synchronous action appears in powerful contractions such as the discharge of the phrenic nerve during inspiration. There is some difficulty in interpretation of contraction results, in that the rhythm may be set by feedback discharges from the muscle (i.e. it is not clear what the entire unstable system is, whether 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 in 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 methods of analysis are not of as much value for the organized elements as the individual signal. They show something of the mechanism but little of the way in which it is built up and controlled.

Consider now the automatic rhythm of respiration as controlled by the central nervous system. The impulses to the muscles increase and decrease in frequency with each breath. A group of nerve cells in the brain stem are 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. It is likely that both loops are involved. Specifically, when the lung is stretched, the stretch excites a number of endings in the vagus nerve, producing a sensory derived periodic discharge which feedback and cut 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. This may be regarded as "reflex controlled", but it is not quite clear what a reflex consists of.

Respiration control is similar in walking or running movements. They 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. Even though there is no sensory discharge frequency, a motor rhythm can be recorded in the phrenic nerve. Buytendijk and Adrian (1931) showed fairly clear evidence of respiratory activity in an isolated brain stem. (A rhythm in range of 1 or 2 cps.) 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. (An isolated respiratory rhythm not generated out of a stretch receptor trigger and a CO_2 trigger, can only suggest a non-linear synchronization. However, there certainly is no modelling basis for the system up to this point. One can only invoke redundancy, the remarkable method of system construction that McCulloch pointed out is necessary for reliability). 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. One illustration of a periodic wave that may appear to be similar to the respiratory type of wave is shown in groups of nerve fibers placed in abnormal chemical media (Again the theme that stability may be affected by the chemical milieu). The discharge appears periodic. However it appears structured out of a decreasing high frequence impulse repetition rate that cuts off for a 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 mechanisms (non-linear oscillations), "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." (Bravo! It is obvious, as biological material has been digested that biologists in the last century and in the 20's and 30's of this century had good physical intuitions, possibly because they were not too specialized, but engaged in fundamental exploration. The authors acknowledge the same empathy for Adrian as was previously expressed for D'Arcy Thompson).

Switching attention to Campbell. The diaphragm is probably the principal, the most important, but not an 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. In addition, there are low frequency waves. Needle electrodes show bursts on the steepest part of the inspiration, shifting toward the peak of inspiration at higher frequencies of breathing, also with low frequency waves. Thus their action is likely 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.

With regard to the control and organization of the respiratory muscles, Pitts (1946) developed the generally accepted account of the respiratory center; and Hoff and Breckenridge (1955) substituted greater complexity. The nerve cells which initiate the contraction of the muscles of breathing are localized in the medulla, and are referred to as the respiratory center. As one goes into greater detail, the concept of a localized center becomes less satisfactory. Liljestrand (1953) has doubted the value of retaining the term. Pitts' model describes an inspiratory and expiratory center, not quite discrete, but intermingled, with the inspiratory center dominant. The discharge of the medullary respiratory center is basically not rhythmic. The events are a discharge from the center down the spinal cord, stimulating the motor neurones 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 the 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 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 investigators 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. However both models appear inconsistent in that the pattern of muscle activity is predominantly active inspiration against a background of passive relaxation. Thus the basic pattern in the muscles of breathing is bursts of contraction against a background of silence. Other authors 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 that adjusts ventilation includes neurones which activate muscles of expiration. The level of activity of the respiratory center and the resulting force of contraction is modified by nervous and chemical influences. Viewed from ventilation regulation, the chemical factors - CO_2, O_2, and pH are most important. The most sensitive cells to CO_2 concentration and pH are within the medulla. While they used to be considered the respiratory center itself, the work of von Euler and Soderberg (1952) and Liljestrand suggests that there are distinct chemically sensitive cells in the medulla. (The detailed mechanisms of the regulation of ventilation, or the respiration rate are in controversy. However 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).

There appears to be continued activity in the muscles of inspiration during the early part of expiration. The expiratory muscles are inactive through respiration during quiet to 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.

These two references show a large degree of consistency in description between 1930 and 1960. Physically interesting is a study on the non-linear respiratory regulator by Grodins (53). Two recent reviews will be briefly touched on: Dejours (54) and a British bulletin on respiratory physiology (55).

First from Dejours. 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. The works of the Heymans and others (1927) demonstrated chemoreceptors in the aortic and sinocarotid areas, as well as in other areas. General requirements for significant or "controlling" 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. However 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. The same type of nervous control, as in other coupled nervous-muscle systems, seems to exist. The senior author once developed a breathing oxygen demand regulator at the Bureau of Standards in which the breathing pressure phase modulated a relaxation oscillator to adjust the regulator output to the demand requirement).

In (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 find out if they always persist in the proposed mean form, and may thus furnish a regulating function, or whether there are other dynamic characteristics that make this summary completely misleading. Other papers that apply conventional servo control diagrams to the respiratory control are of little help in a physical analysis).

Widdicombe 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 concluded that there must be a pulmonary stretch receptor, possibly in the airways. Cooling the vagus nerve causes slower and deeper breathing. (This physically perplexing paper should warn against casual analogue circuit modelling of physiological mechanisms and recall the dictum that to be sure of a model of a non-linear process, the model and the real process must agree substantially in every major and feasible type of input and network connection).

Cunningham, on regulation of respiration during exercise, suggests increased respiratory rate with exercise is likely due to neural involvement at the fast rate of less than one breath, and a hormonal cycle involvement in a scale of minutes. However it is widely held that changes in hormone level are minimal, and 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 (with some deviations). Arterial P_{O_2} is essentially unchanged in 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 over the range of exercise, 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 quasi-static chemical stimuli to respiration can continue to account for ventilation during exercise. (These reviews enrich some 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 dynamics of the human as a energy transforming source both in rest and exercise. Evidence for chemical engine dynamics was found in a time domain of a few minutes. Ventilation rate and oxygen consumption, and therefore metabolism, as computed from oxygen consumption measured at the mouth, were essentially proportional, as found 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, ventilation cycles of the order of 2 minutes, 7 minutes, 35 minutes, and 3-1/2 hours were found. In a quiescent subject changes in ventilation rate of the order to 6 to 1 exist in any five hour period. Independent of familiarity with the work of Dejours (1959 or later), it was hypothesized that the high frequency (2 minute) cycle must involve a hormonal cycle, as the only possible mechanism that might fit the time scale. (Such studies suggest and furnish evidence for a second layer of oscillator cycles, slower than the local neural timing oscillators, and 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 the fast power elements, the motor units with a "ten" cps frequency response, into a slower rhythm at the minutes level?

The question of this interrelation of the neural and hormonal systems becomes decisive. In some undisclosed way there are follow-up characteristics in the hormonal system).

Current automatic control views of parts of the respiratory clock networks are in Grodins (53).

Defares (57), Clynes (58), Horgan and Lange (59), or Grodins (in press 1962) (These efforts are quite excellent. Another physically excellent paper is Defares and Visser in the same volume as (57). Editorializing if the somewhat artificial transform techniques of automatic control theory were dropped in favor of the kind of analysis that Gradins or Defares and Visser give, the limitations, assumptions, and successes of the models would be made clearer. Nature, in a classical physical view, plays out its laws 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 non-linear 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 methods of solving these equations, including extended methods in integral equations; generalizations from systems of equations to the kind of abstractions of the Lagrange-Hamilton-Jacobi formulations; variations principles; etc. The physical scientist is at present troubled at both steps. How does one formulate valid wide-range physically founded - not correlation founded - equations? How does one solve 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 is neglected for the sake of mathematical expedience) is not 'isomorphic' with the real system, but an abstract scheme at the first, primitive stage of development. Such candor and understanding is refreshing. Thus at present, the type of static analysis of Lloyd's even though of lesser significance in the long run in showing system operation, is more significant than correlative theories in forcing criteria that dynamic theories may have to fulfill).

4. The Muscle "Engines"

Although much of the nature of the muscle motor unit network has been discussed (47), an interesting reference is Stuart, et al (60). Shivering oscillations at 10 cps seems to be identical with physiological tremor. Physiological tremor or "microvibration" has been described in the literature. It is a regular oscillation with dominant frequencies in the 7 - 13 cps range with a 10 cps mode. In a resting limb, this tremor is seen as a composite of heartbeat pulse, as part of a high frequency ripple on postural change, and of muscle tone (i.e. it appears as a limit cycle). Changes such as pulse rate or position change the tremor. It persists under drugs. Neural connection is shown during postural excitations of the body by bursts of electrical potential with the same frequency as the tremor. At rest the muscles show no electrical activity, although it may only involve too few motor units to detect. Chilling results in an appearance of activity in a resting muscle of a thermal muscle tone, or a "preshivering tone". It shows similar vibration 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 bursts of potentials during contraction in each shivering cycle and complete silence in the relaxed phase. Each isolated motor unit fires once during a shivering 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 tremor and physiological tremor seem to have a common underlying mechanism for a number of reasons. Antagonistic muscles are involved respectively in contraction and relaxation during shivering. The shivering muscles are 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 rhythm. Considerable further discussion attempts to elucidate the mechanisms underlying the shivering oscillation, in biological and in network terms, without any satisfactory resolution. In conclusion a number of points are raised to be accounted for. Shivering is preceded by increased contraction, has a nearly constant frequency in all muscles, frequency doesn't change with amplitude changes, are synchronized in antagonistic muscles, deafferation disrupts the rhythm but not the occurence 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).

Extensive demonstration of the nature of muscle oscillation in its status of tremor is given in Rohracher (61). All through life the body shows microscopic vibrations, mainly with amplitudes in the range 0.5-3 microns, and with frequencies in the 7-15 cps range. They show an unbroken series of larger and smaller waves that change in irregular manner; there seldom are long series of regular frequencies; most show a second frequency of different size. However the frequencies are not stationary, nor purely sinusoidal. Typical records show a strong non-stationary fundamental, and non-stationary waning and waxing. If near arteries, for example, the pulse rhythm will also be found in the vibration. In a large sample of people, the vibrations were found throughout life with very little deviations, and in sleep and under drugs. Even in death, in animals, the rhythm has been found to persist 50-70 minutes or with separation of the medulla or extirpation of the heart. 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, involuntary, or from drug, 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, because even when electrical activity is not found, as in sleep, the microvibration is continued.

Possible ideas are discussed as to the function of the microvibration. For example, a function 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. only 2-1/2% 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 pointing to the reality of muscle oscillators, in suggesting that all muscles are generally in the same frequency domain as the brain waves, that a constant limit cycle oscillation continues, and that this oscillation could be the precursor to the power control of muscles both for external work and heating).

Returning to earlier discussion (56), in seeking the 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) finally suggested that the active power source had to be located at the juncture of these distributions, basically in the muscle sheaf plus re-entrant pockets of other "muscle" elements. Thus metabolic variations of these muscle elements should be the major regulating heat source, and yet must be available also to do external work. The microvibrations identify a reality of high frequency, neurally mediated, oscillations (reasonably local limit cycle oscillators). Thus a high frequency electro-chemical-mechanical domain (in which the chemicals are fast internal or synaptic traces in or near the nerves) is secured. (56) argues that the experimental data, at much lower frequency, show a muscle engine at the minutes level, and suggests that this must be under hormonal control. (However, Grodins' work suggests careful review of this reasoning). Other slower frequencies are also found, as limit cycle oscillators, which become increasingly vague in function. A 3-1/2 hour limit cycle is interpreted as being a thermodynamic cycle, whose reason for closing is not clear. (Further at longer time, the likelihood of circadian rhythms exist. The tentative conclusion arises that there is a rich frequency spectrum of just limit cycle oscillators in this main biological actuator mechanism, the muscles. Each frequency domain has different regulating or control functions. The highest frequency, 10 cps, is likely the primary A.C. frequency, which is used at near communications levels. A 60 cps A.C. in the home can be used to run communications nets at much higher frequency. If however, only one type of element is available for high frequency, one will not expect much higher frequencies than 60 cps. Thus it is unlikely that there are local electro-chemical-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. The difficult problem that exists, as it did on the motor unit coordination, is how to coordinate the entire body muscle system to produce the long cycle. It is this coordination that likely requires a cooperative effort from the hormonal system and higher nervous centers. Possibly the body can take action from sensory inputs and electrically connect up quick acting responses to motor elements using chemical messages dropped along the network. If major power energizing is needed, the 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 various bits of "information" about the system into a cohesive picture of a central computer control system. Control functions are not necessarily an intrinsic portion of the system, whereas regulating functions may be. When the system wants a particular control function, it can set it up from its available networks. Thus the characteristic property of the system may be that it can operate in control modes, rather than possess 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 that seemed to involve a localized neural-chemical-mechanical chain. Transition to slower rhythms seemed to involve somewhat direct chemical level mediation of longer chain relaxation oscillators. Finally a longer, less direct, chemical mediation from the hormonal system appeared. Possible involvement of even longer chains is immediately apparent in the very first examination of the system as a whole.

Suppose one wants to do a static 'isothermal' 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 it stops. The previous oscillators were not affected, to the point of stopping, by these intermittencies. Thus they were described as essentially autonomous limit cycles. The present cases do not permit this easy escape.

The usual 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, it emerges that there are rhythms of behavior and a considerable range of variability. In physical terms, one would say that both coherent signal and noise are considerable. In many phenomena the signal is quite weak or very poorly coherent. However clearly, rest-activity; eating-drinking and stopping; voiding and non-voiding 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. However one can vary the time keeping of relaxation oscillators through phase injection near the triggering point. This helps to account for a considerable frequency jitter).

With regard to triggering eating, voiding, and drinking, while Cannon (36) noted chemically mediated hunger pang oscillations, considerably more detail may be found in Alvarez (62). The small bowel is the most important part of the digestive tract. There appear to be 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 argument arises as to distinguishing rhythmic oscillations in the muscle by itself as compared to the nerve. Alvarez argues that there generally is cooperative endeavor, but 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. (Again the local oscillator theme seems to have value). There is 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, or 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 notthe sole cause. People get hungry for specific foods. The very thin, who should be hungry, are not. Hunger does not increase during fasting, but lets up after a number of days. Then a few mouthfuls of food can make the sensation disappear. Blood sugar does not always influence hunger. 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 gastro-intestinal mechanisms, no connection has been shown to eating and drinking rhythms).

Anand (63) indicates that while hunger, appetite, and satiety were formerly considered in the domain of digestion physiology, the problem has turned toward being a function of the central nervous system, and the regulation of food intake becomes a problem in the regulation of the interior. The review is concerned only with food intake.

Theories of the orign of hunger sensation, which determines food intake, consisted of a peripheral theory - 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. (The discussion indicates that it is not a "rapid" regulation which is being considered). A feeding and satiety center are proposed. Electrical stimulation in the region has been shown to increase daily food intake. While these centers act to faciliate 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; and in the hungry state with a decrease of blood sugar level, the circulating adrenaline 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 multiplied 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, however 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 most certain that the calorie level is what is regulated in the long run. However in a shorter run, it is suggested that food intake may be adjusted to the water intake. However 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 is most suggestive in pointing up common or unified problems. As physical argument, if an approximate equilibrium situation exists - except for sleeping-waking cycles, and for possible daily frequency entrainment - such as humans or rats in some kind of standard daily situation might show, then a nominal standard activity and almost equilibrium weight level exists. Thus an 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 for example the following somewhat suggestive parallel. In ordinary activity - such as talking, etc. - individual breaths can be delayed one or two breaths, or speeded up. However the "noise" tends to drop out over 5-7 breath averages. On the other hand, in the extreme, the breath can be held for 30-60 breaths. In eating, individual meals can be delayed one or two meals, or speeded up. However the "noise" tends to drop out over 5-7 meal averages. On the other hand, in the extreme, meals can be delayed for 30-60 meals.

The various components that tie together the cycle in a physical engine do not have to be made of identical mechanisms or similar schematics. However, it is not impossible to use common wiring or sequencing schemes. It would not be surprising if the body tends to use a similar organizing scheme 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 the brain stem for the ventilation, one could be found for the food intake, and water).

A recent example of work on electrogram responses of the stomach is shown by Sobakin et al (64). Potentials from the stomach are recorded on the skin with a 3 cpm rhythm. These are strongest 1/2-2 hours after eating. The same rhythm is found at the mucous membrane of the stomach when free from food.

A recent symposium (65) on the regulation of food intake is of interest. A paper by Anderson indicates that water balance is maintained by mechanisms controlling water losses via the kidney and by those concerned with regulating water intake, the hypothalamus playing an integrating role for both. Actually knowledge of central regulation of water intake, obtained by lesions, is piecemeal, so that the thirst mechanism is still puzzling. However, 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 seems to be also connected with the drinking urge but not the eating urge. The pallidofugal fiber system in the lateral hypothalamus seems to be essential for both eating and drinking. (The hypothalamic region has been involved in a large number of local oscillator engine elements both in short time signals, up to the 10 cps range, as well as various suggested regulation functions in longer time domains. It seems clear that the region is 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 sorts of time domains. A thought emerges that there may be a major keying input, possibly temperature in the vicinity. Its truth may add substance to Benzinger's thesis. At present he has shown a most sensitive response in the body. A current short-coming is that the regulation dynamics of the region have not been exposed, for if the area as a whole is an alarm switching station, involving a very sensitive temperature key, it is essential that the full static and dynamic behavior of the connected mechanisms be traced. It appears that explanations of system operation awaits this very primary first 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 then seem to provide the regulator of caloric balance, by which energy intake is adjusted to energy expenditure. Some anatomical evidences are reviewed. (It may be that this paper is oversimplified. However it brings focus and clarifies 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, say an oscillator in the present context, or really 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 whatever are the excitations for the anterior pituitary - may code or key these brain stem area on-off switches, say by changing their set points, so that a constantly shifting level of on-off switches exists, with constant receiving of input alarm signals, and a continued shifting of networks that change the stability of all sorts of motor oscillators removed from the center.) Soulairac adds another element of complexity. While the hypothalamo-rhinencephalic elements may perform the on-off switch function, certain neo-cortical regions may mediate, say hunger, or food intake. In particular the importance of the 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 by means of neurohormonal messages that affect degrees of wakefulness. It is well known that a certain fundamental wakefulness exists that essentially regulates waking and sleeping, and that the element responsible is the mesencephalic reticular formation with an adrenergic hormonal function. (Apparently a restlessness type of function). A second type of specific wakefulness, with the thalamic and rhinencephic structure as the responsible element, 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 a second review, Anand states that there is enough evidence to suggest that the pattern of nervous regulation of food intake, water intake, is similar to that of most other visceral and autonomic activities such as the cardiovascular, respiratory, gastrointestinal systems, body temperature, etc., that these, with the hormonal systems, are ultimately responsible for the regulation of the interior. (Thus the path of disentanglement chosen in this review for physical orientation is supported). Rapid messages from the organs involved are received but 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 a moderate time "day to day" regulation of food intake might be temperature sensitivity in the hypothalamus, but not of longer time effects.

Hervey remarks on the signal that informs the hypothalamus about the state of energy balance, and talks about a short and long term response. However, no correct theory of the regulation of calorie balance explains how the balance state of the body is actually measured. (What is most disturbing in these discussions, is that no satisfactory tests are described of the steady state of the system.)

Janowitz eliminates hunger contractions and epigastic pang as a regulating element or even a cue for food intake, and gastro-intestinal elements as a cue for cessation of feeding. Yet determinants of the food volume per feeding is needing. They are thus, speculatively, neural and non-specific, and likely multiple factored.

LeMagnen's remarks are complementary. The individual intake per meal is essentially computed in advance of the eating to correspond to a metabolic requirement. The action of the food on mouth and stomach receptors then mediate the short term regulation of food intake. Time delays are then involved before the system catches up with its metabolic requirements.

Teitelbaum accepts the hypothalamus as an on-off switch state to excite and inhibit feeding for both single meals and longer time. However he is also concerned with the food urge. This too involves the hypothalamus.

A summary of the symposium is given by de Ruiter. One key thought is that in the study of the food intake regulation, one is dealing with a vast and intricate network of information channels. (While it is clear that cycles exist in food and water intake, it appears obvious that the experts in food intake regulation have not considered this an important facet of their problem. However it is also clear that they have not been able to get any real mechanistic picture of how the rate of food intake becomes 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 devastating.)

There is a recent paper by Shapiro (66) on rest-wake. While daily sleep is most familiar, and there are some obvious and contradictory theories as to function and mechanism, it is not known 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 they 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. The work of 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 similar to waking appear. Ultimately a 90 minute cycle appears to be 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 7-1/2-9 hours after going to bed the subject awakes. Most prominent is the 90 minute cycle. This was likely first shown by Ohlmeyer, et al (1944). This cycle is suggested as being a periodic oscillator in the brain, and that sleep is an aperiodic modulation of this cycle organized into a sleep segment. (Presumably these sleep segments are then periodically recurrent. Thus only a limited amount of information may likely be cited as to the precise mechanisms of these oscillators).

6. Hormonal Rhythms

(It has emerged that all of the major interior oscillator mechanisms, as well as autonomous systems, thus far viewed as immersed in the regulated chemical interior are under the coordination regulation of a portion of the brain associated with the hypothalamus, more inclusively the limbic system, and that the chemical signalling system - the hormonal system - may be similarly coordinated. In fact it quickly emerges that nervous signals to hypothalamic centers in mammals influences hormonal correlates; illustratively hypothalamic regulation of anterior pituitary function. There is the current thought that the pituitary stalk is the final common pathway between the central nervous system and the endocrine system. The present interest in to find evidence for oscillator mechanism. Animal "heat", menstruation, are examples of hormonal mediated cycles. However, one note in the estral cycle of the rat, if there is no coitus, the cycle is repeated every 4-5 days; yet rats submitted to continuous illumination will show a state of constant estrus -- Desclin (1954). Light level has abolished the rhythm. Again the evidence points to level mediated instabilities, now on a long, long time scale compared to 10 cps rhythms).

In a 1950 treatise of Pincus and Thimann (67), the first chapter on ovarian hormones points out that the cyclic nature of ovarian activity - estrus and menstrual cycles - is well known. These cycles include a follicle growth phase under hormone influence and then a "spontaneous" luteal development and discharge phase from ruptured follicles with a secretion of hormones. Follicle rupture may be triggered in some animals by nervous stimulation in mating, originating in the hypothalamus and acting on the anterior pituitary to release hormone to trigger rupture. (The question as to how long time delays may exist, as required by long period relaxation oscillators, is answered plausibly. Hormones can regulate a growth process, under the secondary supervision of a hypothalamus on-off regulator center - connected in as yet undisclosed fashion to a possible central hormonal regulation center, probably also on-off, likely the pituitary - to help regulate a slow growth process, which at some phase "spontaneously" discharges, and as a result of discharge produces other hormonal signal. The last two parts are still very vague).

In a later chapter, the essential role of acetylcholine in conduction at the nerve junction is stressed in illustration of chemical control of nervous activity. (One notes in this material that the dynamic or cyclic nature of hormones received little consideration in the conception of their biological action, likely because of the seeming impossibilities of the analysis.)

In a later 1959 Symposium on human pituitary (68) the only evidence of oscillator actions involving these hormones cited are in an article by Ikkos and Luft on metabolic action of human growth hormone. There are possible cycles - of the order of 5 days - shown in say creatin secretion and changes in level when human growth hormone was given; there may be some weight rate cycles, but certainly weight rate changes with administration of human growth hormone, and a relaxation time of the order of 10 days with cessation; there may be similar cycles in excretion of ketones. (Metabolic associations are thus quite real, here evidently on longer time scales).

In an article by Loraine on pituitary gonadotropic assays in human urine, he shows hormonal excretions during menstrual cycles. The work reported is more meaningful quantitatively than any previously reported. Gonadotropic and oestrogen peaks occur at midcycle and are presumed to be associated with ovulation. The gonadotropic peak occurred either simultaneous or delayed by 1-4 days behind the oestrogen peak. The result of insemination showed itself in a rise in gonadotropin after 9 days, and the rise and maintenance of a high luteal phase level of pregnandiol and marked delayed rise in oestrogen excretion. In the discussion there is a very 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 very excellent work touches on the fact that dynamic assays of hormones is just barely in its infancy. Thus seeking to expose hormonal mechanisms of dynamic chains or oscillators, except by inference is not too practical yet. It likely becomes 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, one may recall the Kinsey studies, which have shown on the behavioral level, a considerable degree of rhythmicity in sexual "appetite" in humans that varies with factors such as age. Frequencies were of the order of a few "feedings" per week. It is not invalid to point toward a hunger analogue, here however at a much lower frequency).

Bottari 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. There is little doubt that 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. He cites a study by Farris (1944) in women that 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 occuring at the time of ovulation. (Here, more dramatically, the reality of longer time "hunger" is shown, as creating an instability that brings a lower frequency limit cycle oscillation into play. In rats, this was shown in a 4-5 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 process, rather than inertia as in L-R elements, or resistances as in R-C elements. Obviously these essentially act as large capacitance elements, but not as passive capacitances).

In later chapters, Beach reviews a large number of indirect ways in which hormones can condition behavior reactions. (In general physical analysis would avoid "abnormal" type of evidence, such as opening chains by lesions, or artificial or "non-physiological" 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 named 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, metamorphosis, moulting, 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 functions, 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 would be foolhardy for a non-endocrinologist to do little more than read and note in passing. However, a cursory search may be made for rhythms).

He cites studies on endocrine control in cyclic processes of metamorphosis and moulting. Illustratively, 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 moulting, likely through activation of the thyroid. These processes may be synchronized. Secondary sex characteristics in frogs may cycle with the seasonal sex cycle. There are hormonal rhythms in seasonal breeding species, particularly of the pituitary. Some animals are believed to exhibit an inherent pituitary rhythm; others may be dominated by environmental stimuli. However the evidence indicates that in most species it is inherently cyclic, and, most commonly, synchronized. It is likely that both day-night and seasonal synchronization exists. Temperature synchronization may also exist. A striking example of synchronization is the ovarian cycle in the sand smelt of about 14-15 days. However there is synchronization, likely 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, that 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 chapter of interpretation of hormonal effects, it is stressed that little is known about the mechanisms whereby endocrine substances exert effects. However certain general tentative conclusions are possible. First, 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 one and 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 their degree of dependence on endocrine products. Every behavioral response is by a complex of mechanisms to internal and external inputs; the mechanisms are neuro-muscular, and neuro-hormonal, whose charactertistics are 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 effects 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 has emerged. In some respects the hormonal system appears to be a system parallel in function to the nervous system, and involving 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 to be at a 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 distributed level, it is not clear which system keys which. However the fast action possible 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 quite mysterious).

Reference (65) covers two short symposia, on brain-gonad relationships, and on mechanisms governing luteotropin release. A paper by Van der Werff Ten Bosch states that the significance of the hypothalamus in the physiology of reproduction is well accepted. The pituitary glands 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 discusses extrahypothalamic regions in the central nervous system that may be involved in gonadotrophin secretion. A discussion by de Groot puts emphasis on 'limbic' brain components. There is an on-off regulation system produced as a higher order of organization, consisting of the hypothalamus, the pituitary and target-organs. (Further complexities in the endocrinology in these papers are left to experts).

Harris' summary 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 (Representing a general switchboard center at which on-off regulation is controlled as parallel circuits to peripheral or remote networks or systems). The function of the pituitary stalk, which Harris described as 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 animal are adjusted in accordance with the endocrine balance are in process of 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 are 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 numoral 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. (Physically high lighting why such attention to the gonadal system is 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. This presently ample summary assigns 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 in a paper by Wolthuis that the hypothalamus acts to inhibit secretion of prolactin from the hypophysis. A summary paper by Desclin, reviews the various facts and ideas about the release of prolactin.

To insure that the accepted foundations of current teaching are not obliterated, Guyton (70), Ruch and Fulton (71), and Best and Taylor (72) were reviewed in conclusion.

In Guyton, 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 oversecrete. Information is fed back to check further secretion. If a gland undersecretes, the feedback decreases and the gland secretes a normal amount. (This is more likely a regulating chain. However there is no certainty that in general even more than force balancing is achieved. The basic problem remains open of the dynamic stability of such action. Thus such a description is only literary). An illustration of speedy action of hormones 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, which in turn causes adrenocortical secretion of cortisol to show up with a time delay of about 5-6 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 percent ripple, perhaps involving a 20-30 day cycle. A thyroid extract injection shows two time constant effects of about 6 day 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. (This is 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. The uterine contraction rhythm during birth, due to hormone action, is discussed. The likelihood of increasing 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, the action of the hormones controls development and growth (aperiodic and periodic), integration of autonomic function and 'instinctual' behavior patterns; and regulation of the internal environment. 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 seems 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 arousal. This principle of regulation is the current useful - if not perfect - framework for viewing the hormones. Examples - increase of blood sugar level stimulates insulin secretion to hasten removal of blood sugar, deficiency of gonadal, thyroid, or adrenocortical hormones bring about increase of pituitary hormones controlling these organs, excess of these hormones appear to depress 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 2 hours. Some adrenal hormone and thyroid hormone time constants are shown. Uterine musculature show rhythmic contractions strongest under the influence of estrogens, and relatively quiescent during the progestational state. Pituitrin increases the contractions if the uterine muscles are subjected to estrogens. The response from humoral elements alone can be shown in isolated uteri.

In Best and Taylor rapid action of adrenaline is illustrated. (The exposition of 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. Current physical metaphysics of causality requires strict association in the time and the order both in presence and absence of elements or responses, in order to assign causal order. It is these long 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, the difficult problem is to separate them from the daily cycle and the possibility of frequency synchronization. Another basic difficulty is impatience with the trouble of the necessary isolation and methodology to establish ultimate steady state performance. Consider the following physical illustration. A linear system, say mass-spring, etc., will show oscillations. However, it will ultimately die down, because the laws of thermodynamics applied to macroscopic systems requires 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. Suppose a few cycles are noted. Is this a limit cycle? The only test is to wait a second observation period, or use a second system, and see if essentially similar data in harmonic content is obtained. If uncertain, further periods must be examined. However, the second law of thermodynamics will enter again, in more subtle form. Ultimately all macroscopic 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 breath skipping, neither 6 nor 60 cycles is necessarily sufficient. "Proof" likely begins in the hundreds of cycles. As an illustration, there is belief in a menstrual cycle because it may be noted as monthly cycles for periods up to 40 years. This must be the elementary background in examining circadian rhythms).

In a significant symposium on Biological Clocks (73), the opening address by Bunning cites DeMairan (1729) and Pfeffer (1875) for early strong evidence for a daily periodic leaf motion in plants in constant light and temperature conditions. Infra-red commonly may be the drive; however an autonomic rhythm exists that is not quite 24 hours, but synchronized by light-dark alternation. Near 24 hours rhythms were then found in plants and insects. He exposed

Drosophila to constant conditions for 15 consecutive generations (1935) without eliminating a diurnal rhythm. A single pulse of "light" stimulus, of the order of 10 hours, evoke the oscillation in living forms raised in constant "light" conditions (1931). There are indications that a relaxation oscillator is being dealt with. (Actually a hard type of non-linear limit cycle is meant, judging from the illustrations). The periods can be changed by environmental parameters, for example red light wave length, alcohol, or alkaloids.

Aschoff, discussing rhythms, stresses the need to exclude environmental synchronizing cycles by using constant conditions, but accepts 5-7 periods as adequate ground for limit cycles. The activity of a bird raised in constant conditions of temperature, feeding, noise isolation, at different light intensity levels shows circadian frequencies that vary with intensity, and entrain with a light rhythm - shown as 12 hours light and dark. Previous work on other plants and animals all showing circadian oscillation are summarized. The length of the period is presented as linear with the log of illumination. The rule is offered that light-active animals increase their frequency with illumination, dark-active animals decrease. (These data lend considerable conviction to the circadian rhythm, except for the limited length of runs. However attempts to squeeze detailed results on time structure and noise from these cycles is not warranted. Much greater numbers of cycles are necessary). 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 do not prove autonomous oscillations if the period remains 24 hours; there may still be synchronization. Besides activity, some organisms show circadian rhythms in such responses as luminescense, space formation, growth rate. Attempts are made to assess the accuracy of the bird oscillator frequencies. (There exists need for spectral analysis, or correlation techniques to assess the nature of the sharpness, stability, and noise levels). Useful references are given. The work of Halberg (who proposed the term circadian rhythm) is alluded to.

Bruce (who adds 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 lasts "forever"). Various cyclic entrainments by light and temperature are discussed. Examples of subharmonic resonance are shown. (These discussions suggest that light-dark and temperature are two sensitive parameters which determine the limit cycle frequency. Sensitivity to these inputs is further shown by the ease with which they can be cyclically used to synchronize oscillators in the body. There seems to be a common circadian oscillator. Its very sensitivity makes it unlikely that is is a continuous sine wave resonator as in precision clocks, but of a general relaxation oscillator nature. The wisdom of Van der Pol is to be noted. Similar thoughts about relaxation oscillators in biological systems was expressed by A. Hill in 1933. Credit accrues to Halberg to stress the significance of near 24 hour oscillations. However the conference does not discuss mechanisms for such oscillators. That it is adapted to need, as a wake-sleep cycle would appear to require, is self evident. However this does not serve for specific chain identification.)

In discussing a DeCoursey paper, Barlow calls attention to a possible non-linear entrainment in an ensemble of coupled non-linear oscillators as described by Wiener (1958) on non-linear processes. From this he draws conclusions about the precision of the frequency of entrainment of a group of fireflies. (The chapters referenced in Minorsky are evidence of much greater potential complexities in assessing entrainment.)

Brown attempts a case for a counter argument 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, electrostatic fields.

Opening remarks of Pittendrigh have physical flavor regarding theoretical appraisal 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." Thus his empirical generalizations about circadian rhythms is a refreshing summary. However, point 7, that the limit cycle period displays remarkable precision is one that makes the scheme less than physically acceptable. (Examine Lewis (74), books on oscillators (39), or a study by one of the authors (75). Precision is obtained in timing systems by the use of resonator oscillators, involving very pure timing phases. It is difficult to visualize an electro-chemical-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 the evidence in this review suggests, is a considerable dense, not too stationary, spectrum of limit cycle oscillators, with entrainment possibilities, and frequency shifting mainly by chemical level, in a poorly regulated interior. That the system could develop a near 24 hour oscillator is not shocking. On the other hand, Brown is correct when he asks that its components be demonstrated.)

Schmitt, more realistically, points up some of the known properties of nearly linear and non-linear electrical networks with regard to oscillator performance. A few elementary model attempts follow.

Harker attempts to relate light sensitivity and some endocrine factors in insects to light-dark entrainment. (However the 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 the stability problem, but it is a beginning of entangling the circadian problem).

A paper by Halberg reviews a considerable amount of the work that he has been involved in.

A paper by Hellbrugge 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 offers an eminently reasonable review of circadian rhythms in man. (Her references are most apt starting point for examining this subject, particularly beginning with Kleitman's work on sleep and wakefulness). Specific results of 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. It is suggested that 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 in (76);(77);(78);(79);(80). (In summary there are long time cycles and cues. However mechanisms have not been discussed).

8. Other Illustrative Oscillators

(While many major mechanisms and associated oscillators have been touched on, it would be unfair not to mention at least a few more).

Uterine contractions, as example of a local muscle oscillator, hormonal mediated, has already been 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

(56), for it establishes a cycle in the evaporate loss corresponding to the 2 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 coordinate it at a quantitative level. Mechanistic models for this can be built. However this constitutes no proof as to how the body does it).

Deman (83) indicates non-linear oscillations in epilepsy.

As a final item, an ecological example is given by Krebs (84). Periodic fluctuations in small mammal populations have not been explained. As illustration there is the 3-4 year lemming cycle in the tundra, a classic example of such cycles in rodent populations.

(Thus non-linear limit cycles are real in biological systems. They cover a wide frequency spectrum. There is obviously an equally 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 in non-linear 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

In physical science, the purpose of finding limit cycles is to determine some of the necessary degrees of freedom of the system. Each oscillator indicates either one or two degrees of freedom - one if it is an exterior degree of freedom (as in mechanical or electrical equations of motion), and two if it is an internal degree of freedom (the thermodynamic relations derive from first integrals of the mechanical motion of molecules requiring two first order equations to produce an oscillator). Limit cycle counts do not exhaust all degrees of freedom. There are others that can decay. To show these, it is generally necessary to excite the system by step, pulse, or periodically, or to introduce a noise input. Maximal information may be obtained most rapidly from pulses. However, it may be the most difficult technique or require the most skill to use diagnostically. There are still other unstable degrees of freedom (i.e. the system can destroy itself). These are not being considered. The human is obviously rich in degrees of freedom, and it would be impossible to attempt to examine all the known transient behavior of the body. A physical limitation generally put on examining a complex system is to deal only with salient power transforming elements, or systems that transmit significant information content. Thus physically one might restrict attention to those system elements that lead to significant behavioral reactions. This point of view must be adopted.

In this present section, general transient behavior is not of concern, whether or not it has significant behavioral reactions. Instead concern will be limited to those system elements that show regulating or control functions, in a physically significant sense. Their relation to the limit cycles must be understood. To a chemical engineer, accustomed to complex chemical 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 the dynamics of electrical or mechanical equipment. In the body the oscillators tend to involve active electro-chemical-mechanical elements, which is novel because of their small size. The most common elements, at all time domains, seem to be 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. However the general idea can hardly be regarded as original. This review indicates that major credit is likely due to van der Pol. No implication is intended that relaxation oscillation is the only content of non-linear physics. It simply appears that the biological system, for adaptability, has utilized the "cheap and dirty" relaxation oscillator for regularization of processes and for the ability to quickly modify the response from cycle to cycle. In fact, what would be quite surprising would be to discover resonator elements in the biological system. Circulation elements, like delay lines, seem to be much more common. A corollary is that the general regulator and control action likely derives from similar elements. The most common elements are probably 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. As a broader commentary on the joke "call me a taxi - O.K. you're a taxi", the body appears adaptable to the inquirer and the inquiry. Through "conditioned reflexes" or other means, it strings temporary and more permanent networks as are required by what must be internal computer controlled hierarchical logic. In general, instead of building permanent controllers, it arranges to operate things in control modes. If a game is proposed, the body may go along until it doesn't want to play. On the other hand there are some games that it has long been conditioned to play. There are eye habits, activity habits, sleep habits, etc. that are thoroughly conditioned. Yet it is likely that retraining is possible. Thus it is not clear what constitutes controller mechanism if the mechanism, although not the functional necessity, can be rearranged. On the other hand there may be limiting controller or regulator type behavior which represents physical limits that the system cannot exceed. A conclusion is that it is difficult to determine, not uncommon in non-linear systems, what is the "normal" or "steady-state" behavior of a self-actuated non-linear system. A few important regulators and controllers will be examined, although somewhat discursively).

1. Body Activity Regulation

To get at regulation or control, one must average over the limit cycles. A "reason" for the oscillator cycles, among others, may be to furnish power in a useful transmission mode. The average of these steady state oscillator cycles represents steady state performance of the system. The quality of regulation, if any, can be examined by the characteristics of these steady state responses.

A wake-sleep cycle has been discussed which either is initiated at the 90 minute level, may be aperiodic for 7-9 hours, and may be circadian, or else is adaptively synchronized at a geophysical day. Thus in examining body performance, one wishes to average over these cycles. However before performing this average, one must note human behavioral performance. In addition to these moderately "definite" cycles, there is obviously a large degree of randomness, or other non-scheduled purpose in human activity, that is implied in a description as "self-actuation". However, one recognizes a twinkling performance. Thus, for example, in assessing animal activity or behavior, the experimenter can use statistical averages over population samples, that is indicative of near monochromatic behavior. The circadian references are replete with examples. This is not only true for lower animals, but also man. Thus it is reasonable to average over the circadian or the synchronous day, or over a population sample, (The ergodic hypothesis sneaks in on usual physical grounds as a useful approximation). What is obtained is the average activity level.

It appears likely that the average activity level is a function of temperature. This is demonstrated in metabolism by Herrington (1) on guinea pig, rat and mouse with normal activity in a cage 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. All of these changes are accomplished in the experiment with no external work. Is this type of activity self-determined, regulated, or controlled? Since it shows steady state errors (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. Previous citation indicated activity level variations with the menstrual cycle in rats and humans, cycles longer than circadian. With less filtered data, it is likely that performance similar to that shown in (56) would be found, of maximum to minimum peaks of the order of 6 - 8 to 1, and average cycles of closer to 1.5 - 2 to 1. These values are not mystical, but show the likely nature of these power systems that are not completely stationary in time.

Beside regulation with respect to temperature, there obviously is regulation with regard to other environmental factors, for it is likely that the development of regulators was the adaption to environmental conditions. This appears to have been the message of Bernard, Cannon, Smith, Charles Darwin, etc. There is likely an activity change with age of the organism. Again since the activity level does not remain constant with age, it is a regulated function with organism age. There is likely an activity change to available food supply. This again is 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 the question of a "normal" activity regulation curve that deals with a schedule of power consumption, there is the question of the power production, in mechanical engineering terms, of the prime mover characteristics. Illustrated with regard to its temperature variation, what is associated with various activity levels, say in particular a quiescent level, is a not quite level metabolic characteristic. Primary data are given in (1), (85), or (86). A regulating "droop" by about 20% from 10°C. to about 30°C.

and about a 10% rise to over 40°C. temperatures is shown. The reason for citing (86) is that other sources show storage of heat at temperatures below 30°C., therefore describing a non-equilibrium situation, and stating that in the cooler temperatures, temperature regulation must take place by metabolic increase, which is however not found. The result of this confusion is to cast doubt on the truth of the metabolic data. However the ASHVE results do in fact validate a heat balance. Systematic data at other objective activity levels is hard to come by, but judging from the quiescent data, one may conclude that the mean power production, at quiescent operation, or other levels of overt activity, objectively evaluated, are also likely to be regulated curves. (Some basic comments are in order at this point. In an ordinary mechanical system, the power consumption curves, here for activity, would be superimposed on the power production curves, here objective activity levels, and the activity level assessed. The ordinary "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. The results derive partly from learning, from practice, and partly from computer control. The physiologist commonly deals with the issue by using a standard task - walk 3 mph on a tread mill, use a bicycle, etc. References are given in 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 work. The next reference is illustrative).

Karpovich (88) shows the energy expenditure for various tasks, such as swimming at a certain rate. (To an approximation, it may be assumed that the external work necessary to drag the body through the water is essentially fixed). A rise in heat production with speed is shown. It is obvious that power production and external work consumption are not perfectly proportional. Thus the system cannot be regarded (nor is it expected to be) of constant efficiency. The results for a poor swimmer are also shown. At a slow speed a power production of up to 4 - 5 greater than for a competent swimmer is shown. (While the example may be dismissed with indifference, it seems to touch on basic ground. Even the engine performance seems to be made up of regulator modes, rather than fixed regulators. This suggests that most networks are wired up by conditioned reflexes rather than by necessarily permanent circuits, and that there is very frequent intervention by the central computer to determine whether to keep the circuit, whether regulator or controller, going. A center for this will be mentioned later. The "proof" is that habits, such as playing an instrument, swimming, even reading, or movements are matters of practice. Stop practicing an instrument and the performance changes; an artist in recording, plays repeatedly, changing details; he makes moderate decisions on subsequent phrasings even in performance; athletes find ways to make considerable improvement in records, that are not just instances of better equipment; the amateur shows high variability in various activities; and finally, even more volitionally, if the computer system doesn't want to, it can balk in very sophisticated ways, as anyone who has carried a heavy load with some second "loafer" can testity, or it can simply balk completely at the task. To speak of a power consumption that is controlled or even regulated is thus not unique. There is a broad range of computer control function that enters in between power consumption, external work, and power production. The instances of practice show that it is not even possible to talk usefully about the "limiting dynamic performance" of the system. By a variety of style changes, weight lifting can range from a 100 pound lift, to a few thousand pounds lift. Certainly there is a limiting performance, a point well made by D'Arcy Thompson. However, it may not be so easily invoked except in extremes. While such extremes are commonly invoked in destructive testing, systems generally operate far removed from such limits. In modern dancing or ballet the muscle strain extremes that the dancer puts himself through in practice is torture, but can hardly be invoked by others. Thus the system likely becomes habituated to a level of performance, not only for the individual but even society. Habituation levels of exercise are accepted today that were not accepted a few years ago. All of these points stress that even the power production regulated levels may be temporary connections, using conditioned reflex paths. However the common "practiced" paths are not matters for constant intervention of the computer controller. Instead, one may visualize the following verbally plausible scheme. The computer 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. "Unconventional" teenagers tend to be quite conventional).

3. Temperature Regulation or Control

Having discussed the problem of power production and power consumption, the salient prime mover characteristics of the entire muscle engine system, it is useful to return to another salient characteristic of homeothermic animals, core temperature regulation. Previous reference has suggested an active muscle sheath engine. One must integrate over the engine cycles, which have been shown physically to be up to 3-1/2 hours long. One must also integrate over the refueling rhythms and the rest-activity level circadian rhythms. What remains is the power production, the heat losses, and some external work levels. What is found is that the metabolic production, at various temperature levels, is moderately regulated. What is clear over the less rapid cycles is that the core temperature is nearly regulated. If the power production remains essentially constant (i.e. regulated) and the losses tend to increase with lowered temperature, the problem arises how does the core stay regulated? The paradox has been answered by pointing out that the amount of core that is regulated diminishes. It is only the losses per unit area in regulated regions that have not diminished. Other areas reduce their losses. This sort of regulation 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, i.e. 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 the thesis has met with objections, it is likely that Benzinger (41) has uncovered a central idea in temperature regulation and control, the ultrasensitivity of the hypothalamus to its local temperature. (Physical objectives centered around questions of systems stability. Benzinger has viewed the hypothalamus as an ultra sensitive thermostat. However the hypothalamus action in itself does not represent the system control dynamics, which still has to be exposed. The true nature of the situation begins to emerge. A region of the hypothalamus is sensitive to temperature. A different 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 of the switchboard. It may cause a muscle to shiver with larger 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, is likely used <u>always</u> as a controlled temperature, i.e. in a permanent controller system. However the modes by which this controlled temperature is achieved are regulator and control modes. (The system must act but it is not clear what the instantaneous algorithm is. The authors once inferred from the great attention to the hypothalamus that the "purpose" of the brain and its activity was to keep the hypothalamus warm. This is now less of a jest).

By operating the body in specific activity modes, one may get some idea of the time scale of the controller action. First, (60) and the referenced Burton-Bronk experiments tie the 10 cps muscle oscillator to action potentials to the muscle from the hypothalamus. An amplitude modulation with breathing is shown. It is conceivable that this modulation results from the thermal proximity of the hypothalamus to the breathing channels. In that case the time constants for controller action are at the one to few tenths of a second level. The next level of 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. The next seven minute cycle is also likely representative of a poorly regulated regulation mode. It is speculated that this involves the 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).

A more conventional view of temperature regulation is given by Hardy (40).

4. Muscular Task Control or Regulation

Detailed elements of regulation and control, particularly in the existence of control modes, is shown in detailed muscular tasks. From a modern point of view, the subject opens with Tustin (89). (This represents the source from which the authors as well as the point of view of many other engineers toward biological systems control essentially begins). Basically Tustin shows that the nature of an eye - muscular system coordination is predominantly that of a linear error - actuated automatic servo controller, 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. (There is a considerable degree of sophisticated non-linear understanding on Tustin's part not shown in many subsequent engineering efforts.) An illustration of another muscle system response, in more conventional control theory terms is the pupil response and a tracking response of the eye by Stark, and his co-workers Young, et al. (90,91).

(It is still true that although these papers indicate controller action, they are most likely controller modes. However, this is, at this point, a controversial statement). Another, even likely 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 that wobbled all over the track; in a subject trained in the general problem, but experienced to slower response, the subject tracked 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 quite possible that the major control modes that the human systems can approach through the conditioned reflex learning process is characteristically here revealed).

5. Regulation or Control in Interior Elements

The review approaches an end by completing full circle. Having touched the exterior responses, mainly regulation and control of external modes of behavior, rather than intrinsic regulators and controllers, it touches again on the interior elements. Cannon's concept of intrinsic regulators of interior parameters still stands up. What did not and has not 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 in (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. Kleiman 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 be useful if adequately justified either theoretically, or by ample experimental evidence. As provisional equations no comments are possible).

A paper by Gerritzen in (76) on the rhythmic function of the human liver is quite interesting. With "continuous" water supply and feeding, an experimental circadian rhythm is shown in humans in water excretion, chloride excretion, and urea excretion. The conclusion is drawn that the kidney functions rhythmically. Increase in the meat supply in the food leads to greater amplitude in urea excretion. Since urea is formed from meat, and 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 appears to be a rather direct demonstration of a regulating function achieved by an oscillator cycle.

The cardiovascular system is obviously a major and a complex system in the body. A common summary is that its basic function is to furnish a pump for pressurizing and circulating fluids and other salient elements throughout the body. In the accomplishment of these basic functions 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 need for detailed review of each system. In general modern physiological summary books, the Physiological Reviews, and the growing Handbook of Physiology can and will represent excellent source material with growing physical references. At present fully systematic static data, 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 modelling and explanation is required. It must be remembered that the purpose of this review was to get some physical view of the status of regulation and control in the biological system. It is against this background that it is suggested that existing data are insufficient for mechanistic explanations of these functions in most biological systems. An added section on waste product regulation and control would invoke similar remarks).

6. Central Coordination Control

In closing, (95) contributes a few added guides. The summary of Denny-Brown's review on the general principles of motor integration points up that most of the motor - sensory reactions are fairly organized up to the mid brain - 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. The final ideas come from Bremer's summary article 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).

III. EPILOGUE

To model the body by dynamic networks begins to be currently plausible. However, experience would suggest that only a most rudimentary Model T model can emerge. Having heard the developers of the virus model describe their changing model pictures, or a variety of other such scientific developers, crudeness in model is not the significant defect. Key ideas and central hypotheses count. The details can improve with time.

The system starts as a watery environment contained in a shell. The watery environment is a valid choice because it permits mobility. More specifically, the biological system faces the problem of achieving a structural, but mobile system, without the use of solid materials such as metal, and essentially using water. In a recent study (96) on measurements of material in the polluted stream, the problem of classifying measurements became difficult from an operational point of view (in the Bridgman sense of defining the measurements) only at a level for very small particles in which the physical state could not be well defined. Skirting statistical mechanical formulation, the problem was located at colloidal level. It appeared as a hypothesis that the particle systems under consideration, whether living or so derived, had the major characteristic of organizing its vicinity by electrical control. One might say that it had developed techniques of controlling water aggregation to nearly rigid states. The mediating element used for the structuring was protein. One might even look at the process as a reversible "polymerization" of water into a structural form. (Oparin (97) discusses an even more primitive process of liquid coacervates). To achieve the freedom to control the state, the elementary system had to be self powered, and thus it became a primitive oscillator. In order to be adaptable to the surrounding medium characteristics, it is likely that a relaxation oscillator was necessary. Thus the basic cellular element with its surrounding milieu, the cell, 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 is not the issue in this review, and the entire structure of molecular biology, the coding, the membrane, etc. is of no present concern. What is of concern is to point up to the chemical engineer that the unit element in the system is probably an engine oscillator, a prime mover of electrical - chemical - mechanical type, a relaxation oscillator, that mediates its water structure so as not to lose its identify or its viability in water, yet retains mobile form with a structural integrity.)

That such a system or group of such systems can be organized into a cooperative local oscillator is no great 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 (one is constantly reminded that the system started out in water, so that self activation had the meaning of movement in water), has to deal with auxiliary requirements of ingestion, waste, etc., obviously it has to have a much more complex chemistry than that just necessary to "sol" or "gel" water. It is clear that a high polymer type or organization, with many signal capabilities, has to be organized, and 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. <u>It cannot be a passive oxidation</u>, whether with or without catalyst. Without going too far afield, one must postulate an enzyme (inside) - hormone (outside) type of interaction, 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 necessarily at the same time scale. (The authors allow themselves a bit of poetic fancy. With regard to this property of relaxation oscillation, not only does it appear that "ontogeny recapitulates phylogeny" but that in the hierarchy of system behaviors, the general type of non-linear 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 behavior. Similar pieces of evidence have likely impressed scientists of different backgrounds with the same conclusion. This time it impresses the authors from a physical point of view.)

The organization of organs and functions are not yet within the province of physical scientists to comment on. Techniques of comparative anatomy and physiology are most useful if the physiologist wishes to bring the organ and function problems to the attention of modelling physical scientists. These organized elements require immersion in a nearly all water bath. Thus Bernard's interior and Cannon's homeostasis are fundamental. One must note the following clarifying idea. In metal and other solid materials structures, mobility is controlled by temperature. At high temperature materials melt, at low temperature they become solid. In the water medium, the temperature range is short. Control thus switches over to chemical control, but more subtly to electrochemical control, as in the gel states. (These casual remarks do nothing to explain the dualistic mechanisms except to hint that they exist). Stability of operation seems to require regulation. In a vague sort of way, it appears that with major regulated items (on a slow time scale), it is then possible to signal chemically or electrically for faster regulation or control functions. Thus chemical signals appear to be used in a duality of time scales. Many of the mechanistic elements seemed to be perched at unstable limit cycle levels, or at near unstable aperiodic levels, in which very small signals will cause aperiodic discharges. The system as a whole is thus very busy with dynamic activity. Fundamental oscillator modes are at a 10 cps level. The prototype oscillator which gives this operating frequency level is not described. At this point, with local coordinated oscillators, capable of performing interior and exterior functions, <u>and supplying their own power conversion</u>, immersed in a regularizing chemical water bath, some central coordination is needed. This has to be electrical to get the long distance transmission. (There may be all sorts of local networks, and even central operators). The coordinating center seems to be at the hypothalamus as a complex switchboard that routes signals, and arranges connections, etc., that routes slow warning and alarm signals, and that is even capable of on-off regulation, using its own switching circuits and even alarm signals at its own site for band control. It is not clear whether the system uses a variety of communications signals such as AM, FM, pulse modulation, etc., or the degree to which the electrical network also provides chemical signal information. A hypothesis is suggested that in transmitting signals, a temporary chemical message may be left at each transmission junction to provide a regularization of chemical information distributed throughout the system (As if a telephone system made a temporary record of every message at every junction point on a line, so that all subscribers who could be involved were actually involved by low level signals). A second chemical system, the hormonal glands, are distributed as discrete entities throughout the entire system, and are capable of being stimulated and discharging chemical signals that can be transported through the circulation to affect other sites. It is not clear why this chemical regularizing system is absolutely needed. The hormones have specific target organs, while the type of electric signals is more general. It may be that the hormones are used for special delivery and to assure certain but slower operation. This hormonal system apparently also has a coordinator, the pituitary, and at present a connection between the electrical and chemical is suspected between these two systems. At a higher level, there is algorithm setting for the hypothalamus switchboard and something like synchronous computation both internally with a computer control setting at the algorithm. Many of the systems have "spies" that short circuit slower centers in case of alarm. The common operation in the hormonal system, by antagonistic pairs, results in a balancing chain operation that may lead to regulation. There is nothing to prevent the higher centers to undertake activity levels in which the hormonal systems operate in control modes (one may suppose adrenaline is illustration of a commonly involved hormone). While the hormonal system seems only vaguely modelled, in the electrical and mechanical systems there are enough details suggested in the literature to attempt to construct some network models. At the higher computer level, the picture again becomes blank. One can only wish investigators sufficient good fortune to be able to decode the information transmission characteristics of the nets.

With regard to the main theme of this review, it appears that the system most often "wires" itself for control modes, and even regulator modes, and only uses a moderate number of fixed regulators and controllers.

SUMMARY

The status of regulation and control in biological systems from a physical point of view has been reviewed. It was first necessary to clarify the different types of physical ideas that could be used for such an analysis. These ideas include:

Static regulator performance- the performance of physical elements that are affected by but are markedly insensitive, by specific design features, to specific physical parameters in their static performance. These are also known as compensators and governors.

Dynamic systems performance - the total program in classical physics by which the Newtonian equations (or the Lagrangian formulation) are set up for both internal and external degrees of freedom, and the mass and energy balances are also set up, all of these leading to a differential equation set to be solved for particular boundary conditions. The solutions of these equations characterize the dynamic systems performance.

Control performance - the program of investigation of a particular subclass of dynamic systems in which the static solutions - what is known in nonlinear mechanics as the singular states of motion of the system - have certain

prescribed characteristics (typically that an "output" variable should be constant, or should follow some prescribed law). The control performance has to do with certain desired limitations on the transient disturbed performance around the desired static solution.

Linear control performance - a particular limited program of control theory in which the dynamic equations are linear differential equations with constant coefficients.

Non-linear mechanics - the most difficult program associated with formulating and solving the dynamic system performance of the equation sets for non-linear systems.

This physical view of the dynamics of systems analyzed by non-linear mechanics is at variance in part 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.

With regard to regulation and control in biological systems, the main biological line of description seems to be:

Bernard's identification and limitation of the watery interior of the body, as the physical field in which the biological materials, mechanisms, and processes operate and exhibit their performance;

Cannon's identification that the major material constituents of the interior and many of the processes and mechanisms are regulated;

The 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 his colleagues Pitts and Lettvin's sustained effort to find a communications logic for the neural nets.

The next step of dynamic systems analysis was to examine the salient active mechanisms, or subsystems in the watery interior. (In electrical network theory, an active network is one that contains its own power sources. From a mechanical engineering and physical point of view, the supply of energy stored in potential form requires a prime mover or D.C.-A.C. converter for availability in active form). As a first step one may look for continued oscillations in a system when immersed in a constant potential external environment of temperature and other environmental factors. Such oscillations, if containing a significant fraction of periodic components are referred to variously as an oscillator output, a D.C.-A.C. converter, an engine, a prime mover cycle, a rhythm, a clock cycle. More basically, in the language of non-linear mechanics, they are non-linear limit cycles of Poincaré. Their presence indicates necessary degrees of freedom in the system.

Examination of a variety of systems in the body indicated a fundamental mechanistic characteristic that they were 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, Cannon's student. It is also greatly to the credit of van der Pol, who systematically developed the quantitative exposition of the relaxation oscillator, to point out its biological applicability at the same time.

A significant property of non-linear oscillating systems is their ability to be shifted in operating point, or to show frequency entrainment either as synchronization or subharmonic resonance. This is reasonably easy to understand in relaxation oscillators. (There exists in electronic circuit analysis a useful elementary view of bistable elements and their development into aperiodic and periodic circuits). 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 the brain wave rhythms, heart beat, respiration cycle, muscle engines, digestive tract rhythms. These are thus indicators of 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, there are quite a few other major oscillator cycles. Illustratively there are eating, drinking, rest-waking, muscle engine power cycles, 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, routes signals to many 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 on and off). The 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 it is required to put out most of the 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 total nature of the interrelation among the various hormones does not emerge clearly from a physical point of view except to suggest that the chemical signalling products tend to be more specific.

The pituitary gland is considered to be a master regularizing gland for the hormones, and in recent years, 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 examined the oscillators superficially, 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 regulation and control in the system resides. The idea of looking for control functions in the biological system most likely may be best attributed to Tustin. It is possible to continue further in the systems analysis by averaging over the cycles - at least the faster circles through the circadian - to obtain the quasi-static steady state responses of the system. One may then examine the system in a mechanical engineering power sense. In turn, this inquiry was conducted 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. As illustrative variables, consider temperature and activity level. For given activity levels, power production - metabolism - 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, as in animal studies, activity level, as evidenced 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 phase of the problem derives from the physiological fact that the core or some significant portion of the core is temperature "regulated". The basic question arises as to whether this is regulated, or controlled for temperature and activity level disturbances. The likely resolution is that the hypothalamus, operating as an on-off regulator, develops a control function for temperature using the fraction of the body fluids in the core that is regulated as a control variable. However, with activity level, the hypothalamus acts only as a regulator of power production.

While paradoxial, this analysis led to the concept that the body tends to act 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, which represent all the likely deviations from standard activity patterns, and which may be regarded as the general "volitional" components, or the response to specific environmental stimuli components of behavior, the same general theme seemed to emerge. It is likely true 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" hook-up 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 the fires indicated at the hypothalamus 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 is suggestive that the individual oscillation levels of the local oscillators are used in the connections.

The chemical communications net still does not emerge clearly. One can only point suggestively to the fact 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 electro-chemically at the nerve snyapse. 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.

References

1. Burton, A. C. 1941. The operating characteristics of the human thermoregulatory mechanism. In Temperature, Its Measurement and Control in Science and Industry. Reinhold. New York, N. Y. : 522

2. Adolph, E. 1961. Early concepts in physiological regulation. Physiol. Rev. 41 (4) :737

3. Jury, E. J. & T. Pavlidis. 1962. A literature survey of biocontrol systems. Electronics Research Laboratory. Univ. of California. Berkely, Calif.

4. Considine, D. 1957. Process Instruments and Controls Handbook. McGraw-Hill. New York, N. Y.

5. Perry, J. 1950. Chemical Engineers' Handbook. McGraw-Hill. New York, N. Y.

6. Cosgriff, R. 1958. Non-linear Control Systems. McGraw-Hill. New York, N. Y.

7. James, H. M. , N. B. Nichols & R. S. Phillips. 1947. Theory of Servomechanisms. McGraw-Hill. New York, N. Y.

8. Brown, G. S. & D. P. Campbell. 1948. Principles of Servomechanisms. John Wiley & Sons. New York, N. Y.

9. Chestnut, H. & R. W. Mayer. 1959. Vol. 1. Servomechanisms and Regulating System Design. Vol 2, 1955. John Wiley & Sons. New York, N. Y.

10. Flügge-Lotz, I. 1953. Discontinuous Automatic Control. Princeton Univ. Press. Princeton, N. J.

11. Loeb, J. 1958. Survey of mathematical networks for non-linear control systems. ASME Paper No. 57-A-104

12. Thaler, G. J. & M. P. Pastel. 1962. Analysis and Design of Non-linear Feedback Control Systems. McGraw-Hill. New York, N. Y.

13. Truxal, J. 1958. Servomechanisms, Regulators, and Automatic Feedback Control Systems. McGraw-Hill. New York, N. Y.

14. Smith, O. 1958. Feedback Control Systems. McGraw-Hill. New York, N. Y.

15. Seifert, W. & C. Steeg. 1960. Control Systems Engineering. McGraw-Hill. New York, N. Y.

16. Horowitz, I. 1963. Synthesis of Feedback Systems. Academic Press. New York, N. Y.

17. Gibson, J. 1963. Non-linear Automatic Control. McGraw-Hill. New York, N. Y.

18. Oldenbourg, R. C. & H. Sartorius. 1948. Dynamics of Automatic Control. ASME. New York, N. Y.

19. Macmillan, R. H. 1957. An Introduction to the Theory of Control in Mechanical Engineering. Cambridge Univ. Press. London.

20. Letov, A. M. 1961. Stability in Non-linear Control Systems. Princeton Univ. Press. Princeton, N. J.

21. Leondes, C. 1961. Computer Control Systems Technology. McGraw-Hill. New York, N.Y.

22. Wiener, N. 1961. Cybernetics: Control and Communication in the Animal and the Machine. John Wiley & Sons. New York, N. Y.

23. Joint Automatic Control Conference, preprints. 1962. AIEE

24. Den Hartog, V. P. 1944. Theory of Vibrations. McGraw-Hill. New York, N. Y.

25. Cunningham, W. 1958. Introduction to Non-linear Analysis. McGraw-Hill. New York, N. Y.

26. Andronow, A. & C. Chaikin. 1949. Theory of Oscillations. Princeton Univ. Press. Princeton, N. J.

27. Whittaker, E. 1944. Analytic Dynamics. Dover. New York, N. Y.

28. Minorsky, N. 1962. Non-linear Oscillations. Van Nostrand. New York, N. Y.

29. Iberall, A. 1954. Static flow characteristics of single and two stage spring loaded gas pressure regulators. ASME Paper No. 53-F-5.

30. Veinott, C. 1948. Fractional Horsepower Electric Motor. McGraw-Hill. New York, N. Y.

31. Newman, J. 1956. World of Mathematics. Vol. 2 ("The Longitude"). Simon & Schuster. New York, N. Y.

32. Lees, S. Aug. 1956. Design basis for multiloop positional servomechanisms. Trans. ASME; Nov. 1957. Design basis for cascade-type positional servomechanisms. Trans. ASME.

33. Olmstead, J. M. D. & E. H. Olmstead. 1952. Claude Bernard. Schuman. New York, N. Y.

34. Virtanen, R. 1960. Claude Bernard. Univ. of Nebraska Press. Lincoln, Neb.

35. Bernard, C. 1957 (republication). An Introduction to the Study of Experimental Medicine. Dover. New York, N. Y.

36. Cannon, W. 1939. The Wisdom of the Body. Norton. New York, N. Y.

37. Smith, H. W. 1959. From Fish to Philosopher, The Story of Our Internal Environment. Ciba Edition. Summit, N. J.

38. a. McCulloch, W. S. 1945. A heterarchy of values determined by the topology of nervous nets. Bull. Math. Biophys. 7:89

b. Pitts, W. H. & W. S. McCulloch. 1947. How we know universals: the perception of auditory and visual forms. Bull. Math. Biophys. 9:127

38. c. Pitts, W. H. & W. S. McCulloch. 1943. A logical calculus of the ideas immanent in nervous activity. Bull. Math. Biophys. 5:115

d. Lettvin, J., H. Maturana, W. S. McCulloch & W. H. Pitts. 1959. What the frog's eye tells the frog's brain. Proc. IRE. 47:1940.

e. Hickson Symposium. 1951. :42. John Wiley & Sons. New York, N. Y.

39. Reich, H. 1939. Theory and Application of Electron Tubes. McGraw-Hill.

1944. Theory and Application of Electron Tubes. McGraw-Hill.

1961. Functional Circuits and Oscillators. Van Nostrand. New York, N. Y.

40. Hardy, J. July 1961. Physiology of temperature regulation. Physiol. Rev. 41 (3) :521

41. Benziger, T. Various articles, such as Proc. Nat'l. Acad. Sci. May 1961 :730. Oct. 1961 :1683.

42. Zinsser, H. 1960. 13th Annual Conference on Electrical Techniques in Medicine and Biology. Renal analogues. 1961. 14th Annual Conference . Dynamic function of the kidney in biological control.

43. Karplus, W. J. & W. W. Soroka. 1959. Analog Methods. McGraw-Hill. New York, N. Y.

44. Munk, W. & G. McDonald. 1960. The Rotation of the Earth. Cambridge Univ. Press. London.

45. Jeffries, H. 1940. The variation of latitude. Monthly Notices Royal Astron. Soc. 100:139.

46. Galambos, R. 1962. Nerves and Muscles. Anchor Press. New York, N. Y.

47. Adrian, E. 1932. The Mechanism of Nervous Action, Electrical Studies of the Neurone. Univ. of Pennsylvania Press. Philadelphia, Penna.

48. Walter, W. Gray. 1959. Handbook of Physiology. 1 (1) Neurophysiology. Intrinsic rhythms of the brain. Am. Physiol. Soc.

49. Rushmer, R. 1961. Cardiovascular Dynamics. W. B. Saunders & Co. Philadelphia, Penna.

50. Schaefer, Hans. 1962. Electrocardiography. In Handbook of Physiology. 1 (2) Circulation. Am. Physiol. Soc.

51. van der Pol, B. & J. van der Mark. 1929. The heartbeat considered as a relaxation oscillation, and an electrical model of the heart. Arch. Neerland de Physiol. de L'Homme et des Anim. 14 :418.

52. Campbell, E. 1958. The Respiratory Musciles and the Mechanics of Breathing. Lloyd-Luke Ltd. London

53. Grodins, F. et al. 1954. Respiratory responses to CO_2 inhalation, a theoretical study of a non-linear biological regulator. J. Appl. Physiol. 7 :283.

54. Dejours, P. July 1962. Chemoreflexes in breathing. Physiol. Rev. 42 (3) :335.

55. British Med. Bull. 1963. Respiratory physiology. 19 (1).

56. Iberall, A. 1960. Trans. ASME Series D. March, J. Basic Engr. 81 (1); Sept., 87 (3)

57. Defares, J. March 1962. A model of the respiratory 'chemostat'. Ann. N.Y. Acad. Sci. 96 (4) :956.

58. Clynes, M. Jan. 1960. Computer analysis of reflex control and organization. Science. 131 (3396) :300.

59. Horgan, J. & D. Lange. Oct. 1962. Analog computer studies of periodic breathing. IRE Trans. on Bio-Med. Eng. 13 ME-9 (4) :221.

60. Stuart, Eldred. Hemingway, Kawamura. 1961. Neural regulation of the rhythm of shivering. Presented at 4th Temperature Symposium. Am. Inst. Physics.

61. Rohracher, H. 1962. Permanente rhythmische mikrobewegungen des warmblüter organism. Die Naturwiss. 7 :145.

62. Alvarez, W. 1948. An Introduction to Gastro-Enterology. Hoeber, 4th Edition. New York, N. Y.

63. Anand, B. Oct. 1961. Nervous regulation of food intake. Physiol. Rev. 41 (4) :677.

64. Sobakin, M. & I. Smirnov. April 1962. Electrogastrography. IRE Trans. Bio-Med. Electronics, BME -9 (2) :129.

65. 22nd Int. Cong. of Physiol. Sci. Symposia Abstracts. Leiden, 1962. 1 (2)

66. Shapiro, A. Oct. 1962. Observations on some periodic and nonperiodic phenomena in normal human sleep. Ann. N.Y. Acad. Sci. 98 (4) :1139.

67. Pincus, G. & K. Thimann. 1950. The Hormones. Vol. 2. Academic Press. New York, N. Y.

68. Ciba Colloquia on Endocrinology. 1960. Human pituitary hormones. Vol. 13. Little & Brown Co. Boston, Mass.

69. Beach F. 1948. Hormones in Behavior. Hoeber. New York, N. Y.

70. Guyton, A. C. 1961. Textbook of Medical Physiology. W. B. Saunders & Co. Philadelphia, Penna.

71. Ruch, T. C. & J. F. Fulton. 1960. Medical Physiology and Biophysics, 18th Edition. W. B. Saunders & Co. Philadelphia, Penna.

72. Best, C. H. & N. B. Taylor. 1961. The Physiological Basis of Medical Practice. Williams & Wilkins Co. Baltimore, Md.

73. Symposia on Quantitative Biology. 1960. Vol. 25. Biological Clocks. Biological Laboratory.

74. Lewis, F. Sept. 1955. Frequency and time standards. Proc. IRE.

75. Iberall, A. DOFL. Feb. 1962. Study of an electronic timer. Report to Diamond Ordnance Fuze Laboratory. Contract No. DA-49-186-ORD-1052.

76. Verhandlungen der Zweiten Conferenz der Internationalen Gesellschaft für Biologische Rhythms - Forschung. Utrecht, 1939. Acta Med. Scand. Supp. 68.

77. Kleitman, N. Jan. 1949. Biological rhythms and cycles. Physiol. Rev. 29 (1).

78. Rhythmic functions in the living system. Oct. 1962. Ann. N.Y. Acad. Sci. 98 (4) :753-1326.

79. Circadian systems. 1961. Report of 39th Ross Conference on Pediatric Research. Ross Laboratories.

80. Cloudsley-Thompson, J. 1961. Rhythmic Activity in Animal Physiology and Behavior. Academic Press. New York, N. Y.

81. Krogh, A. 1959. The Anatomy and Physiology of Capillaries. Hafner. New York, N. Y.

82. Randall, W. & A. Hertzmann. Feb. 1953. Dermatomal recruitment of sweating. J. Appl. Physiol. 5 (8); also May 1958, 12 (3).

83. Deman, E. Nonlinear oscillation and epilepsy. Electromagnetic Radiation Laboratory Project 5635. AF Cambridge Res. Lab. Astia No. 282659.

84. Krebs, C. May 1963. Lemming cycle at Baker Lake, Canada. Science. 140 (3567).

85. Newburgh, L. 1949. Physiology of Heat Regulation. W. B. Saunders & Co. Philadelphia, Penna.

86. Heating, Ventilating, Air Conditioning Guide. 1960. Am. Soc. of Heating and Ventilating Engineers.

87. Carlson, L. Aug. 1954. Man in Cold Environment. Monogram for Alaskan Air Command. Arctic Aeromedical Laboratory.

88. Karpovich, P. 1959. Physiology of Muscular Activity. W. B. Saunders & Co. Philadelphia, Penna.

89. Tustin, A. 1947. The nature of the operator's response in manual control and its implication for controller design. J. Inst. El. Eng. 94(part IIa) :190.

90. Stark, L. 1959. Stability, oscillations, noise in the human pupil servomechanism. Proc. IRE. 47 :1925.

91. Young, L. & L. Stark. June 1963. Variable feedback experiments testing a sampled data model for eye tracking movements. Trans. IEEE PTGHFE. 4 (1).

92. Cacioppo, A. J. 1956. Pilot information utilization. ASME Annual Meeting. Paper No. 56-A-149.

93. Danziger, L & A. Elmergreen. 1956. The thyroid-pituitary homeostatic mechanism. Bull. Math. Biophys. 18.

94. McDonald, D. A. 1960. Blood Flow in Arteries. Edward Arnold. Baltimore, Md.

95. Handbook of Physiology. 1960. Sec. 1, Vol. 2. Neurophysiology. Am. Physiol. Soc.

96. Iberall, A. & S. Cardon. July 1962. A study to develop improved water pollution measurement techniques, first quarter report. Public Health Service Contract PH-86-62-106.

97. Oparin, A. I. 1957. The Origin of Life on the Earth. Oliver & Boyd Co. Edinborough.