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A STUDY OF THE GENERAL DYNAMICS OF THE PHYSICAL-CHEMICAL SYSTEMS IN MAMMALS

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INTRODUCTION

In the course of this program, the progress of the work has been periodically summarized in progress reports, technical reports, and publications in the open literature. A total of twenty such reports, (1-20), exclusive of biomonthly progress reports have been issued. This final report will summarize some of the more important findings, salient features of the work and the general concepts that have been developed, several of which are finding increasing acceptance and application in the fields of biology and systems science and engineering. More recently, there are indications that they may be useful in monitoring and diagnosis, and for the specific NASA application of the search for extra-terrestial life. For specific details, reference should be made to the original reports.

The current program was an outgrowth of an earlier NASA program headed by the principal investigator culminating many years of research on problems of bio-regulation which he began in the 1940's in studies on space suit design and some of its physiological aspects. Some pertinent reports from the earlier programs are included in the bibliography to complete the program picture to date.

In addition to these reports, a joint paper of Ehrenberg and Cardon with Drs. Bloch and Ostermeyer of Case-Western Reserve University is being revised for submission to the Journal of Microvascular Research. Another paper is also in preparation on the nature of the relation between intracellular and extracellular oscillators in mammals.

The last report [27] was for a program on the development of a primate simulator which made use of our background on physiological oscillators and the electronic competence of our staff.

A current program in this laboratory is concerned with the development of a general science for all systems, a science of science. The generalizations proposed in that program have been found to fit in many respects to those found in this program. Thus, this similarity is reinforcing the starting postulate of this program, that the biological system can be studied from the same basic tenets and with similar approaches as those used for study of physical-chemical-engineering systems, generally.

Results and Discussion

In the course of this program, studies have been performed on the dynamic aspects of the temperature regulating system, the cardiovascular system, the hormonal system, and the central nervous system and behavior. One major idea has become the keynote of the studies, that homeostatic control in the biological system originates from dynamic regulation in which the stability of non-linear chains of near-relaxation oscillatory types is mediated near the boundary between aperiodic and periodic instability. The biological system shows sustained or intermittent operation of a great variety of oscillators. This system may be regarded as an intrinsically non-linear unstable system which is mediated by chemical and electrical mechanisms into marginal stability. The term "homeokinesis" has been proposed as a replacement for the Cannon (Bernard-Sechenov) concept of homeostasis to indicate the dynamic aspect of bioregulation.

The dynamics of the bio-systems has remained the focus as these studies sought to explain temperature regulation starting at the level of the microcirculation where the monitoring of oxygen supplies to tissue and the governing of heat production takes place, overall control and transmission characteristics in the cardiovascular system, hormonal regulation through interactions of the products of the endocrine system with regulated parameters and blood constituents, and in the behavioral system for consistency of orienting physical views of the dynamics of a complex computer control network with psychological and physiological overtones.

Life itself has been redefined, as a complex system of sustaining non-linear limit cycle oscillators, and a similar system of algorithmic guiding mechanisms, that is capable of regulating its interior conditions for a considerable range of ambient environmental conditions so as to permit its own satisfactory preservative operation, that is capable of seeking out in the environment and transferring and receiving those fluxes of mass and energy that can be internally adapted to its own satisfactory preservative operation, that is capable of performing those preservative functions for a reasonably long period of time commensurate with the 'life' of its mechanical-physical-chemical elements (i.e., clocks made of parts that should wear for hundreds of years that run for two seconds are not such systems); and that are capable of recreating their own system out of material and equipment at hand. The purpose of this definition is to guide the physical search for 'explanations' of the operation of the biological system; and to bring the physical scientist close to a physical base from which he can model, build, or assess systems that resemble naturally living systems by suitable 'operational' definitions; and a clue that 'life' does not have to be explained by only one mechanistic scheme per system, but may involve many possible types of successful operation.

The importance of the concept of instability in life processes first described in this program has been found to be of more general application to all systems. In this program it has been noted that life itself is an active engine process. However, it is an unstable process that tries to 'burn itself up'. The affect of all of the detailed equipment is to take the basically unstable engine (the opposite of the Arrhenius type reaction relation) and to throttle and choke it. Thus the system 'runs away' and degrades or explodes at a finite rate. It is the increased number of active engines that keep adding more engines to fire the system. This is what makes the living system viable. This is what make the living system expand into its environonment, regardless of the difficulties, with an explosive rate constant, until some dissipative rate saturates the process and turns the result toward a more passive relaxation process.

Though much of the program has been concerned with the theoretical treatment of such pertinent biological data as is in the literature an attempt has been made to develop new data consonant with the developing theory. The experimental work has been mainly in the fields of mammalian thermoregulation and on the chemistry of blood constituents which appear to be homeokinetically regulated by hormonal and electrical mechanisms. Some work has also been done on overall system parameters like body weight. An interesting 3-4 day cycle has been found, apparently a water balance cycle, and attempts have been made to determine the regulating mechanism.

Further, in connection with the work on the heat production aspect of temperature regulation, studies have been conducted on the oxygen supply to tissues, which takes places essentially through the supply of red cells to the capillaries. In these studies we have been fortunate to have had the cooperation and collaboration of Professor E. H. Bloch of the Case-Western Reserve Medical School. This has been especially valuable as his laboratory contains the latest equipment for viewing in vivo microcirculation preparations and he and his staff are among the most knowledgeable and respected in this field.

In yet another area, the temporal properties of glucose levels in mammalian blood, we were able to do some of the work in collaboration with Dr. Simenhoff of the Jefferson Medical School. Also, discussions and experiments have been conducted at the Joslin Research Institute of the Harvard Medical School. The reality of the oscillatory nature of blood constituents is finding wider acceptance as a result of these studies and collaborative experiments and we are confident the concept will find practical application in monitoring and diagnostic problem areas.

The discussion of results has been divided into the major section areas of thermoregulation, hydrodynamics in the cardiovascular system, dynamic regulation in physiological systems, hormonal regulation, and behavior. A section is also included on the use of the concepts in the spectral analyzer approach to analysis of living systems.

Thermoregulation

These studies have been concerned with furthering a phenomenological description of temperature regulation in mammals. The ultimate goal has been to develop a theory and a model of heat regulation that is both physically and physiologically sound. Initial observations indicated that the core temperature is regulated at some value near 37°C and that a depth survey through the body would show a uniform temperature over most of the core, with a linear rise near the surface. The source of heat energy must be an equivalent oxidation of food. Further observations show that the average heat production, the metabolic rate, changes only moderately although the external temperature is changed at a given activity level. Regulating characteristics are shown here, but the metabolic rate changes considerably with activity level.

Any surface temperature of the body is regulated in a 30-36°C range, unless the heat is not available, in which case vasoconstriction would cut off an area to conserve heat. This peripheral vasoconstriction is responsible for the apparent drop of mean surface temperature with lowered ambient temperature. Experimental studies validated these ideas and clearly showed that at any ambient temperature, most surface temperatures are crowded into the 30-36°C band, with 30°C being the lower limit of surface regulation. At low ambient temperatures, there are surface zones where the temperature drops below the regulation band. This results in two surface temperatures: the 30-36°C regulation band and a near ambient temperature. However, very distal zones show temperatures below ambient.

For heat production to be adapted to work-demand requires an engine-type conversion of the heat of combustion. Such an engine cycle has been shown experimentally by demonstrating a series of high frequency and longer-duration oscillatory cycles. These cycles consist of the following frequencies: 120, 400, 1500, 4500, and 12000 seconds. The two-minute cycle is an engine cycle for heat production likely mediated by the oxygen supply and the red cell flow in the capillaries; the seven-minute cycle is hormonally mediated, arising from the hypothalamus and released into the blood via the hypothalamic-pituitary link; the 20-minute cycle is gas storage in the tissue (CO_2); the 60-minute cycle is not known and the 3-hour cycle results from heat storage in the body in a temperature regulated system.

Similar cycles have been found in the guinea pig with no size-scaling law. The engine-cycle frequency is independent of animal size.

Additional guinea pig studies were carried out to determine the temperature characteristics in a motor system (hind leg) by measuring temperature differences in an artery and a vein. The resultant data indicated that the hind-limb motor system does not serve as a heat contributor to the overall system. The cutaneous blood flow functions primarily as a heat dissipator since the cutaneous venous return was lower in temperature than the hind limb main mixed venous return as well as the deep musculature mixed venous return was significantly higher in temperature than either the cutaneous mixed venous return and only slightly higher than the main hind limb mixed venous return. This seems to indicate that the muscles function as a local heat supplier. Interestingly enough, though, the oscillatory nature of the temperature cycles was clearly observed with frequencies of 3-5, 30, 60, 100-200, and 350-400 seconds. The amplitudes varied by only a few tenths of a degree.

An overall view of temperature regulation mechanisms has been proposed by Iberall in (19). Observations in mammalian muscle has shown that the microcirculation is responsive to changes in temperature and exercise, that "tissue is blanched up to 25-27°C; a fraction of the capillaries are open in the range of 28-35°C; and there is a substantial increase in vascularity in the range of 35-38°C". It would therefore appear that local regulation in skin temperature, which had been shown to occur at about 30°C, likely is due to changes in local vascularity which occurs around this temperature. Histamine is suggested as a most likely hormone mediator of this change in vascularity. A hypothalamus temperature lower than the general body temperature found in a warm ambient environment is explained as being due to a shift of fluid outward which thereby raises the temperature of the external layers while lowering the hypothalamus temperature. In the cold, there is a shift of fluid centrally which results in a slightly raised hypothalamus temperature. Metabolic level in a homeotherm depends only on activity. In the cold there is a small rise in metabolic activity which is likely due to an extra metabolic burden associated with increased blood flows centrally. Similarly, in the warm there is extra metabolic loads due to increased flows peripherally (and also the rate of oxidation should go up somewhat with rises in temperature). The differences reported in day-night temperatures are also presumed due to changes in activity level.

The temperature sensitivity of the vascular system is further seen as a possible mechanism for an active tissue to obtain increased blood flow as needed. Increase in tissue activity results in a higher local temperature which opens the vasculature to higher blood flow rates. These temperature rises transmitted to the hypothalamus calls forth a more generalized increased blood flow, though likely in a slower time domain, likely the 7 minute cycle process.

The introduction of the concept of local temperature sensitivity of the vascular system thus appears promising for explaining some aspects of heat production regulation and temperature regulation and should be studied further.

The fluid flow control is thus appearently a factor in temperature regulation at the faster 1-2 minute and seven minute cycles. The paper goes on to point out that the 3-4 day cycle in body weight is a further correction of these fast cycles as well as of a diurnal water balance cycle. It is further noted that serum flow is likely independent of red cell flow, the former being used to a considerable extent for heat transfer and the latter for oxygen supply. This spectrum of regulating processes of water flow at several time domains lends weight to one of our philosophic comments on living material - that such material is effectively a mechanism for organizing water, structurally and functionally.

Cardiovascular System

The dynamics of the cardiovascular system have been developed progressively beginning with the "windkessel" model and advancing through transmission theory in arteries to an analysis of the arterial system based on its anatomical characteristics.

First, a quantitative analysis for coordinated pressure and flow data at the entrance to the aorta and at the venous return to the heart was presented for the "windkessel" model. The problem was posed as to how pulsatile transmission characteristics throughout the arterial system, essentially distributed L-C characteristics, are to be reconciled with over-damped source characteristics, i.e., lumped R-C characteristics. Although a one dimensional transmission line theory cannot provide sufficient damping, the experimental pressure and flow characteristics in the arterial system seem to suggest that attenuation in the system must be appreciable and the reflections from terminations and branches somewhat indifferent. The theories and quantitative derivations are supported by an extensive bibliographic survey of the literature on the dynamics of cardiovascular pressure and flow systems.

The modelling was continued by considering the propagation of a slightly decoupled pressure and flow wave at the inlet downstream into the arterial system. In the aortic tree, the pulse shape shows little difference. The changes appear to be in the arterial branches after leaving the aortic tree. The pulse of flow, transformed by the windkessel into a pulse of pressure, is propagated down the aorta to the end of the arterial line. Because of damping that occurs, strong resonances are not expected in the short flow pulse in the aortic tree.

When the aortic valves close, the high frequency longitudinal oscillation appears at the upstream end of the aorta as a damped notch in pressure and overshoot in flow. This high frequency pulse is dampened in the aortic tree.

The source characteristic of the aorta is basically a near triangular pressure wave with a time delay and a dampened notch with further progression down the aortic tree. If such a source characteristic is applied for a large number of branches, then the system characteristics may be understood. The flow characteristic is a highly dampened negative pulse of flow with a zero flow after the first negative pulse. Thus, the flow reservoir for all the branches past valve closing is the elastic storage in the aorta, and there is no essential damping in the aortic system. The damping resides in the many arterial branches. This may be shown by hydrodynamic transmission line theory.

A model of the arterial system has been developed which considers the larger arteries as tapered, porous tubes. Considering the large numbers of branches from each artery, this model is a good approximation of the real physical artery. Using this model, it has been shown that the reflections back into the artery from the individual small arterial bifurcations effectively average out and the characteristic pressure pulse form is satisfactorily accounted for. The model has been taken up by the other investigators and modified as to details though no significant improvements have been made in it.

A comparison has also been made of the three major previous models of transmission line characteristics in tubes (the Witzig (1914) and Womersly (1957) analyses had been done with arteries in mind; Iberall (1950) had worked on elastic and non-elastic tubes generally). Essentially, all the models were in agreement though Witzig was the most complete and precise. This program however, was the only one to attempt a model of the real arterial system. In fact, the solution for arterial transmission developed in (4) is likely the first complete systems analysis in mathematical-physical terms for any biological system. (There exists other physical analyses of individual actions in various biological systems, and various descriptive models of system events, but no other quantitative models. The only other somewhat complete analysis that we are familiar with is van der Pol's 1929 analysis "The heartbeat considered as a relaxation oscillation, and an electrical model of the heart". Efforts have been made, since Grodins' 1954 paper to model ventilation dynamics. However, the models are not yet isomorphic. Preliminary efforts have also been made by Danziger and Elmergreen , and Yates and Urquhart to model some endocrine dynamic cycles. In addition to such efforts of mathematical physical modelling, there is of course the magnificent structurally descriptive theoretical modelling in molecular biology).

As a result of this type of analyses, the next step was to lay out data around the aortic tree and from its arterial branches for both pressure and flow. In order to do this, it became apparent that another problem was present, namely how can the branch conditions be applied in a systematic way as to completely describe the arterial system, One way is to devise a physical, mean geometrical model of the arterial tree. This branching problem was treated as an equivalent distributed system. A concept of levels was developed. A level is regarded as a tube with its branches until it bifurcates into equal tubes. Then a new level begins. Using data from the literature, together with the concept of levels, tables were constructed in which the arterial tree geometry and resistance were estimated for the aorta, its branches, etc. down to capillary level. The derived table of arterial parameters was shown to be consistent, in its geometric properties, with the DC resistance characteristics of the arterial bed and with the internal volume available to the blood. The internal geometry of the arterial system, as derived in these studies, has been applied to the development of transmission dynamics of pulsatile (AC) flow. [10] [13]

Data have been assembled to show that the homeostatic regulation of the normal cardiovascular system in quiescent operation seems to be at a constant mechanical power level. Deviations from normal in this system appears to be a function of increased requirements for higher power levels.

The modelling has further developed a treatment of the pressure pulse as a transient phenomena. While the steady state analysis was adequate to account for the characteristics of the arterial pulse it is not the real-life situation since it is known that every heartbeat is essentially an independent action; that the pulse passes through the system and the system essentially comes to rest before the next heartbeat.

Using the geometrical model of the arterial system developed by Iberall, Young(14) has shown the practicality of formulating the transmission problem with respect to transients in the time domain and uniformly with respect to "frequency" or pulse width within the domain of lenearity assumptions of Witzig, Iberall, and Womersly. The transient analysis has been applied to a whole class of systems embracing in principle the normal range of mammalian arterial systems, which helped to clarify the meaning of "equivalence" among the various models mentioned. The causal relations between familiar wave distortions seen in arterial trees and the basic geometry of the trees has been traced. The relation of transient analysis of fluid lines to harmonic analysis has been shown.

The analysis considered small arteries appreciably below 3 mm, represented by driving point impedances which are identical to a simple resistive-capacitive network. Up to 3 mm size there is a hybrid line impedance and an equation showing the effect of this on the driving point impedance was developed. Immediately above the 3 mm size, there is an effect due to mismatching between line impedance and terminal impedance. Finally, arteries larger than 5 mm appear essentially inductive-capactive.

While there has been discussion on methods for applying these models to practical monitoring and clinical work, there has been no opportunity to carry this into practice though we are certain this can and will happen.

Dynamic Regulation in Physiologic Systems

This phase of the study consisted of several parts each of which was a separate investigation. The studies performed in this area consisted of experimental study of the time dependancy of the circulating blood sugar concentrations, the oxygen-carbon dioxide system as determined in the circulating blood, the dynamics of the microcirculation, dynamic regulation of body weight.

In the blood sugar study, it had been suggested that the blood constituent concentration would exhibit oscillatory cycles with a fast cycle determined centrally by the interaction of pancreatic insulin and hepatic glucose. Blood glucose would be affected in the lower frequency blood flow cycles. Using wet chemistry analyses of blood from the guinea pig femoral artery and femoral vein, it was found that oscillations occur in blood sugar concentration with a frequency spectrum of 1-2, 6-7, 20-40, and 80 minutes. The amplitudes of these oscillations varied inversely with frequency so that the highest frequencies had the smallest amplitudes and the low frequency cycles had the largest. These cyclical oscillatory patterns may contain the key to glucose regulation and control where the high frequency cycles are intrinsic or local mechanisms and the low frequencies are superimposed central regulatory mechanisms. These results were discussed in relation to the studies reported in the literature. It was found that although such oscillations had been seen before in many cases they were not recognized. It was then postulated that these cycles represent different stages of regulation, e.g., a 30-second cycle (reported by Anderson et al, 1956) may be the local regulatory mechanism for sugar input; the 2 and 7 minute cycles represent local and peripheral regulation of removal of blood sugar; and the 80 minute cycle may be a reflection of a blood flow cycle not necessarily connected to sugar regulation. Also, it is likely that insulin is similarly elaborated in a pulsatile manner with frequencies not unlike those of blood sugar.

We have repeated this work in collaboration with Dr. Simenhoff of the Jefferson Medical School[20]. There were two objectives in these experiments, to demonstrate the high frequency oscillations and to show how automated analytical instrumentation can be applied to high frequency studies. The reason for this was that some investigators have taken issue with our results and those of Anderson though the much earlier paper by Hansen (1923) had clearly shown a seven minute cycle in an extensive carefully controlled study. Since completing this program we have run a series of glucose determinations at the Joslin Research Institute and have again been able to demonstrate a 40 second cycle as well as indicate the 1-2 minute cycle.

In the Jefferson experiments it seemed clear that casual use of automated instrumentation may tend to even out the rapid variations. In the Joslin study, we have learned that the sampling technique is very important and may be misleading. Thus, if large samples are taken too rapidly, the cycles are reduced in amplitude. A normal flow and small samples appear to be essential for exposing the cycles.

After completing the Joslin experiments, a discussion with Dr. Cahill, chief of the Joslin Research Institute, brought forth the comment from him that in the light of the large amplitude blood glucose cycles (and indications of similar insulin cycles in other Joslin experiments), all the modelling of glucose regulation done heretofore in their institute and elsewhere is likely worthless. 'Where is all the glucose coming from' he asked. We pointed out that such large scale amplitude would require a process analygous to the heart pumping action for blood pressure. However, it is clear that the dynamics exposed in this blood constituent will likely require a complete revision in regulatory concepts. (It should be noted that Hansen in 1923, commenting on the seven minute cycle in blood glucose which she found, suggested that this cycle was undoubtedly the mechanism by which the blood glucose is regulated.)

The vascular oxygen-carbon dioxide concentrations were studied because of their roles in heat production and metabolic balance. Partial pressures of 0_2 and CO_2 were determined in guinea pig and rabbit blood obtained from the femoral artery and vein. Since anesthesia interferes with normal rhythmicity, after implantion of electrodes, data were recorded from unanesthetized animals. These showed distinct oscillatory cycles in both arterial and venous pO_2 and pCO_2 as follows: arterial pO_2 cycles frequencies of 30-60, 100-200, 400-500, and 1000 seconds; venous pO_2 showed cycles of 30-60, 150-300 seconds; venous arterial pCO_2 exhibited similar cycles of 1-2, 6-8, 30-60, and 100 minutes. In the oxygen system, an inverse relationship existed between frequency and amplitude, but in the CO_2 system, the inverse relationship of frequency to amplitude was absent. These results were discussed in relation to the literature in three sections dealing with ventilation, transport, and tissue systems.

The search for a mechanism to explain the 2 minute cycle led to the investigation of the microcirculation where the nature of the flow dynamics was studied. Since dynamic measurements on total blood flow or total oxygen concentration in small vessels are difficult, the rate of red blood cell could be done simply. The RBC's are readily observed in their passage through small vessels and since they are the main oxygen carriers, the rate of blood flow would be an indication of the rate of oxygen flow. A series of counts were done on the exposed mesentery. The flow rates varied from over 500 cells per second to momentary periods of zero flow. Although cyclic red blood flow was demonstrated, objections were raised to the use of a mesentery. Hence a technique was devised to observe an active, working muscle preparation. For this purpose a window was placed in the skin of the guinea pig's hind leg to observe the quadriceps muscle *in situ*. Here the flow in capillaries (ca. 15 μ diameter) was studied. The RBC flow was slower than arteriolar flow and the apparent RBC flow-rate was from 1 to 28 cells per second, with an average of 10 cells per second. The flow appeared to be cyclic with frequencies of 10-15, 30-60, 100-140, and 300 seconds. An inverse relationship existed between cycle frequency and amplitude.

Another series of experiments have been run in collaboration with Drs. Bloch and Ostermeyer of Case-Western Reserve Medical School, using an Algire chamber in the back skin of a mouse. A television pickup of the microscopic image was used to expose the microcirculation and the red cells flowing in a capillary were counted visually or by examination of high speed movies. Essentially, the same frequencies were observed. In order to test the effects of hypoxia, the counting was also done on animals breathing reduced concentrations of oxygen in nitrogen. The oscillatory flow patterns persist down to breathing concentrations of 8% oxygen at which level the patterns change to reduced variations and mean flows. At still lower concentration, 4.5 to 5% oxygen, the animals die. Thus, it appears that the regulation ceases at 8% (activity goes down sharply as well). This technique likely would be very useful as well for the study of other kinds of disturbances to the system, chemical, physical, or electrical.

An interesting point is that the cycles found in red blood flow in skeletal muscle vessels correspond to similar cycles previously observed in temperature, ventilation rate, blood sugar, and carbon dioxide concentrations.

The dynamic regulation of body weight seems to be a manifestation of a water balance process. The 3-day weight cycle represents a water balance process regulated by hormonal activity. A three-month study of weight variation in a group of volunteers showed a clear periodicity with cycles of 3.5 days and amplitudes of 0.5 to 2.75 pounds per cycle. There is also some indication that a 10-12 day cycle may exist.

Attempts were made to determine the mechanism for the three day cycle on the assumption that a long acting hormone was responsible. Since the thyroid hormone has a time constant of the order of days (as contrasted with adrenaline, for example, which acts in seconds with a decay time of about a minute, and has accordingly been suggested as a mediator of the 1-2 minute cycle), it was proposed that this hormone mediates the water balance. However, preliminary experiments in which the thyroid was removed from guinea pigs did not result in loss of the three day cycle in these animals. Other long time constant hormones should be studied.

Hormonal Dynamics

As a forerunner and an introduction to an experimental program, an extensive review of the endocrine literature was conducted to characterize the hormones, outline their chemical properties, summarize their biological action, and give some idea of the currently accepted mechanisms of their activity, In the overall view, two basic mechanisms have been suggested for hormone action:

indicator spectrum that is available in a complex biological system may be listed as follows:

nerve cycle	0.1 second/cycle
heart beat	1.0 second/cycle
respiration rate	4.0 seconds/cycle
heat production engine cycle	2 minutes/cycle
blood flow	7 minutes/cycle
intermediate hormone cycle	2-20 minutes/cycle
gas exchange	30 minutes/cycle
thermal cycle	3 hours/cycle
food-voiding cycle	4-8 hours/cycle
diurnal cycle	24 hours/cycle
water cycle	3 days/cycle
estrous-lunar cycle	28 days/cycle
seasonal cycle	1 year/cycle

The major ideas that have been proposed for hormone study are:

Correlate the times of action of the hormones with the time domain of the oscillator processes. Either type of hormone interaction, biochemical chain or membrane effects, occurring at same rapid locally determined time scale, is sufficient to produce phenomenological transport coefficients on the macroscopic field scale. One might expect hormones to mediate biological field properties by as many types of transport characteristics as we are physically familiar with. This would have to include such properties as linear coupling coefficients (i.e., linear dependence on concentration or other potentials), degradation of energy (analogous to the dissipation function in hydrodynamics), non-linear thresholds, non-linear freezing out of degrees of freedom, and non-linear limit cycles. Thus the physical approach to the hormones proposed is the correlation of their phenomenological action with their phenomenological time scales. This correlation enhances the possibility of associating meaningful bio-chemical chains. One can proceed along a path of discussion that is independent of molecular biology, a process similar to the one of classical physics avoiding molecular physics except at the statistical mechanics interface.

Some illustrations are the following. We have postulated a major heat production control action to adrenaline at the 100 second time scale. This neglects another, much faster, time scale of adrenaline involvement in other tissues. Vasopressin appears to be involved in a rapid time scale affecting blood pressure. Insulin may be associated with two different time scales, a high frequency 30 second involvement with sugar inputs into the blood from storage and a longer involvement in the range of hours as a response to large scale input disturbances of glucose into the system. ACTH is probably involved in a range of minutes in overall central chemical regulation, likely under nervous control through the link of hypothalamus to the pituitary. A current key concept in endocrinology, more generally, is that the pituitary is the master hormone regulating gland, and that the hypothalamus-pituitary link is the main electrical to hormonal connection. Thyroid action seems to be in the domain of days. Growth and sex hormones have similar or even longer time domains. In the action of the sex hormones one can see the typical nature of a relaxation oscillator process at the base of the non-linear limit cycle operation in which the timing phase is quite clearly determined by a growth rate.

Thus, the work reported under the preceding section on dynamic regulation in physiologic systems, can be seen to be the experimental counterpart to the theoretical dialogue carried out in this section on hormonal dynamics.

Organization of Behavior

A model of behavior has been developed through an evolutionary process

A very primitive physical view was developed in which the governing characteristics were outlined as a nervous system communications net: the hypothalamus was postulated to act as a switchboard with a temporary algorithm (code book) under cortical control; a cortex acting under a self-adaptive algorithm to control the hypothalamus; a hormonal chemical communications system linked to the hypothalamus through the pituitary; the neural system capable of being acted upon at sensory sources by chemical product, or along its path by chemical product, and interacting by producing a chain of chemical product along its length; and a cortex capable of internal communications and examination. In this analysis, a Freudian frame of reference was sought for the development of this model. The existence and dynamics of the unconscious, the circulating memory, repression, the validity of the methods of free association and dream analysis, a scheme of internal excitation as developed in the principles of hedonism, a proposed etiology of neuroses all seem consistent with a communications computer-controlled network system involving large signal amplitude, non-linear element characteristics. It is possible that the system involves dual governing complexes - a weak, ill-defined, built-in system that governs early behavior, and a second adaptive control system that grows to maturity before the age of 8-10 years. A characteristic mode of behavior of this system is synchrony in which a guided behavior complex locks into step with external entities, persons or ideas. Behavior may be modelled around the primitive signals afforded by the physiologically governed oscillators, and this is largely devoted to the preservation and maintenance of the metabolic reaction. The physiological system is founded on a series of elements. Common to all internal systems is that their actions are organized into unstable closed chains of a biochemical-mechanical-electrical nature involving the solids, liquids, and gases of the body. They usually end as stable non-linear limit cycles passing through transient stages as the organism is affected by changing contingencies in the external milieu. The collection of these chains forms an extensive system of non-linear oscillators whose action is controlled by inhibition. This collection of oscillators represents life. The scheme of regulation and control by which these oscillators are modulated is known as "homeokinesis".

What makes these chains run are catalytic reactions called "enzyme-hormone" links. The spectrum of these chains is not continuous, but instead is a limited time fracturing or time locking through which processes tend to form around and be cooperatively involved. Not all species use the same chains, or even the same time scales, but the density and distribution of number of chains is similar. These chains are mediated through the nervous system otherwise their predominant linearly unstable characteristics would show up. The nervous system mediates between information received as sensory input and the unstable motor and glandular systems. The resultant is a controlled synchronization in which most systems are inhibited (regulated) to a limited oscillatory range; others are released from inhibition to go into orbit. System motion proceeds by the scheduling of these orbits in time as a series of postural elements of the body as a whole enfolding its repertoire of behavior moment by moment. The characteristic schedules enfolding as patterns in response to excitation make up the behavior of the animal.

A basic biochemical intervention regarded as an alertive reaction is furnished by noradrenaline which outlines the active nervous system paths as they conduct information. This leakage flux provides the microchemical change-producing tonus to the system. A concomitant chemo-electric action is shown in muscle tremor; its neural involvement is shown by disappearance of the vibration upon a barrage of motor nerve impulses. Nervous output outlines the system with adrenalin at the tenth-second level. The reticular core furnishes discrete informative signals to the rest of the nervous system in the 0.1-0.3 second range that supplies the sustained grouping signal. The adrenals furnish large scale regularizing signals throughout the blood system at the 2-minute level (considering a number of distributed lags makes it effective at the 4-minute level). The hypothalamus then provides follower action at the 7-minute level. A meaningful hypothesis would be that signals from all sources run up and down the reticular core, which contains the potential command system, to commit the organism as a whole. The basal ganglia may be regarded as the highest center for programmed acts, i.e., a storehouse for routine actions. The basal ganglia act as a deductive system. They have the rules (action analogues). They are presented with a case under a particular rule and they prescribe the corresponding motor action.

The reticular core assigns the role of induction to the cortex. If the input pattern is not a case that is fitted by the standard analogue patterns immediately available from the basal ganglia, the case is then referred quickly to the cortex (within 0.1 sec.). The cortical memory is an analogue memory of many past cases. Presented with external patterned facts, it guesses at a law. The cortex takes habits and once these are set up on the motor side, the cortex is often no longer involved and the solution analogue may be transferred or formed with the basal ganglia.

A significant element in the organization of behavior is the use of cues. In case of a temporally or spatially cued input, the animal will develop a ritualized fill of behavior, a ritual being a patterned response which is stereotyped. An animal cannot maintain undischarged nervous excitation energy, but must seek to release it by releasing the inhibition on some motor response system so as to unstabilize into orbital action. The sterotypes of behavior are learned or may arise from genetic unfolding.

Non-linear rule of behavior is that a non-cortical routine of patterns must be arrived at that fits the cue space with small integral cycle numbers. Then things come off on time and the system is not in sustained stress. Regularized pattern groupings of internal and external oscillators occur. These patterns are experiences out of which orbits gradually shorten, become smoother and more practiced to form a more determinate pattern or orbital paths that make up the life postures. The system locks into a more permanent pattern to form a focal imperative and thereby does not drift aimlessly. The animal, man in this case, selects a central theme around which his behavior develops. The choice of his life's focal pattern fits his ego ideal, or rather becomes part of his changing ego ideal.

Man seems to have a physiological endowment for knowing his internal as well as external states. There seems to exist definite poles of behavior that must be satisfied and other that likely have to be satisfied. Thus boundary conditions can be specified from which patterns of behavior emerge. These patterns can be described for limited periods of time (seconds,minutes, etc. to months). Outside of the question of compactness, systems could be built that behave in that patterns could be established for the middle time range. It could be made to function, to do things, to become anxiously unstable, and to become euphorically stable enough to persist in its orbits until time domains become established for each of the system functions.

Application of Dynamics to the Spectral Analysis of the Mammal

In the last year of this program, an attempt has been made to apply the results of the dynamic analyses of biological systems to practical problems of monitoring and clinical diagnosis. The premise has been that change from normal in the state an animal (or human) would be reflected in alterations of the patterns (frequency or amplitudes) of oscillators associated with important body processes. This of course, has been known to the medical profession for a long time and the heart rate, respiration rate, brain waves, etc., have been used for the detection of pathology. Most recently, the diurnal temperature cycles have been used for monitoring treatment of surface and subsurface tumors. The purpose here was to provide for the greater in-depth examination using many more oscillators with more thoroughness.

The main effort has been concentrated on obtaining background information and developing suitable techniques for studying the temporal characteristics of blood constituents. Bypasses have been placed in arteries and veins of guinea pigs and rats. Windows through the skin have been used to observe living tissue in unanesthesized, minimally restrained animals. The overall objective is to be able to separate and analyze the blood constituents rapidly, if possible, by physical means.

Some success has been achieved in the use of silastic tubing for bypasses though the flow has only been maintained for short periods, up to a few days. The flow generally becomes impeded by white cells and platelets and finally stops completely. There is some hope that recent work on the nature of the process by which the stoppage occurs may lead to newer techniques that will permit continuous flow. Then it will be possible to take up the problem of separation and analysis.

Meanwhile, the work on levels of blood glucose, lactic acid, etc., have contributed to our overall knowledge on the nature of time dependent characteristics of these constituents in the blood and the analytical techniques which may be available for analysis. The oxygen and carbon dioxide electrodes can be used now. Likely electrodes can be developed for other constituents. Observation of the microcirculation is possible now for animal other than man. Much important information can likely be obtained now from appropriate surface temperature measurements (as is being done in thermography connected with cancer detection and treatment; in this field, more could be done with variations in temperature than is being done with simple use of the mean temperature changes).

We did begin some preliminary experiments with Dr. Simenhoff of Jefferson Medical School on the nature of blood glucose level patterns in subjects with known metabolic diseases, Addisons disease, Acromegaly, etc. Preliminary results from a few subjects suggest the patterns are altered though it is far too early to draw any conclusions.

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We have been encouraged by the growing acceptance of the dynamic approach for biological research. This has been reflected in the willingness of respected investigators to collaborate with us and the invitations our principal investigator has had to deliver seminars at Universities and research institutes.

We believe the program has been successful in developing the beginnings of a mathematical-physical analysis of biological systems that will be fruitful in helping toward greater understanding of living systems. This should be useful for those who are seeking evidence of life outside the earth as it may help to define what they are seeking. It should be helpful in monitoring the healthy and diagnosing the sick and as a guide in their treatment.

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