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PROGRESS TOWARD THE APPLICATION OF SYSTEMS SCIENCE CONCEPTS TO BIOLOGY

authored by

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Acknowledgement and Dedication

Few in the technical-scientific circles outside of the Federal service, and not too many inside, may be aware of the considerable debt that science owes men who devoted their careers to the performance and administration of research within the Government. Four such men are Drs. Richard Weiss and Orr Reynolds, W. G. Brombacher and the late Paul Siple. The undersigned is so highly indebted to these men for the encouragement, support, and friendship that has made this and many prior efforts possible, that it would not be seemly not to acknowledge that debt at this time of Dick Weiss' retirement. In doing so I am only a mouthpiece for countless other scientists who were also touched. For in science we really are a community.

Arthur S. Iberall
project leader

ABSTRACT

Further content continues to be developed for a biological systems' science. (See NASA CR-1720 for an earlier portion.) A number of themes are pursued. The first is the character of the command-control system for the complex human organism; that is the character of mind. The second is an outlook on how the biological system can become self organizing. This is pursued by examining J. Monod's theses in Chance and Necessity, and then attempting to write an alternate supplementary view on organization. A fourth theme, not reported on here, is the kinetic character of molecular transport at the membrane level. A fifth theme is the systems' character of a number of organ or functional systems. These include the thermoregulatory system, the cardiovascular system, the water system (including the kidney), and some further work on metabolic systems. Some isolated comments are made on the character of experimental limit cycles. The content of some invited talks on biological systems' modelling are included.

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I. INTRODUCTION

Considerable progress toward the development of a systems science of biology was made this year. The unfortunate state of affairs is that we have had no general publication outlet, as we had with earlier NASA Contractors Reports, to pursue the evolutionary path that our efforts are taking. Evolution, we find, is essentially a chancy branching process. It emerges by diffusion. Thus we will have to permit our various 'random walk' steps to emerge as they may, part in this report, part in reference to material which has been published or is in review, and part in reference to books in preparation.

We find that the diffusion of new ideas is quite difficult, particularly in its diffusion into standard publication sources. We are not against the process. We simply wish to point out that the process takes from 1 to 2 years, and this has become unsatisfactory for the development of a coherent though diffusional framework of new ideas. It is this state of affairs that has led us to the thought of aperiodic book publication. It permits packaging up a set of related ideas for common fairly widespread publication.

Thus we regard a book that emerged from a previous Army Research Office study on general systems (1) as a significant background statement as to how we regard systems.

In this year of effort, the following themes have emerged. First, at the base of systems' biology, we have tackled transport at the membrane level. In our previous study performed for the Army Research Office and NASA (covered in (2)), the weakest section of our final report was Section V, which provided a review of membrane information. The material covered therein is not wrong. In fact it reflects the changing outlook toward structurally specific protein in unit membrane theory, which perhaps is to be replaced by a mosaic theory. Morphologically, this point of view was well epitomized in a N. Y. Academy of Science meeting held in June 1971, whose transactions have just been issued (3). Structurally, it has been quite confusing for the past few years what to accept for membrane modelling. That state of affairs certainly cast a shadow over any attempt to discuss and clarify transport function at the membrane level. Thus our previous remarks went as far as we thought we could safely go toward discussing tranport function.

But it was clear, preparing that section, that our colleagues were dissatisfied with it. Thus we have tackled a review and reframing of the transport issues, not at the general membrane level, but at the level of capillary membranes. We are issuing this as an independent monograph (4).

That monograph is in progress of being edited toward a final version.

At the other extreme of systems' modelling, at the upper reaches of command-control of the human organism, we have made significant advances toward a neurophysiological theory of human behavior, so as to distinguish it, say, from other primates. This began first with an attempt to describe the primitive aspects of the logical manifolds of the mind. (We had previously identified the logics of the brain (5)). As a consequence of that brief essay (see Sec. II), the next thought that was developed was a suggestion to the control engineer, who is becoming increasingly involved in social control systems (e.g., transportation, urban planning, etc.) on the simplest view he could take of human outlook as a command-control function (see Sec. III). Such issues will become increasingly prominent in computer simulations of man-machine-societal systems.

'Finally', a third piece fell into place. This was a hard physical idea on how the difference between the human brain and other primate brains determine human behavior (see Sec. IV). It is speculative, but it is in process of review by those individuals who are concerned with the particular brain structures involved in the modelling.

We had a chance to assemble our ideas on the biosystem as a whole by the following chance circumstances. It is the 25th Anniversary of the American Institute of the Biological Sciences (AIBS). A number of our collaborators were asked to provide an integrated view of the organism (see Sec. V).

Late in 1971, Monod's CHANCE AND NECESSITY was reviewed in a number of publications. In response to one such review (S. Toulmin, N. Y. Review of Books, Dec. 16, 1971), an essay was written on global stability, on what basis systems' organization could take place by self-organizing rules (see Sec. VII). Among other points touched in that essay was a primitive dynamic view of catalysis. We came to this question because it lies just beyond our kinetic work on membrane transport. To find the question being raised in global fashion by Monod (and Toulmin) without answers as to the intervening mechanisms required us to attempt an answer from our work.

But that countering discussion wasn't sufficient. We believed it necessary to take up the issues that Monod discusses. Thus we attempted a review of Monod's book (see Sec. VI).

The problems we are concerned with in systems' biology are not only the 'large scale', 'pure speculative' questions. We have also pursued various intermediate organ systems' problems. Our purposes were two-fold. In the first place, organ system organization must reveal in significant ways how the principles that we find exhibited at higher and lower levels are organized. It thus serves as our real training ground. In the second place, it is the only basis on which biologists could ultimately accept our efforts as at least being involved with 'real' biology (i.e., wherein both morphology and spectroscopy are involved, namely where form and function hold confluence). But that does not mean that our analyses will automatically receive any more immediate acceptances. Cases in point are our work in human thermoregulation, cardiovascular dynamics, metabolic dynamics.

We offered a 'next piece' in our thermoregulation studies in 1971 in our joint Army-NASA study (6). That piece, approximately 13th in a line of continued discussion, stressed two ideas: That in the cold, to avoid contradiction with the laws of thermodynamics, either the metabolism would have to rise in the cold or there would have to be appreciable zonal vasoconstriction. We offered evidence for the latter hypothesis. In the warm, to avoid a similar contradiction, evaporative heat would have to be removed below the surface, or some additional source of cooling of deep body here would have to be found. We argued a case for subsurface evaporation. A year of review for publication, answering reviewers' criticisms one by one, and bringing in a wider and wider circle of reviewers with some competence to debate the issues (e.g., the subsurface evaporation or the distribution of blood perfusion near the skin) indicates some of the difficulties in proposing new themes. One finds a rapidly diminishing number of investigators with competence to deal with an increasing number of facets of complex systems' problems. Those expert in details are reluctant to face broader integrative issues. Thus the path of providing convincing 'proof' is quite tedious.

In order to develop some competence to deal with ever widening complexity, we have been able to infer only one kind of general strategy from our experiences. One must be involved intensely with a preoccupation with experimental detail for a certain time scale, then follow it by a similarly intense preoccupation with integrative theories. It is only by successive alternations of such endeavor that one has any chance for successful convergence to more 'truthful', or 'isomorphic' modelling. Most scientific hangups, in the history of science, seem to occur because established figures hold onto cherished beliefs too long. Absolute truth (at least in this time epoch) is not to be had.

As Max Planck noted at the time of triumph of his new ideas, "This experience gave me an opportunity to learn a fact - a remarkable one, in my opinion. A new scientific truth does not triumph by convincing its opponents and causing them to see the light, but rather because his opponents eventually die, and a new generation grows up that is familiar with it."

We hold no adventuristic base for our proposed thermal modelling, only that it seems to have some merit that public debate can better test. It is this inquiry that we hope yet to get.

We are involved in a similar but yet lesser argument in the cardiovascular (CV) system. A 'Guytonian' view has been forming of the CV system (i.e., after the view of Arthur Guyton). In fact such a view was presented in our Army-NASA report (2). A countering dialectic was not given there. But we have written one, which is included (see Sec. IX). It is not a complete view of the CV system, yet it attempts to estabiish some of the fundamentals on the basis of 'biological laws'. Thus it is very fit for controversy.

It is fortunate that Guyton, who is a most worthy opponent in the important sense that he will debate the pros and cons of his beliefs, has recently provided his systems' overview of the CV system (7). It is fair to say in the tradition of Darwin, Marx, Freud, Einstein, that Guyton has now provided a mark in systems' biology that can no longer be overlooked by biologists. We are thus happy to respond to the challenge - to examine issues in detail and in general. Truth, we believe, is better served by pro and con dialogue than by unanimity of belief.

As an excellent example of the latter is our own internecine battles over the nature of metabolic dynamics and regulation. The existence of high frequency concentration oscillations of glucose - lactate - O_2 - CO_2 - free fatty acid (FFA) - catecholamines in the blood explored and shown by some of us (the group under Iberall and Cardon) is disputed in part by others of us (the group under Yates and Marsh). Nevertheless, the running argument, with the USC group 'up at bat', have revealed a remarkably rich, somewhat slower, dynamic picture.

Since our original purpose was to attempt to expose the pituitary - pancreas - adrenals - liver (P-P-A-L) core coordination of metabolic processes, we do not find ourselves at such odds The purpose of the original glucose studies (as many many before) was to clarify the insulin - sugar system coupling. That we found high frequency (as well as lower frequencies) that have been reported on a few times before (Hansen, Anderson) may have been unexpected to some, but not infinitely surprising. The whole story is still in process of formation.

We are still trying to home in on two complementary 'entities', one the form of the functional units that dominate the structure and function of the organ systems at their 'microscopic' base, and the other the functional form of the chains, the 'languages' of the brain and body that dominates its command - control operation.

Another basic system we have begun to try to organize is the water system, underlying to all of the organism, but with its specialized adaptive organ subsystems.

And finally, other material which has been in progress (or completed) or of interest in this period is the following:

Blood flow and oxygen uptake in mammals - we have been able to review the coupled correlation of these variables at rest and in activity with mammalian weight. This provides a basic challenge to develop a 'design' theory for mammals.

Key problem in the physics of biological systems - we have been able to put that challenge forth before the physics profession, plus a second (social) systems' problem - the analysis of human population dynamics.

We have been invited to present a number of talks, all of which have provided opportunity to summarize, sharpen, integrate our positions and to proselytize. These include talks to:

Case-Western Reserve bioengineering group - a lecture on modelling of complex systems.

NASA-Ames biosystems group - a lecture on the irreversible thermodynamic modelling of the interacting systems of geosphere, hydrosphere, biosphere, and chemosphere, by which the surface ecology of the planet earth can be monitored and described.

ARO - a global view of the dynamics of systems.

IFAC Congress, Paris - a commentator's summary of the status and issues of biocontrol as it faces the biomedical engineer or control engineer with new interests in biology.

As a last activity, one of our number (Iberall) is involved as program cochairman with Arthur Guyton in an attempt to develop a joint control engineering - physiological international symposium (sponsors - AACC, IFAC, APS, IUPS, ASME). The development of that program has provided an opportunity (it turns out the second opportunity - the first was in providing American input to an international symposium on technical cybernetics in Yerevan, ASSR) to note the state of international interdisciplinary systems engineering and physiology. It appears that at this point in history there are only an almost 'negligible' number of individuals well enough trained to provide broad systems descriptions or syntheses from either side - engineering or physiology. Thus Guyton's group effort, our group effort, a few more group efforts (e.g., Goodwin's) are, for practical purposes, still unique in the world. The apparent intense efforts of the past decade has not changed the picture. Strong leadership of a few individuals with wide outlooks, and a willing cooperation of a few well trained intellectually secure persons voluntarily banded together, have still held more than their own with perhaps artifically cultivated bloomings (in which the power of money was the sole fertilizer).

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II. ON A THIRD DIMENSIONAL MANIFOLD OF HUMAN MIND - A SPECULATION ON ITS EMBODIMENT

As a result of earlier systems' programs, both in biophysics and as contributions to a science of managing R & D, conducted for NASA and Army, we arrived at a description of the logics of mind. Operational implications are discussed elsewhere. Our flow of ideas has continued and we are thus compelled to report on these new ideas as their time comes ripe. The following piece, in press for late 1972 or 1973, provides a 'clue' to how we resolve the mind-body problem for reductionist purposes.

Abstract. The brain-body-external milieu play out their roles within a space-time construct. The mind manipulates three logics within these two dimensional manifolds of space and time. It adds a third dimensional manifold, the ordering of 'reverie'. The metalogic of this manifold is not known, but it creates the patterns of order - which is spaceless and timeless - of mind. To build embodiments of such systems is operationally feasible.

The Systems Problem of Mind and Body[1]

It must be understood that there is an enormous gap between the concept of mind and body and a reduction of the concept of operative mechanisms that may be able to represent a brain and functioning organism. If the reader fully accepts that premise, then he may be willing to grant that the philosophic path of exploration between concept and mechanism cannot be easily discerned, and that each explorer must attempt the search as he sees it. I will use this as my introduction to an effort to try to visualize the path. I am a physicist, and my concern is with bridging the gap, in an operational Bridgman sense, to where mechanisms that act like the brain and body are physically realizable.

I am indebted to my dear friend Warren McCulloch for having put me on the path - of what are the embodiments of mind - and through him, with discernable connection, to David Bohm and Gregory Bateson. More about these men later.

A Point of View for Systems

To bring the biological systems, as one example of all viable systems, into focus, I view 'living' systems with the following outlooks:

[1]In response to a reviewer's comments, a glossary and explanation of some terms is appended.

The first is:

<u>form and function</u>

As part of a systems description, there are force-bound microscopic elements in any macroscopic system by which form is held together. At the macroscopic level, then, functional transformations, e.g., flow processes, can take place. The flow processes may be either fluxes of mass, or energy, or momentum.

The second is:

<u>motor processes and communication processes</u>

Since this outlook seems particularly specialized for biological systems, a comment is in order. I mean something applying to all viable systems in a broad context. Most generally, motor processes are power engineering processes (i.e., the macroenergetics of processes), and communications processes represent those fluxes which are used not so much for power - although they must contain at least small power levels - but to produce novel or changing patterns of the state of the system through power amplifiers (i.e., the signalling pattern provides power which differs appreciably in measure with the changes in state it produces).

The embodiments of form are most often tied to motor processes (namely formed containers provide the carrier for formal[1] thermodynamic engines);of function to communications processes (namely communications content is contained in aperiodic functional processes).

The third is:

<u>hierarchical ordering</u>

A simple system will consist of one or more active chains or loops, in which various subelements are linked together in equipollence, i.e., in equivalent measure. (This implies a tight connective link of the elements in their measure. As an example of equipollence, in a network $\Delta V = L\ddot{q} = R\dot{q} = q/c = -E$. A voltage drop ΔV can be 'created' by the rate of change of the rate of change of charge q passing through an inductive path. The metric is L the inductance. A drop may also come into existence by passage of charge or derivatives through resistance paths R, or capacitances C. Or voltage drops may be created by batteries, albeit as a negative drop; namely a battery is a source. These elements are equipollent. As another example, if in a society a tight bartering chain exists, 10 cows = 1 automobile = $2,000 = ..., these are equipollent.) In a complex system, there may be an ordering of levels in the system, in which elements on one

[1] As opposed to processes that may appear casual or incidental.

level are not equipollent with elements on the next level. Nevertheless it is the organization of elements at one level that makes up a formed or functional subelement on the next level. This loosely presents the idea of hierarchical ordering.

Microscopy and Spectroscopy in Systems

It has been characteristic in biology to use a particular tool for analysis - microscopy. This is one dimensional manifold (that is an entire connected spectrum of spatial fields) in which form (morphology) is discovered in biology.

We have contributed to trying to add a second dimensional manifold of time (similarly a connected spectrum of temporal configurations) in the form of stressing the tool of spectroscopy for biological analysis. It is in this manifold that function is to be discovered in biology.

Since it is obvious that function is to be noted and discovered in time, our statement cannot mean that we have discovered the need to watch change in biological systems. No, it is a much more specialized tool, the tool of dynamic systems analysis, that we have tried to bring to biology. It is the use of methods for systematically extracting information about periodic and aperiodic phenomena, and relating these phenomena to descriptive and causal mechanisms that we have attempted to transfer from the physical sciences and engineering to biology. For example, this point of view is also coming into prominence in currently emergent ideas in developmental biology (Goodwin (1969)).

My colleagues and I have used these ideas to build up a conceptual structure for the biological system. We have attempted to extend the ideas from the physiological mechanisms and events within the body, to the behavioral mechanisms and events both in and out of the body (Iberall (1964-1969)). We have even arrived at some idea of the logics of the brain, and are convinced that we have enough license, thereby, to start experimentally building a brain, or rather attempting to simulate brain-like functions. Yet there seems to be a piece missing, namely a background broad enough to carry brain function structurally. We will attempt in this essay to suggest the missing piece.

The Need for a Third Manifold

Let us suggest in primitive but profound illustration that a piece is missing. If I say to you, "Be a choo-choo train or a horse" as children will say to their fathers, you simulate such a system. You 'wire' together your nervous system and your motor system, and, within functional and formal limitations, you simulate a choo-choo train. The child, or the charade player, recognizes your actions.

However, I can also say to you "Be a clock", and within accuracy limits you can be a fast clock (10 counts per second), a medium clock (1 second counts) or a slow near 24 hour clock, etc. This act is equally profound. You have the capability to manipulate your motor and internal systems to keep time.

However, there is another manifold, a third 'dimension', in your mind which permitted you to perform and simulate and order these and many more diverse functions. How can we discover this manifold from these functions?

A Transition to This New Manifold

I can present to the reader the genesis of our ideas up to this point. It is contained in the references appended. As a key concept for the embodiment of the living system, we have proposed the idea of 'homeokinesis', as a modification of Cannon's homeostasis. We defined a living system - (Iberall (1964)) - "...as any compact system containing a complex 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 to 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 these preservative functions for a reasonably long period of time comensurate with the 'life' of its mechanical-physical-chemical elements...". Homeokinesis - Iberall (1966, 1969) - represents the totality of dynamic processes, essentially achieved by mediating the states of these physiological-psychological oscillators, by which the central or mean regulation of the many state variables of the system is realized.

Before introducing our new ideas, it is useful to summarize some key thoughts of David Bohm and Gregory Bateson. I am certain that they each feel the power and strength of their own ideas without my praise and it is I who must acknowledge my debt to them. They have been seminal for me. Thus even if we diverge (or agree), I am grateful to them.

This Manifold is Related to the Concept of Order

Bohm (1969) strikes the key that the concept of order is a timeless process. "Without ...vast totality of topological orders, there would be no meaning to measuring intervals of time and space. ...wherever one looks, whether outwardly at nature, or inwardly at the thoughts and feelings that are the expressions of the operation of the mind, one finds that the essence of things is always one kind of order or another. Thus, order may well be the basic factor which unites mind and matter... ...Moreover, the notion of order is evidently more fundamental than other notions, such as, for example, that of relationship and classes, which is now generally regarded as basic in mathematics. ...if order is more fundamental than almost any other notion ...how then can we hope to define it? ...Of course, we cannot... ...Rather, we must begin with the fact that every one already has a vast totality of tacit and implicit knowledge about order..."[1]

Then later

"...the breaks or changes in the order of a given process can themselves be the basis of a higher order of process...".

This is only introduction to Bohm's thoughts, but it may set the tone for the remainder of this piece.

In the 1970 Korzybski Memorial Lecture, Bateson explores the Korzybski thesis that the map is not the territory, to determine the character of the mind-body problem. Should one relate the quest to the substance of the mind, he asks, or to its pattern? This has been the classic dichotomy in western thought. The oscillation between considering the primacy of the states of mind or of its patterns has shifted since cybernetics. We can now say what a mind is. But we must take note that the unit of survival of a living system, its viable organization, its domain, is not only that contained within the living unit, but the total surrounding environment with which it reacts.

When the brain views the external world, that unit of the territory which gets on the map is not the territory - if the territory is uniform, nothing gets on the map - but the discerned differences. However, a difference is a highly abstract matter. It is not a unit of energy; it is a unit of pattern.

A piece of chalk can't enter the brain; there are a nondenumerable number of facts or differences to be noted about a piece of chalk. The brain selects its information. What we mean by a unit of information is a difference.

We never know what a territory is, only a representation, say as produced by the retina. Thus we deal, in the brain, with an indefinite regression of maps. The territory never gets into the brain; only maps of maps of maps. The mental world differs thus from the physical world.

Where is mind? Differences can't be located. If a difference is in some sense an idea, it is not a physical event of an ordinary kind. - And so forth.

It is not appropriate for me to attempt to detail all of the delicious profundity contained in the thoughts of these two men. Their published writings will have to speak for themselves. However, Bohm's disquieting

[1]Immanual Kant "Time is a way of ordering percept" is another view.

thoughts have run through my head for 3 years. 'Suddenly' upon hearing Bateson's talk, and having just finished editing a manuscript on the science of general systems, a concept occurred to me that went beyond the modal and hierarchical ordering of behavior in which I have been involved (Iberall and McCulloch (1968), Bloch et al. (1971), and Iberall (1971)).

'Reverie' is the Third Manifold of Mind

While space and time are the two manifolds manipulated by man and all viable systems,[1] there is a third manifold by which the mind of man manipulates man himself. This third manifold cannot be endowed by metric, though it may be by number. It is in my interpretation - sounded out through Bohm's concept of order - a non-metric topological outlook. This outlook is an ordered point of view taken of both the body and the world. Connected with motor elements and sensory elements to the world, it allows its own fluxes (i.e., the fluxes that pass through the physical mind, the brain structures, with all of its 'levels', spinal, reticular, cortical, limbic, mid, autonomic and the lower nervous systems) to determine its patterns of mind.

Basically 'mind' can only be the pattern of processed data in the physical structure of mind. Such data, representing both spatial field information, temporal field information, circulating information, and processed 'affector' (outgoing) information, must exist in the form of transformed spatio-temporal patterns. Wherein lies mind? It likely resides as such patterns in the general field known as the reticular core - neocortex - limbic system complex. (Perhaps one of these is not necessary.) What is mind? It is the topology of pattern, a space-time reverie of differently ordered relationships. Its manifold 'dimensionality' is made up of super-relationships. The first is a super-relationship of logical systems. There are three logical systems contained in mind-body - a naming logic, a counting logic, and a geometric field ordering logic. The mind cannot encompass its own fourth logic, a super-relation, i.e., it is not complete. This fourth logic involves the 'metalogic' of the order of its ordering. For that reason, we have chosen the term 'reverie'. It muses or chooses, as if in a dream. The mind regulates motor action or the internal (in)action of thought, and also the direction of attention. What the mind can view as hierarchical ordering is to be discovered in these super-relations. Whether the mind can discover its own ordering relation is of course moot.

Thus space, time, and the ordering of reverie are the proposed three dimensional manifolds of mind.

[1]It is perhaps desirable to point out that the space-time dimensions of the physical world represent a common background in which space and time of the brain and mind are embedded.

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Appendix - A Glossary and Some Explanatory Notes (in the order of presentation).

Mind-body — One of the great classical philosophic problems. Each age attempts its interpretation of mind and body. This is an attempt at a physical reduction.

Reductionism — The concept of attempting to explain phenomena at one level by their component elements at a subordinate level of formal elements.

Mechanism — While in a literary sense, mechanism might be equated to descriptive explanation, in a physical sense, mechanism always implies reduction to actually being able to build devices that act like the description.

Bridgman's operationalism — Bridgman's concept that our way of defining a thing is only through the instrument measures that our senses or their augmentation can bring to bear in perception.

Form, function — Many persons in biology, in recent times, are indebted to D'Arcy Thompson's writings for the thought that form is a property to be abstracted and subjected to mathematical, physical, and chemical probing. Before him, Helmholz was responsible for a similar idea, etc. Thus form and funct on are commonly viewed and have always been viewed as two aspects of a complex system worth exploring.

Power and communications engineering — Roughly speaking, starting from the work of Steinmetz, the analysis of electrical machinery by formal network analysis became highly developed. A major distinction that then arose was that many networks were used not for their power characteristics but for communications. This emerged from the confluence of attention to the telegraph (e.g., Morse), the telephone (Bell), the wireless (Marconi), the vacuum tube, and electrical machinery. The cyberneticists brought this intellectual apparatus to brain function (see Wiener, and the early Macy Foundation Conferences).

Hierarchy — The concept of hierarchical ordering in complex systems is one that is growing in interest. While its meaning has been extensively explored in philosophy, its much more recent view in systems engineering is still ill-defined. Loosely, many writers agree. However each man has his own ideas on how to identify the levels. Roughly speaking, we consider that communications command-control passes down the levels, and that both structure and function pass up the levels.

Microscopy — The tool for the discovery of morphology of structure and form. The dimensions to be discovered here are related to spatial ordering.

Spectroscopy — The corresponding physicist's and electrical engineer's tool of frequency analysis or harmonic decomposition of the time course of functional variables in a system. Time or frequency parameters are used to identify processes.

Physiological mechanisms — As a physical view of the biological system, the physiological mechanisms are those physical-chemical mechanisms that carry the various process chains to completion. Obviously - since the body is not run from external command-control sources - it must contain mechanisms for its own command-control system.

Brain function — The summation of mechanisms that represent the command-control system.

Simulate — In a technical sense, to build or temporarily put together a set of mechanisms that will operate like another set.

Mind — That structure or group of mechanisms (the writer, being a physicist and not a metaphysician, must be concerned with mechanisms) that can both receive input information and transmit output information without having to operate immediately, by coupling, to either. It can both withhold decision as well as redirect the thrust of reaction.

Homeokinesis — As defined, homeokinesis is the dynamic scheme by which we believe body function is achieved. In fact the problem posed in this paper is how to bring mind into the same scheme.

Order — The fixing of reproducible patterns. Bohm's thought must speak for itself. Order cannot be defined. It is discovered. If human mind were not capable of discovering order, this discussion would not take place. One could say that such students as Piaget are attempting to discover the development of order in the young.

Korzybski semantics — The author cannot take on an extensive presentation, but roughly Korzybski's work is concerned with the form of non-Aristotelian logic by which the mind works. Gregory Bateson was one of a distinguished number of men who have yearly given their views of this problem to the Institute for General Semantics.

Substance versus pattern — This is a question, posed as a dialectic, as to whether form or function governs the mind-body problem.

Cybernetics — Essentially, cybernetics is the study of the mechanisms by which the command-control function of the mind emerges. It is clear that neurophysiologists and the like were originally concerned with brain functions in an attempt to define this problem. Out of such concern a physically founded field, cybernetics, emerged. The problem area is not only open to physical scientists, but basically the common bond is an attempt at a reduction to physical mechanisms.

Information — Information is the technical concept prevalent in information theory, which is not simply Shannon's coding theory, but an entire theory of signs. See for example C. Cherry's writings.

Metric — The basic problem in measurement is concern with a physical realization of a mathematical concept of measure. This reduces to a series of problems. The first problem in defining a metric is that the phenomenological observations must not be evanescent. They must be reproducible. A unit measure must then be abstractable; and it must be storable. Finally its rules of association must be determinable (e.g., addition, commutation, association).

Mind's metrics — While many observations may be reproducible, it is not clear that the unit response to an observation is reproducible. One's head may feel like a pin after making a stupid mistake, or like a balloon after a hangover. Your son's rights may be your son-in-law's outrages. Today's pleasure may be tomorrow's pain.

Logics of mind — The brain is not a Boolean algebraic computer. It has mechanisms which succeed in performing logical operations according to three different logical systems. It can name things, and it has rules, etc. for forming such names. It can count things, and it has an extensive aruthmetic capability. Finally it can encompass geometric fields. In the author's opinion, speculative, this exhausts the classes of logical operations that the brain can perform. The mind has a superlogic. (The purpose of the paper is to identify this superlogic.)

Reverie of mind — The choice of this word is beset by serious constraints. It must denote out of time and out of space. We have taken refuge in a Freudian-like concept. It is as if out of a dream - i.e., reverie. However, no idle philosophizing is intended. We believe this can be translated into operative mechanisms.

III. INTRODUCING SOME OPERATIONAL CHARACTERISTICS OF MIND - THE HUMAN OUTLOOK AND THE DYNAMICS OF SOCIETY

In addition to those rare individuals or groups concerned with artificial intelligence or neurophysiological constructs, and the many concerned with the clinical consequences - normal and pathological - of mind, there are also the many engineers who are becoming increasingly concerned with man-machine loops in which long term 'cognitive' processes are involved. The 'transfer characteristics', man as a mechanistic element in the servo-loop, were developed in the control engineering field (e.g., Craik, Tustin, Wiener, etc.), particularly for gun control and control of high speed high performance craft.

In approaching further generalization from motor transfer functions to cognitive transfer functions, there will be a great temptation for engineers to attempt to represent the human operator within a linear vector space as a linear operator in which various characteristics, e.g., amplifying, differentiating, integrating, are represented by superimposable addition, i.e., $0 = 0_1 + 0_2 + 0_3 + \ldots$ where the 0's are mathematical operators. In order to forewarn them, the following piece was written. It is in press for late 1972 or early 1973 publication.

Abstract. For the engineer to deal with social questions, it is necessary that he have some basic view of how human behavior is governed in a technical sense. A foundational view is presented for the outlook of mind. This view is based on a neurophysiological abstraction regarding thought and action, not a sociological abstraction. Sources for the neurophysiological abstraction are proposed, but not herein detailed. It turns out that the neurophysiological characterization agrees with a philosophic-sociological truism, the law of the wings. It is offered here as the polar axis of response from radical to reactionary, as generalized transform characteristic of the mind joined to the body and to the body of society. This axis of response is not simply a political polarization. It represents the transform by which any input set of impinging information hurls the mind-body into thought and action. This paper is concerned with the nature of that transformation.

The engineer is being drawn increasingly into man-made and natural systems' problems in which the command-control function of the human being is operationally involved. The concern is not only with the kind of problems that have become accepted as biomedical and human engineering, but also with a broader scope of social engineering problems. These are concerns increasingly removed from the disciplines generally considered within the traditional scope of engineering. This note offers a few interdisciplinary guides of a general systems' character to the nature of the operational transform by which human beings translate input vicissitudes into output though and action. A central hypothesis is offered the engineer to unify a large amount of neurophysiological and behavioral findings.

For a brief and sketchy historical perspective of a technical convergence on the 'transfer characteristics' of the human operator that is taking place, the following lines of development can be noted:

1. The division of labor as part of the human condition has a long sociological tradition. An excellent illustration of that tradition as it took form in the 19th century is furnished by Durkheim (1). A modern synthesis is offered by Neff (2).

2. At the turn of the 20th century, a foundation was laid for human engineering. The Transactions of ASME provided an active vehicle for the transmission of that material. Many of the important contributions have been summarized in a 50th Anniversary ASME volume (3). If that early industrial engineering literature is regarded as a contribution to the open loop 'work' characterization of men, then an extremely interesting modern view of some 'open loop' regulation design characteristics of systems involving men has been written by Kelley (4).

3. Stemming from operational needs in World War II, a formal identification of man-dynamics in man-machine systems was begun by Craik (5) and Tustin (6). It is fair to say that their contributions were instrumental in generalizing the concept of transfer functions from purely physical man-made systems to a broader class of systems, including man himself. The well-known work of Wiener in cybernetics followed very closely.

4. An 'ultimate' reduction of the command-control characteristics of the mind to the principles of the brain and behavioral sciences neurophysiology, psychology, ethology, etc.,- has not been achieved as yet. A fair sampler of that literature is offered (7). The selection of references has been made on the basis of what might be of interest and comprehensible to the engineer. The author's summary of individual behavior written in collaboration with Warren McCulloch, one of the neurophysiological fathers of cybernetics, is outlined in (8). This work is related by loose intellectual ties to the modelling of Kilmer et al. (7). These efforts are representative of a common search toward developing modelling consequences of neurophysiological and ethological findings. An extension to the physical foundations for social behavior was proposed in (9).

5. There is a line of general systems' philosophy, i.e., methodology for viewing all systems within a common perspective, that began essentially in the 20th century with Bertalanffy (10). Its development can be traced in the General Systems Yearbook of the Society for General Systems (1956 - present). Machol (11) illustrates a 'state-of-the-art' for what is con-

sidered to be systems engineering. A recent contribution of the author to general systems science is (12).

The problem that this communication proposes to face is what is the response of the human being as an individual and as a member of society. The question is directed at not only his mechanistic n-degree of freedom motor responses but more generally how he transforms input into action and thought and communication. It is clear that his response is not purely mechanical. It is adaptive, it is capricious (stochastic), it has dead-bands, it has memory. In addition it has 'emotions', a character different from other systems. Yet it has a character, a style, an outlook that other human observers can identify. The task chosen here is to suggest the most primitive outline of that characteristic of 'outlook' that represents a human being's response transforms. The author believes that he has caught a description which is nearly logically isomorphic with the function of mind regarded essentially as a neurophysiological structure. It is most pleasing that the essential construct is also isomorphic with a sociological truism. But the basic difference must be noted. The sociological truism can only be inferred from statistical evidence of a social nature. It is believed that the 'neurophysiologically' based assumption can be examined by experimental design at the functional level of the brain.

In the past decade, anthropologists have grasped that they could no longer limit their study only to remote and primitive cultures. In fact, it became apparent that the study of their own cultures was a most suitable subject for their discipline. (This of course immediately brings the interaction problem of observer and measured system into considerable prominence.)

If we in systems' and measurements' science propose to get at the analysis of complex social systems, we must begin at the most primitive note of assuring ourselves of concepts that are capable of carrying the system's structure, and of identifying suitable parameters that have objective merit. The purpose of this paper is to introduce one such primitive note. While it may be obvious to some as a sociological or philosophical truism, the statement of the concept is worth making for its more primitive character.

A human society and each individual in a society operate within a frame of reference. Roughly this outlook characterizes its life style, and is related to 'goals' (8, 9). As was discussed earlier (8), the life style is a patterning among the physiological and behavioral modalities. The concern is now with identifying the abstract forms of these overall patterns.

It appears that one basic frame of reference of an individual or society can be identified along the following scale:

irrational 'right wing' reactionary
reactionary
conservative
middle-of-the-road
liberal
radical
irrational 'left wing' radical

In fact it has been identified by Feuer as the "law of the wings" (13). Feuer points out that in any social confrontation with a new set of circumstances, there is a spreading out of belief along a radical to conservative philosophic outlook.

For historical reasons (just as the naming of the electron's charge as negative) these divisions have been identified as the gamut of beliefs from the 'left' to the 'right' wing. However these labeled states are only connected to political belief and action as an effect rather than as a cause of behavioral organization. The nature of the outlook does not depend on political organization. It is essentially a concept to be abstracted from neurophysiological evidence. The engineer who wishes to examine evidence for his own summary of the abstract properties of the outlook of mind is referred to a sampling of sources (7).

A middle-of-the-road outlook of an individual is not one that is exclusive to democracy, monarchy, anarchy, dictatorship, or oligarchy. It is simply the outlook that represents the status quo operation of the system. Whatever was the path that worked heretofore was the path to project to the future. Since such an outlook might be viewed as being a little rigid (i.e., since it carries the connotation of a linear extrapolation from the present), one likely should add to the prescription that a middle-of-the-road outlook faces the changing vicissitudes of each succeeding day in the pragmatic spirit of using the individual's accumulated knowledge to permit change within rates of change that are customary. Namely there is a diffusion of change, as a random walk, within the bounds of a well-defined space-time tunnel. The individual holds in his mind a model which is essentially a running average of the near past. He is cognizant of both its average state, its trend, and the common magnitude of the vicissitudinal fluctuations. His ideas diffuse from that trend.

The conservative outlook, on the other hand, prefers to face each day within the spirit of attempting to conserve the learned customs, and holding or reducing the rate of change to lesser values.

The liberal outlook, examines the changing vicissitudes of each day within a spirit of change. While the individual, too, depends on past learning, he is willing to use that as a guide for a course of changing rate.

One must understand that the daily vicissitudes, that is the impulse spectrum of effects encountered each day is not a highly reproducible temporal sequence. (Even though we are embedded in continuous fields of temperature, pressure, etc., events occur as impulses - it does not rain continuously, grass does not grow continuously, nor are people spread out continuously in space - you meet them head on as discrete individuals.) The human is faced by decisions - at the fast scale of tenths of seconds, every few minutes, at the scale of tens of minutes, each number of hours, each day, each week, seasonally, within the decades of his life (8). He himself goes through a developmental schedule; in addition, he learns and adapts as time goes on. The feedback of being able to associate cause and effect and adapt to past experience, if nothing else, will result in moderate changes in operating confrontations to these changing vicissitudes. Thus it would appear that even the middle-of-the-road outlook requires modest rates of change, compensations for changing conditions. Thus liberal or conservative is an attitude relative to the amount of normal change that a middle-of-the-road outlook permits for the normal changing exigencies of life.

The radical and reactionary outlooks, then, are characterized as more extreme outlooks toward change. The radical generally believes that the existing course, or the moderate rates of change that the liberal envisages, are fundamentally incapable of directing a satisfactory operation of the system. He has an offset model different from the existing system's model. He thus seeks 'radical' changes, ones that differ largely in rate and direction from the middle-of-the-road. His 'goals' are different.

On the other hand, the reactionary believes that the rates of change of the present and recent past have so far removed the system from a satisfactory state of operation that he wishes to return it to some relatively remote past functioning of the system, which he considers to be more nearly ideal. His 'goals', too, are different. These past functions, generally, he believes are tied up with long removed customs and traditions. These ideals, 'oughts' of behavior, he believes, are the only sound way to direct system motion. He is 'reacting' to the present.

Beyond these five outlooks, there are two more extremes - identified as the irrational reactionary, and irrational radical. Their proposals for action and conduct of the system do not lie within a comprehensible program in the common sense of rationality. One will find that all five 'centrist' outlooks will agree on the irrationality of these extremes. But you cannot ask a reactionary or radical whether a certain 'radical's' or 'reactionary's' outlook is irrational. You must ask, respectively a radical and liberal, or a conservative and reactionary.

The measure of the five 'centrist' groups is that they are more concerned with the preservation of a working system, than in its destruction according to preconceived ideas. This does not mean that the extremes of the center are satisfied with the system - they propose to work actively to change the system - but they are willing to work within the system's rules to bring about change.

With a mild amount of disagreement, the author believes that it is possible, by examining people's attitudes, for men of good will to agree, by the common sense, on a description of the status of any group of individuals within their systems. However, it is not similarly possible for persons outside of the system, unless possessing a large degree of objectivity, to judge the lineup in other systems. Very few Americans are capable of judging the 'centrist' lineups in such national 'cultures' as the U.S.S.R., Czechoslovakia, the People's Republic of China, Great Britain, Sweden, Tanzania, etc., nor they in ours. The exercise of attempting such identification is self-instructive.

In recapitulation, this scale of reactivity, while it may have appeared to be a political spectrum, is more fundamental. It is tied to the function of 'mind'. A man's position on the scale represents the guiding outlook of his life style. The conservative-liberal polarization is not a polarization around the issue of more or less freedom for human conduct but over the preservation of form and function or the functional evolution to new form and function. (The reader may ponder a Harris poll on this issue, reported in the January 18, 1971 issue of leading U. S. papers, e.g., the Philadelphia Inquirer.)

The same principle might be applied to lower forms of life. The range is likely more restricted than for humans (i.e., most animals are therefore middle-of-the-roaders). However, this principle is a subject for greater exploration by ethologists.

While this finishes the rudimentary classification of dynamic outlooks of the individual, the problem of describing the dynamics of society is worth some additional introductory remarks. The following thoughts, albeit quite speculative, are worth consideration by operational engineers.

If one believes in acting by reason, to whatever extent one can control ones actions (whether individual or societal), then the five centrist positions are all reasonable. The two fringes are irrational.

What might one see as a guideline toward a style of life (again, to the extent that it can be controlled)?

If things are in reasonable shape, then the most plausible coalition of styles for conducting society that is likely most conducive to sustained stable operation is

liberal - dead center - conservative

radical reactionary

a broad coalition of the three center groups, with tugging from the extremes. A balance of power among the three centrist groups keeps things shifting gently with the slowly changing direction of the 'middle-of-the-road'.

If the past is better than the present then the most likely desirable coalition is

radical——liberal——dead center
conservative
|
reactionary

namely let a radical-liberal-dead center coalition govern. This may also be viewed as the response for 'falling expectations' (e.g., the future might be made better than the past; move toward it with change).

If the past was worse than the present, then the most likely desirable coalition is

dead center——conservative——reactionary
liberal
|
radical

This may also be viewed as the response for 'rising expectations' (i.e., the future may be perhaps prevented from getting worse and may even become better).

Note the autoregulatory property contained in implementing these governing concepts. If one imagines a perceived image scale extending in the positive direction toward good, and in the negative direction toward bad, with a zero neutral or indifferent state of affairs, and a state vector moving monotonically with the time axis, then the following regulation is being proposed:

If the state of affairs is either good or bad but moving toward the better, then attempt to govern to conserve the state. If the state is moving toward the worse, then act to change. This provides an algorithm which, while linearly unstable, makes the social system responsive and tends to keep it regulated within bounds.

Unfortunately, a common social response is opposite to this regulatory response. In times of rising expectations, social groups tend to radicalize, and of falling expectations, they tend to react toward a return to an imagined past.

The problem in social regulation, most often, thus is a choice of directed community leadership that can buck the tide of unstabilization. Most often what ultimately stabilizes a society, as a highly non-linear mode, is saturation. At peaks, a society can only glut its expectations to a limit, and at valleys, grief cannot be indefinitely sustained. The sun generally continues to rise the next day, a new spring is born. However these latter thoughts are all still quite speculative.

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IV. ON A 'NAIVE' BIOPHYSICAL MODEL FOR HUMAN BEHAVIOR

We are occupied in joint programs in both biosystems and man systems. The confluence of problems has forced us to seek a very specific stand on what is the real operational difference between the human mind and the mind of other primates. The following essay proposes an essential difference. We believe the concept is strong enough on which to build an individual and social behavioral science. But only time and criticism will tell.

Introduction

Our group at General Technical Services has been engaged for the past decade in an attempt to develop a biophysical construct for the complex organism, mammals and man in particular being our major target system. As we have gained insight about the system, whether from newly acquired experimental data or from forceful thrusts of new tenable hypotheses, we have written summaries as reports in progress. At this point, we believe that we can add to our earlier work (see for example (1)) by a construct that attempts to link anatomical form and nervous system function into a closer relation. The following foundation, characterized as 'naive', is proposed:

A Biophysical Outline

1. We are occupied with work in progress on the kinetics of transport through membranes. What we find fundamental to an understanding of kinetics is a theory of atomistic fluctuations. It has finally occurred to us that the unit electrical impulse in the nervous system serves the same atomistic role in the nervous system as do the fluctuations of atoms, ions, and molecules. This realization is not proposed as new. Such diverse investigators as Sechenov, Freud, Pavlov, Hull, Hebb, McCulloch and Pitts, each attempted rather complex constructs based on that observation. The only point we wish to make is that the complex phenomena that represent more nearly continuum behavior of a system arise from the correlation or covariation properties associated with such temporal fluctuations (1).

2. We believe that one may now assign generalized functional roles to brain structures (in particular, keeping the primate brain in mind). We assume as a base all well established neuroanatomical findings (see for example (2)). Our object is not to supplant such descriptions, but to propose a rudimentary organization that will permit further biophysical modelling. Thus we will not touch on the ramified nerve system except to note that it is a chemoelectric transducer and transmitter; or the spinal chord except to note that it has fairly definite wiring in both outgoing and incoming paths. In addition, it is our contention that most of the large biochemical

chains concerned with organs and pools in the body are operated as self-regulating systems. We will identify:

Hypothalamus - a complex automatic electrical switchboard which itself performs some of its switch functions by sensors specifically located within its structure. For example, a main switch function is the control of the constrictive state of the vasculature.

Pituitary - a complex automatic 'chemical' switchboard which is coupled on one hand to receive chemical instructions from the hypothalamus via the blood, and on the other hand is coupled catalytically to glands and organ pools also via the blood, to regulate the organ states.

Basal ganglia - routines of action are here programmed. After very few trials past childhood, when the primary routines are developed, the organism has quick recourse to a routine by which a motor action can be realized.

Thalamus - a regularizing (e.g., smoothing, filtering, connecting) function is here performed which makes the body's actions fairly smooth.

Cerebellum - a clocking function is here performed to provide a timing base for body action and coordination.

Limbic system - the 'old' cortex. Here basic 'hunger' responses are given form. These include feeding, sexual, and agonistic (e.g., aggressive) behavior. One of its strongest inputs is the sensory input of smell.

Cerebral cortex - the 'new' cortex. Novel motor responses to sensory cues, to the vicissitudes of instantaneous living, originate here. A distributed memory storage aids in the development of routines for behavior. The system effectively discharges internal excitations arising from sensory inputs and the existing states of internal organs and pools so as to achieve an expected operating level.

Reticular core - probabilistic voting by all major systems is here registered; changes in the operating mode of the system are then made to conform to an operating ideal formed in childhood. Whereas the basic chemical chains in the body are self-regulatory, the executive logic represented in the reticular core samples all states and changes the patterned direction of involvement of the organism.

We take responsibility for making these assertions in such bald fashion. However, we have been guided to taking such views by the writings of H. Jackson, Magoun, Sechenov, Freud, Sherrington, Pavlov, Hebb, Lashley, Papez, Arieti, Klein, A. Freud, McCulloch, MacLean, Delgado, Luria, Penfield, N. Miller, Gesell, Piaget, Scott, to name a few.

Without attempting to offer any further detail, suffice it to say that the structures whose salient functions were briefly outlined are essentially adequate to permit an animal in a reasonably familiar environment to continue with the tasks of living. He will arouse after sleep, be aware of his environment, search for food, void on his path, attack his prey, eat, defend himself from predators, seek out his own kind, procreate, tolerate or care for the young, and return to sleep. The animal's actions will in general be traceable to comprehensible functional goals, many or most immediately discharged, some discharged in longer temporal chains, and some that will be caught up in what would seem to be inordinately long but still programmed chains (e.g., yearly cycles of performance, emergent phases that arise aperiodically perhaps once in a lifetime; or, as in the case of menstruation, that start once in a lifetime and that stop once in a lifetime).

3. But we wish to come closer to the biophysics of the human brain (3). We can note that when the primate becomes upstanding - or as Freud suggested, when he took his nose away from the genitalia - an evolutionary pressure based on the incessant visual signalling in the neocortex come into being. One may surmise that tool making and then speech emerged as advantaged from the chance of genetic mutation. But in particular we wish to call attention to the significance of the coordination center, unique in man's cortex, from which speech originated.

As a result of the coordination center, the human being is capable of 'abstraction'. Signals arising in one 'sensory' modality can be quickly translated and related to other sensory modalities. It is the consequences of this capability which we believe have not been adequately expressed in a biophysical sense.

4. There is a sustained input of external and internal sensory signals into the cortex, in which the wavelike patterns of nerve impulse are processed and organized into coherent pictures, a continuously updated view of a body and world image. It is quite likely that there is a reasonable separation of the various input modalities entering to the cortex. However, it is not clear that the outgoing signal from the cortex remains as well isolated. There is a coordination center. As a result of interaction with the coordination center, one may surmise that there is a transformation of input signal into other modalities. This is circulated throughout the brain, particularly the limbic system, the older brain. At that point the signals become intermingled. The sustained signal passing through the limbic system, focused onto the hypothalamus, and the pituitary with its glandular couplings spread diffusively throughout the chemical pools and return through multiple paths back to the executive reaches of the brain. If we view this process basically as an electrohydrodynamic coupling, a feedback with gain, one can suspect that the system becomes unstable and reverberates, circulates information, or hunts. Why? Because of the divergence of its internal abstract communicational languages. The pathways are not confined to the immediate one which would discharge the message negentropy.

Of course nervous inhition, and the damped nature of the biochemical reaction chains, ultimately degrade the oscillation after the input excitation ceases. But at the same time, the end of the process, together with the existing sensory input, helps set up conditions for the next modality. A probabilistic Markov chaining in behavioral modes takes place. Thus the memory trace of the last meal, or the last sexual encounter, or the last aggress lingers for awhile, or quite commonly, somnolence follows food or sex. As we coined the phrase in the past, sexual encounter, eating a sandwish and swimming simultaneously are ruled out, not because of the lack of desire, but because incompatible demands are placed on the CV system. These and other demands may also be incompatible with other systems, e.g., the nervous system.

Like quantum mechanical states, behavioral modes are not unique, they may occur with state weights. But there is also an exclusion principle. Not all chemoelectric states can be occupied simultaneously. The overall human state emerges from the coupled instability of a coordination center in a highly active cortex vectoring against a limbic system and catalyst-producing pituitary with the glandular systems it controls caught up in the turbulence of internal chemoelectric chains. The basic construct is this chemoelectro-hydrodynamic 'informational' instability.

5. We can carry the construct one step further, indicating its essential Freudian nature, as follows: We may regard part or all of the nervous flux passed by the cortex through the limbic system as the flux of libido (we regard it as part of the flow, if the human's reactivity were highly weighted in terms of one type of activity, e.g., sexual; otherwise it would be the more diffuse total flow). We may regard the characteristic chemoelectric patterns by which the coordination center of the cortex diffuses signals through the limbic system and thence to characteristic excitation of the hypothalamus and pituitary, and characteristic motor response analogues from the basal ganglia as the ego ideal or super ego. In long term, this becomes likely marked in the reticular core as the characteristic style both of the species and, with more detail, of the individual.

6. We must distinguish between fast processing and slow processing of signal. We find this characteristic of the kinetics of all systems. We can use a biological example. The carotid sinus has a sensor for fast processing of blood pressure data. The sensor regulates the differential pressure response, heartbeat to heartbeat predominantly by the pressure rate action of the last beat. For slow processing, the kidney dominates the pressure level picture. Changes here take place in determining the water balance level and thus operating point of the kidney at the few months level.

In the brain, we are confronted by the fast processing of the limbic system focusing on the hypothalamus. On the other hand, a slower processing comes from the reticular core, which requires voting from a preponderance of organ systems to redirect the thrust of the animal. In animals with a well developed cortex, the sensory inputs and data processing of the cortex generally rapidly puts signals into the limbic system to sharpen up the appropriateness of the animal's action.

In the human, it would appear that the reticular core would still have to remain relatively isolated from cortical signalling, else the ensuing instability could make a rather schizogenic animal.

If we judge from Richter (4), there exists long term (typically monthly) cycles in a considerable number of behavioral disturbances. Richter attributes these to endocrinological sources (namely, interference in chemical chains). Clearly in such schizogenic states an exclusion principle is in action. The organism behaviorally is in one state or another. The slowness of response suggests that the disturbance is in the slow processing chains (typically, perhaps one of the pituitary chains). Although weak, this is evidence of self-consistency in regarding the reticular core, or the attention direction system, as relatively isolated from the fast decision-making system. Otherwise schizophrenia in the human would be a high frequency fluttering kind of instability.

Thus there seems to exist a biochemical rather than a bioelectric foundation for a crude Freudian construct. As such it is infinitely more obscure to read the structure and function produced by a chemical 'weathering' logic rather than an electrical communicational signalling logic. This makes psychoanalytic treatment as is presently constituted a rather dubious proposition. A much more strongly chemically oriented construct is required.

In summary, the new key concept that we have added is that, whereas nervous system communication is laterally inhibiting, which keeps signals from spreading and thus channeled within 'appropriate' paths; and that, whereas it is through strongly conditioned reflex paths that animals with complex nervous systems can develop associations other than those which immediately and directly discharge inputs; in the human, cortical processing via a coordination center laterally spreads input signal so that it spreads through many processing channels. The specific target 'organ' at which signal becomes multichanneled, we believe, is the limbic system; that is we believe that sustained circulating signal in the limbic system is no longer immediately appropriate to input. That property provides the foundation for 'abstraction'. The sustained circulation of an input signal via 'translation' or 'transformation', both abstractional constructs, through all compartments of the brain provides the foundation for cognition, for 'thinking'.

Since at this time we propose to furnish no other details other than the hypothesis, we have characterized our view as 'naive'.

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V. INTEGRATION OF THE WHOLE ORGANISM - A FOUNDATION FOR A THEORETICAL BIOLOGY

An AIBS invitation to write an overview for the biological organism provided an opportunity for three of our group to collaborate on this task as a common statement. It was fortunate (though not so viewed during the process of preparation) that considerable biological criticism had to be met. Thus this version represents a statement that has withstood fairly intense intersection with more classical views of the biological system. We regard it as one that many young people will adopt as their futurity model in biology.

Prelude

In science it is often true that 'believing is seeing'. Therefore, as we contemplate the future of biology, and wonder how the enormous complexity of integrated structures and functions will be understood twenty-five years from now, we must decide what it is that we 'integrative' biologists should be seeking. A scientific conservative would probably point to further development of principles and concepts already present in modern physiology and integrative biology. He would extend what T. S. Kuhn, in his provocative book, THE STRUCTURE OF SCIENTIFIC REVOLUTIONS, calls 'normal science' (1).[1] However, as Kuhn points out, great advances in science may occur when the context of explanation supplied by 'normal science' is replaced by a new framework of explanation - by a new paradigm.

In this essay we suggest that the great advances in molecular biology which have provided us with new facts concerning ontogenesis and evolution (2) have failed so far to include an explanation of the dynamics of complex organisms. Our purpose is to set forth a general principle of design, based upon physical considerations, that we believe applies to living systems and explains their thermodynamic characteristics. This principle, which we present as a set of five propositions, provides a paradigm new for biology, that we expect may ultimately replace the biochemical paradigm now dominating the life sciences. It seems to us that this revolution in paradigms will be necessary if we are to find concepts broad enough to encompass the new facts of modern biology.

The new facts of modern biology have revealed the intricate and com-

[1] A new and revised edition of this book has appeared, but we prefer the initial version of the ideas, which, though more susceptible to attack, is also more definite.

plicated machinery of whole organisms, integrating both structure and function, and manifesting adaptation, invention and goals of self-preservation and reproduction. They challenge our comprehension and embarrass our current explanations. We do not go far in trying to explain human goals in terms of molecules before we feel frustration and impotence. The synthesis of molecular biology i· to an integrative physiology of whole organisms eludes us. We lack a philosophy of hierarchical systems adequate to our task of understanding the behavior and the organization of whole organisms, and we are left with a persistent dichotomy between reductionism and holism. Fortunately, this dichotomy generates a valuable intellectual tension.

The recent triumphs in the life sciences have come in the world of the small. Some outstanding molecular biologists convey a confidence that the fundamental problem of life has been solved in the discovery of the cooperation between nucleic acids and proteins, and that what remains is to explain how these two classes of macromolecules formed an alliance in the first place, and how the human nervous system subsequently emerged from their association. Yet among many who study the integrative aspects of biological systems, a vague dissatisfaction stirs because no guideline exists to tell them how to reconstruct function at higher levels of organization in biological systems from the knowledge we have of their macromolecular processes.

In his very thoughtful book, Monod (2) claims that the molecular theory of the genetic code "does today constitute a general theory of living systems". He admits, of course, that it doubtless will never be able to predict and resolve the whole biosphere and points out that complex structures and functions of organisms cannot be deduced from this theory, nor are they always directly analyzable on the molecular level. He then proceeds to consider properties at higher levels of organization in the light of properties at lower levels in an appealing fashion - but without providing formal rules of procedure. What is missing from his treatment is the exhibition of common properties of dynamical systems operating at various scales between molecules and man. Monod's thesis for evolutionary development assumes the invariant reproduction of DNA. However, this invariance involves arrangements of components including repair enzymes and polymerases. Beyond the invariance of DNA lies another system with invariances! We believe that the molecular biologist confronts a crevasse between his world and that of the mammalian neurophysiologists as philosophically treacherous as is the gap between the world of atomic physics and that of the molecular biologist. We shall try to indicate how a new paradigm can help to close these gaps.

In contrast to the optimistic view that macrophenomena in the life sciences will find adequate explanation in knowledge of microphenomena, stands the bias of the holists who argue that complex systems always have emergent properties - properties not found in their separated components, and not analytically or intuitively extractable from their arrangements.

Holists believe that there must be something beyond (as Arthur Koestler (3) put it, there must be a "ghost in the machine") and therefore that analysis must ultimately fail to provide sufficient explanation of phenomena occurring at high levels of organization. Holists give most emphasis to one level - that of the complete system.

We believe that both those who see the whole as greater than the sum of its parts, as well as those who believe that the essential principles of organization are discoverable at the level of small parts and their connections, overlook the design of life. Both the reductionist and the holist views fail to recognize a common principle behind all hierarchical systems - that the basis for explanation is the same at all levels within the system. In the description of the new paradigm we hope to specify that basis for explanation, and to show how it applies at any level of organization ranging in scale from atom to solar system.

This essay, dealing as it does with revolutions and the future, takes us far beyond the edge of certainty. We travel there because we agree with Colodny (4) that "a rather common feature of the history of science is the preparation by one age of the mathematical and technological instruments to be exploited fully by later generations of scientists who will work in a philosophical climate that may be completely different". It is to today's student who may wonder what that climate may be like that we address this essay.

To begin, we first consider the questions to be answered.

The Questions

To formulate our questions clearly, we must identify some universal properties of systems and processes. In physical systems of objects ranging in size from the atom to the solar system, all observed processes involve some degradation of free energy. These systems also involve some random statistical elements at any level out of which the organized processes of the next succeeding levels emerge.

All living systems are "objects endowed with a purpose or project" which they "exhibit in their structure and carry out through their performances"; they are self-constructing, and show reproductive invariance (Monod (2)). They also persist, are hereditary, and evolve. The basic persistent living system is the species - the ensemble of individuals capable of providing a succession of generations that progresses down the corridors of time. DNA, RNA, proteins, cells (or in multicellular organisms, the individuals) are subsystems, albeit complex in themselves. These subsystems, though less persistent, also resist degradation and dissolution, as does the species.

Relation Between Living Systems and Physical Systems

Living systems conform to the known laws of physics but are not derivable from them. Molecular biology is no more derivable from statistical or quantum mechanics, or nuclear physics, than is the function of the human brain provable from the principles of molecular biology. Both cases might not have happened. The most that can now be said is that the human brain, when it is understood in detail, will be consistent with the principles of molecular biology, and with those of physics. These views, though sound, are not satisfying. What is missing is a viewpoint that explains the above characteristics of physical and biological systems, that relates the two types of systems, and that gives us some basis for judging whether life was improbable or inevitable, given the physical conditions that preceded it on earth. We wonder if there is a general principle of design applicable in our corner of the universe that embraces all phenomena - living as well as non-living.

We believe that a general principle of design does exist, and that it will be found adequate to answer the basic question underlying the issue we have raised above. That question may be stated in various ways, several of which are given below:

1. What physical principles account for that most intriguing of all processes - organization? (To be definite, we define organization in space as structure, and organization in time as function.)

2. On what physical basis are we to explain the observation that out of randomness, uncertainty and dissipative processes, interactions can lead spontaneously to stable forms and behavior?

3. What is it that underlies the tendency for local accumulation of 'order' and 'design' instead of progression to homogeneous chaos and macroscopic uniformity?

4. How does chance breed necessity, all in a universe running down?

Until the underlying basic question is answered, we are likely to have only deceptive philosophies concerning the remarkable integration of whole organisms. We have not discovered in present day biology, dominated by the biochemical paradigm, the clue to the answer, and so we propose a revolution in paradigms to find it. Our approach has been to examine critically four prominent classes of paradigms, all lying outside 'normal' biology, from which future understanding of integration of whole organisms might come. These paradigms are not mutually exclusive and we do not claim to have found a basis for 'proving' that one is absolutely superior to the others. However, the purpose of this essay is to call special attention to the attractions of one of the four.

Possible Directions Towards the Answers

We wish to consider briefly three directions from which an explanation of the phenomenon of organization might arise: 1) further development of an abstract, general mathematical theory of systems; 2) further applications of control theory, including techniques of systems identification and of criteria for maximization, minimization or optimization; and 3) further exploration of the nonintuitive behavior of complex, nonlinear, hierarchical systems by means of computer simulation. We will consider each of these possible directions separately, and give our reasons for offering a fourth - the new paradigm.

Abstract Mathematical Theory of Systems

Mathematics is rich in concept, but is only loosely tied to physical reality. Its abstract theories often consist of tautologies about conceivable relationships, built on the idea that some correspondence with a real system may be possible (Kalman (5)). It is true that these tautologies sometimes contain surprises that the originator did not foresee. They may guide attention back to 'realities' of the physical system in examining real systems. Some mathematicians approach physical systems from sets of data, often in input-output form, to indicate the space-time transformations within the capacity of a given system, and then attempt to put bounds on what logical relations might connect inputs and outputs. But this endeavor usually results only in conclusions about internal mathematical relationships. Contributors to an algebraic approach of this kind have been McCulloch and Pitts in their modelling of neural nets, as well as von Neumann, Ashby, Arbib, Grossberg, Bellman and Kalman.

The abstract mathematical approach to systems has no obligation to acknowledge realities of any kind, and indeed, realities are often ignored in an attempt by the mathematician to extract a smooth description of a single level of the world whose real graininess would defy his abstract methods. But for those who view mathematical physics not as a branch of mathematics, but as a branch of physics, there is no longer much warmth to be had from those dim fires of the abstract provided by mathematical formalisms devoted to elucidation, say, of principles of optimization (e.g., principles of least time, least action, minimum energy, etc.). Vitiated by its lack of physical content, however fertile it may seem, a mathematical-abstract systems theory tends to spawn only sterile offspring. These offspring, the new logical equivalences, may help in the manipulation of data, but they lack the substance to lead toward a theoretical biology capable of explaining integration at the level of whole organisms. The emptiness of formal mathematics as employed by the algebraicist is especially noticeable when he is asked to cope with hereditary or evolutionary systems. The features of such systems and the perplexities they provoke have been well described by Pattee (6), and by Monod (2).

A different, and, we think, striking mathematical approach to systems can be found in the work of René Thom (7). His approach, in contradistinction to an algebraic approach, has been to apply a geometric construct to the design of life. Although algebraic structures and geometric structures under proper conditions can be made mathematically isomorphic, the assumption of geometrical structure adds content missing from the algebraic approach. Other attempts to link some aspects of the mathematical approach more closely to biophysical reality also seem promising. Examples can be found in the three volumes of TOWARDS A THEORETICAL BIOLOGY (Waddington (8)), and also in an article by Wolpert (9).

Control Theory

Modern control theory, like the abstract mathematical theories of systems, derives much of its inspiration from notions of optimization. It begins by assuming some criteria defining the 'desired' performance of a system. It then specifies how that performance might be achieved. However, in so doing it overemphasizes the communication (small signal) aspects of systems, and underestimates the equally important contribution made by the higher power, energy-converting machinery (the 'plant processes'). Connections between power fluxes and communicational processes are fundamentally important. Among contributors to control theory who attended to this issue are S. Lees (10, 11) and C. R. Kelley (12). Designers of real control systems must deal with this problem, but the available theory is inadequate to do so.

Control theory fails in two respects. First, it does not respect the test of matching, which says in effect that although you can imagine many possible ways to couple controllers and systems being controlled, only those involving some matching between scales of energy or mass - or some trick to avoid the necessity of close matching - will operate effectively. In other words, an ant cannot control the behavior of a horse unless you make very particular arrangements for him to do so. Secondly, control theory cannot assure the biologist that the way an 'ideal' controller might work is in fact the way a biological controller does work. The problem for theoretical biology is to discover how the attributes of power and control arise together, rather than to determine what one of these aspects should be like when the other is already given. In biological systems, these two attributes are inherent in the genetic code. However, the capability to join them resides in the system itself during its unfolding; this capability is not in the genetic code.

Computer Simulation

Although computer simulation is merely a technique, and not a theory, we consider it here in order to provide a perspective for judging the likelihood that computer simulations may capture the general principle of design that we seek. The great advantages of computer simulation over verbal language in the explanation of complicated systems are that the computer can deal with many variables at the same time, and it can 'solve' sets of nonlinear equations. Modern computers have a high capacity for information, and so simulations may have great complexity. But simulations cannot account for the origin or the actual design of the model system. No general theory of systems can arise from simulation because a simulation extracts specific case solutions where general solutions are not available. Therein lies the merit and the limitations of simulation as an approach to the understanding of systems.

Physical systems work 'on line and in real time'. For such systems, computer simulation of special cases becomes an extremely valuable expository art, especially so since the most interesting properties of a system arise out of nonlinearities. Complicated systems can behave in ways that defy human intuition (Forrester (13)), and we have no other means than simulation to explore most of them. Simulations force the user to codify his facts and beliefs about relationships, and they can take his assumptions to their logical conclusions.

Simulations can, of course, be based upon some physical insights. They usually begin by recognizing within each unknown system the existence of thermodynamic 'plant' processes, of controlling processes, and of information flows that convey decisions to control points. No doubt much of the future progress toward explanation of the phenomenon of integration at the level of the whole organism will require the use of simulations, based upon physical and chemical unit processes, and we too have encouraged such activities (Yates (14)). But such efforts will be insufficient even at their best for the elucidation of the design principles underlying life.

A Statistical-Mechanical Theory of Systems

Having considered, and found wanting or incomplete, abstract mathematical systems theory, modern control theory, and computer simulation as the appropriate general direction to be followed in creating an understanding of organization and the integration of structure and function in the whole organism, we now turn to a more promising route, along which we believe the future lies. We propose the development of a general theory of systems based upon a mixture of concepts from quantum mechanics, statistical mechanics, and nonlinear mechanics. In this brief article, the mixture can be held together only by literary devices. For a defense of the declarations, and for justification of the physical claims, we direct the reader to TOWARD A GENERAL SCIENCE OF VIABLE SYSTEMS (Iberall (15)), where an extensive bibliography and more rigorous discussion can be found. Present day physics, as we shall show, cannot provide all the theoretical structure we require, but we see in the above three branches of physical knowledge elements out of which a comprehensive, and content-rich theoretical biology can emerge. We call our synthesis a statistical-mechanical view of systems, but it should be understood that the principles we here develop include some not ordinarily encompassed by the classical science of statistical mechanics.

A Statistical Mechanical View of Systems

If, as biologists believe, living systems obey the laws of physics, we might profitably look for explanation of these systems in the forms of ex planation that comprise physics itself. In what follows we briefly review prominent characteristics of mechanical and hydrodynamic systems that have served as the basis for the development of powerful explanations in physics. We believe these features of physical systems offer a useful starting point for the development of a theoretical biology. Therefore, we hope that the reader will follow us through a discussion of those topics in physics out of which we suggest biologists can assemble the answer to the basic question before them: What is the design of life? In the course of this discussion we shall introduce five postulates or propositions, and a corollary, to provide a physical basis for explanation of organization and integration in living systems. These five propositions comprise the physical paradigm we think will gain ascendancy over the biochemical paradigm in biology over the next 25 years.

Components of Explanation in Physics

The physicist explains organization by considering four forces (electrical, gravitational, nuclear binding, and weak) plus a few constants or coefficients (e.g., velocity of light, Planck's constant, Boltzmann's constant, Avogadro's number, electronic charge and mass, the acceleration of gravity), and by using arithmetic. From such primitive building blocks and processes, the physicist exercises his scientific art to build patterns to represent the world around us. His explanations are not totally abstract, even though the primitive construction materials themselves defy explanation.

Stability and Cyclicity in Active Systems

Systems can be regarded as being either active or passive. A passive system is completely dependent for its behavior upon the relatively immediate application of external forces or agencies, and it cannot defend itself against wear and tear, or dissolution, and it does not renew stores of energy through its behavior. Active systems, in contrast, manifest energy transformations and storage for an appreciable period of time. They contain or are themselves sources of potentials. The most interesting class of active systems is that of autonomous systems. These systems sustain themselves by their own activities, and can resist dissolution. All living systems are open, active, autonomous thermodynamic systems. (A few primitive autonomous systems have been built by man - for example, the latest generation of Perceptron-like devices that seek out an electrical socket for recharging their batteries whenever their internal energy stores run low.) To provide an explanation of the design of living forms it is therefore necessary to identify the requirements for persistence of autonomous systems generally.

The notion of persistence implies some notion of stability. If we place a marble in a bowl and shake the system once, not too hard, the marble will eventually return to a point at the bottom of the bowl. This passive system shows a simple, statically stable performance. However, if we put a rat in the bowl, or a man in a swimming pool, we observe instead dynamic behavior, yet both the rat and the man are stable in some sense, since 'ratness' and 'humanness' are preserved in the individuals from moment to moment, day to day, and are only slowly altered by aging. How then shall we describe the dynamic stability of living forms? Bacteria in a bowl filled with a paradisial medium provide a clue, for they show a remarkable dynamic behavior. Their observed behavior is an autonomous, cyclic process: grow, divide, grow, divide, grow, divide ...

In the above cyclic process the bacteria preserve their essential nature, and the system persists as long as the environment provides a rich source of chemical potential to support the processes of growth and replication. More generally, open thermodynamic systems may exhibit either of two relationships with their local environments. Either their local environment exists as a boundary condition providing a constant potential that supports the activity of the system (as in the case of a device driven by a solar battery), or else the system operates by providing its own variable interactions and couplings to its immediate environment, which need not be available as a pure source of constant potential (as in the case of a man). In the former case behavior is limited, and persistence is unlikely because of the limited repertoire of behavior. If the environment changes (e.g., if clouds come by) the system may be doomed. Only in the latter case is persistence to be expected. Of course, the bacteria in the bowl superficially seem to resemble the first case more than the second, because eventually they would die out as the medium becomes exhausted. But actually, bacteria in the world at large with its vicissitudinous environment have not died out! Therefore, they must comprise in the wild a system of the second kind.

These considerations hint that there is a general principle relating the phenomenon of persistence in an open-autonomous thermodynamic system, and the cyclicity of processes within it. The bacteria in the bowl still show the cyclicity that preserves them in the wild, but they do not persist, so we see that cyclic energy transformations are not alone sufficient to guarantee persistence - in addition, there must be a somewhat hospitable environment. The important point is that autonomous systems are able to persist because they can maintain their activity in a wider range of environments than can those systems that fail sooner, and this maintenance of activity always seems to be associated with cyclic energy transformations. The principle is general, and applies to automata made by man, as as well as to the self-constructing automata we call living forms.

Nonlinearities, Cyclicity and Dynamic Stability

Behind the general principle that associates persistence of an autonomous system with cyclicity, lies a fundamental relationship between nonlinearities and periodic behavior. The grandfather's clock periodically taps the potential stored continuously in its hanging weights by means of a nonlinear device called an escapement. Similarly, with all other continuous engines built by man, or by nature, nonlinear processes dominate and these nonlinearities account for the dynamic stability manifested by these machines. The only known stability regime for a nonlinear system whose processes degrade free energy (as all real processes must) is a dynamic stability consisting of periodicities, cycles, or repeated motions.

We can now state the first of several propositions that constitute the new paradigm we propose to account for integration of whole organisms.

PROPOSITION I - All real, active, thermodynamic machines (including all living forms) capable of sustained performance manifest a dynamic stability characterized by nonlinear, cyclic processes. The primitive function is periodic; the basic element of temporal organization is the cycle.

Emergence of Structure

The first proposition, described above, provides a fundamental element of function (temporal organization) but it does not account for the emergence of structure (spatial organization) in a universe presumably moving overall toward a state of homogeneity and uniformity that has been called 'thermal death'. To account for the emergence of structure we first note that the basic form of matter in the universe is atomic (particulate or granular). Second, we note that the particles attract each other from long distances (e.g., by gravitational attraction) and repel each other at close range (e.g., by nuclear repulsion). Interactions are universal, and electrical interactions are especially important at the scale of distances found within living systems. These interactions may either attract or repel.

Systems of interacting particles have an astonishing and important characteristic: as the scale of the system is changed the system may change from continuous to discontinuous, at any one level of observation. For example, water vapor has the smooth and uniform character of a gas at the macroscopic level of observation (in spite of its underlying, microscopic atomicity). However, if we contain the water vapor in a stout vessel, and then introduce one after another additional water molecules, we eventually obtain a new atomicity; a phase change occurs and macroscopic water droplets appear. The change in scale (in this example, an increase in number density) has led to the appearance of a new structure, the droplet.

A more interesting example of the principle that a system of interacting particles will change between atomistic and continuous forms as a function of scale effects has been provided by an experiment performed by G. I. Taylor (see Goldstein (16)). He placed water between two concentric cylinders that could be rotated in opposite directions, and varied the relative velocity of the cylinders. (One could also vary the size of the chamber, or the density of the water by adding solute and creating a solution, or the viscosity of the water by changing the temperature.) In hydrodynamic systems, scale effects are related in the Reynolds number, R, which gives the dimensionless ratio between inertial and viscous forces:

$$R = \frac{DV\rho}{\eta}$$

where: ρ = density
V = velocity
D = length
η = viscosity

As is well known, at values of R below a critical value, fluid flow is smooth (laminar), but above that value it may become turbulent. Taylor showed that as a result of scale effects only (increased velocity) laminar flow would become turbulent, and the turbulence would progress into stable, organized patterns or vortices, often with complicated geometrical structure. The phenomena described above lead us to the second general proposition:

PROPOSITION II - Although matter is fundamentally atomistic in character, it has continuous properties if the scale of observation is large compared to the mean free path of the particles, and if the time of observation is long compared to the relaxations after collisions of the particles. New (atomistic or quantized) structures will emerge from the apparent continuum as a result of interactions among particles, scale changes, and constraints (such as initial and boundary conditions, etc.) on the system. These three agencies (interactions, scale, and constraints) account for a universal tendency for structure to appear out of chaotic, random, atomistic backgrounds. As a result of this tendency, all systems may be viewed as consisting of a hierarchy of atomistic (A) and continuum (C) levels: ACACAC ...

As an example of the applicability of proposition II to living systems, consider the properties of lipid/water systems. If the lipids are amphipathic, the interactions within the mixture lead to spontaneous organization into membranous structures or micelles if the scale of the system is favorable. Similarly, separated components of phage particles can reassemble spontaneously from a more homogeneous solution of smaller component particles. Thus, we see the principle operating in the transition of water gas to water liquid, of water liquid to geometrically complicated vortices, of lipid/water emulsions into membranes, of proteins and nucleic acids into the phage virus ... of man into families, families into neighborhoods, neighborhoods into cities ... of stars into galaxies ...

The Fusion of Structure and Function

Proposition I offers a basis for temporal organization, and proposition II offers a basis for spatial organization. But an autonomous system must fuse the two characteristics so that its function can maintain its structure. It is in this fusion that autonomy can be created, and it is here that living systems are commonly thought to be too rich in behavior to be described by known physical principles. Yet we take a contrary view. We postulate that the nonlinear mechanics accounting for the emergence of temporal organization and the statistical thermodynamics accounting for the emergence of spatial organization merely describe different aspects of a more general physical tendency we have embodied as a third proposition.

PROPOSITION III - The combination of the effects of scale, constraints and interactions in a system of interacting entities always produces a tendency for the local emergence of structures capable of persistent, cyclic energy transformations and self-preservation.

At this point the reader may wonder if we are not deducing physics from biology instead of providing a physical basis for understanding life. Unfortunately, the physical issues we address have not been popular in physics itself, where most of the conceptualization has dealt with idealized situations. Our hypotheses address exactly those aspects of physical reality that arise out of the interactions and constraints that cause systems to be 'nonideal'.

The notion of nonideality is closely tied to the analytical intractability of the equations describing a system. Nonlinearities, inhomogeneities, nonintegrable constraints and interactions lead often to equation sets for which no closed form solution has been shown to exist. Therefore, physicists have had no clear way to proceed with attack on those problems we here emphasize. Since this article addresses the future, it seems unnecessary and unwise to confine ourselves to the established physics or to the established biology to prophesy it. We believe that a general systems science built along the lines indicated here and more completely in the book, TOWARD A GENERAL SCIENCE OF VIABLE SYSTEMS, (Iberall (14)), will contain the explanatory power sufficient to encompass living systems. In the next 25 years we see physics being inspired by the problems of the life sciences. The resulting solutions will be in terms of the evolving physics. That evolution seems to us to require a synthesis of some of the themes of quantum mechanics, statistical thermodynamics, and nonlinear mechanics.

Scientists differ in their tolerance of mystical extensions of their fields into new domains. Some prefer rigor at all points, and accept the narrow range of problem solving that results from their choice. Others, like us, rely on an informed intuition to press the boundaries of their science and extend its range. When such efforts are successful and useful, rigor follows. In the interim, the appeal is to intuition, and the value of the theoretical effort is unclear. But if the future were clear, why bother to predict it?

Invariants

A chief aim of science is to identify the invariants in any phenomenon of interest. In mechanical systems, following collisions, the invariants are the individual, total sums of energy, momentum and mass. In a crude sense we can say that the 'goal' of a mechanical system is to conserve these quantities (called summational invariants). The properties that Monod has found especially descriptive of living systems are heredity and evolution, self-construction, invariant reproduction, and goal-directed behavior (Monod (2)). These properties are richer than those seen in mechanical systems, and their richness suggests that living systems have at least one additional invariant whose conservation or satisfaction may be said to be a goal. We propose that the additional summational invariant is preservation of population density (i.e., number of functioning organisms from generation to generation).

In every meeting or coupling between person and person, cell and cell, the goal is to preserve each organismic mechanism, each cell, and at the end to replace one mechanism with another, its offspring. Biological ensembles surely behave as if they mean to persist in numbers, and thus attempt to preserve number at all levels, from macromolecules to whole organisms and individuals. Both number and function will persist. If you remove one kidney, the other will hypertrophy; if you remove all but one bacterium from a container of enriched medium, you will soon find several billion.

Since populations may grow or dwindle, the invariant described above has a slightly different character from those of simpler, mechanical systems. It is not the absolute number of individuals that is defended, but rather, the tendency for interactions to be carried out so as to assure that there will always be some functioning individuals left is invariant. This tendency is seen directly in the invariant replication of DNA, and less directly in the vigor with which threatened social groups attempt to ensure their persistence (and dominance) by encouragement of profuse breeding of their kind. (That this invariant tendency has led to the difficulties of overpopulation for some human societies hardly denies the existence of the tendency - it merely attests to its strength.)

The additional invariant constitutes proposition IV:

PROPOSITION IV - Systems that arise spontaneously and preserve themselves as individuals act also to preserve their kind, often through interactions with others of their kind. In the simplest case, periodic crystals seed the growth of additional crystalline structure. In a more complex case, the aperiodic fibrillar crystalline structure of DNA tends to duplicate itself (even without the aid of catalysts). In the most elaborate case, men and women have children.

Selection for Compatibility and Fast Processing - Matching of Information and Power

As a system emerges according to the propositions we have set forth, the form that persists is the one that is selected by the system itself to assure compatibility and fast processing. It is not only competition among organisms that exerts the immediate selection pressure, but competition within an organism among alternative forms. Monod has aptly remarked in this vein: "... any 'novelty', in the shape of an alteration of protein structure, will be tested before all else for its compatibility with the whole of the system already bound by innumerable controls commanding the execution of the organism's projective purpose." (Monod (2), page 119.)

Eigen has developed an impressive acount of the physical issues involved in the evolution of biological macromolecules (Eigen (17)). From his themes we conclude that fast processing can lead to dominance. If several system elements compete for the same materials, the faster elements will be better assured of persistence in numbers. The same principle of selection operates as effectively between organisms or species as it does within organisms. We consider it as our final proposition.

PROPOSITION V - A persistent, autonomous system by its physical nature is ultimately forced to select from among alternative internal processes those that are most compatible with its persistence, and these usually are the faster processes. Among autonomous systems, those capable of faster processing (faster transfers or transformations of energy, matter and information) tend to exclude or dominate their rivals for the available sources of power, whether or not these are limiting.

Fast and effective transfers or transformations of energy, matter and information always require efficient coupling between information fluxes and power fluxes, and it is the above selection principle that accounts for the impressive operation of biological controllers. Their principles of optimization appear to be those of proposition V.

Reliability and Integration

A theme common to all five propositions is that persistence, and therefore reliability, of processes is likely to occur in systems of interacting entities. As a corollary, we conclude that under geophysical constraints, life is probable. Integration of structure and function, of parts with other subsystems, of information flow with larger scale thermodynamic processes will tend to arise spontaneously. The deep issues raised by the reliability of biological operations have been well discussed elsewhere by Pattee (6).

We conclude that a comprehensive and meaningful explanation of integration of the whole organism must take into account the fundamental properties of all autonomous systems. Any theory that does not do so will be incomplete. The combination of partial insights from statistical mechanics, quantum mechanics and nonlinear mechanics embodied in our five propositions, we believe provides a physical basis for the expectation that order will always tend to arise out of chaos, and that cyclic thermodynamic engines will always tend to appear and sustain themselves. If this is so, then the mathematics of dynamic processes may permit us to gain insight into the interactions and constraints, and thus into the directions which evolutionary unfolding may take, through chemistry and into life.

From our view that biosystems are ensembles of nonlinear oscillators, coupled and mutually entrained in various clusters at each hierarchical level, new descriptions can be derived for their stability, their remarkable time-keeping properties, and their metabolic and behavioral states, all of which now lack precise designations. But, most important, we can expect to be able to rationalize with the new theory the behavioral goals of biosystems, including man, by encompassing them within the general requirements for stability and persistence shared by all autonomous, open systems in our region of the physical universe. That, we believe, is what it will mean to say at last that we comprehend the design principles underlying the integration of whole organisms.

Experimental Tests - Biospectroscopy

We have attempted in the foregoing to pose a question central in biological science today, viz., what is the physical basis of organization? We then proposed a direction in which the answer may be found. In describing the direction we have dealt with theoretical considerations. We now turn to some possibilities we see for experimental validation that will be required along the way if any systems theory is to have acceptance in the life sciences.

Scattered through the biological literature are various unrelated accounts of periodicities, with periods ranging from the domain of milliseconds to years. Cycles of one day (the circadian rhythms) have gained most attention because they are conspicuous, and often easily entrained by daily geophysical rhythms of temperature and light. There is little doubt that daily cycles of solar radiation were influential on the course of evolution at a stage when photochemical reactions were incorporated into life processes. However, only a tone deaf biologist would insist on hearing merely the the circadian pitch in the symphony of processes that characterize life.

We predict that an important aspect of experimental work in the next twenty-five years will be the development of a disciplined field that one might call 'biospectroscopy'. Experiments will be conducted with proper sampling technique and precautions to minimize errors, such as those caused by sampling too infrequently, in order to discover both in the power flux domain and in the information flux domain, at all levels of organization, those many particular frequencies at which business is conducted. We predict the discovery of numerous oscillators and evidence of their mutual entrainments. Hints of causality in biochemical chains will emerge from correlations of frequency, instead of from correlations of magnitudes or levels only, as is now the case. (Correlations do not prove causality, but they raise questions of causality, and the human mind finds a strong temporal correlation highly provocative in the formulation of hypotheses. As experience shows, it is rightly so. Unfortunately, mathematical techniques for correlations of frequencies in nonlinear systems are so far poorly developed.) The experimental description of integration of structure and function at the level of the whole organism will in the future give new emphasis to fluctuating processes, and less to constancies and static morphological structure. We expect to find this new emphasis applied to biochemical processes within cells, to metabolic and endocrine phenomena among organs, and even to the most difficult case of all - that of animal and human behavior.

Although much data in the field of experimental psychology are in the form of frequencies (of pecking or lever pressing, etc.) little data on behavior provide a spectral description. That is, the data do not show the distribution of frequencies within the system in a particular state. Thus, the new emphasis might even contribute to a fresh view of human 'personality' and behavior. For example, the past two decades have made much of the content of human sexuality. The content of the sexual mode may be autoerotic, homosexual, or heterosexual. We do not dispute the pertinence of such data. However, we point out that simultaneous considerations of frequencies of hormone, metabolic and behavioral events also provide a basis for classifying sexuality. The endocrine system discharges independently of the love object. A person who is sexual (toward whatever object) twice each day differs from one who is sexual (whatever the object) only twice each month. The goal measures of the two systems cannot be the same, nor can the requirements for internal system stability.

To illustrate the spectroscopic approach, we show in Table I the various discrete behavioral modes of humans. We believe that there are twenty such modes, though the exact number can be settled, if at all, only by experimental observation. The table also specifies our estimates, based on a variety of reading and personal observations, of which modes are periodic, and which are not. We have further specified a mean (ensemble or population average) period or frequency for the periodic modes. Matters of interest in this approach are the transitional probabilities from one mode to another (i.e., if you are in mode 9, what is the likelihood that you will enter any one of the other modes next?), and the historicity of the path through the modes (i.e., how do the modes entered in the recent past affect these transitional probabilities into the future?). For a fuller discussion of the underlying principles, the reader may consult Bloch, et al. (18). Here we merely point out that experiments designed to fill out the matrix in Table I are likely to lead to fresh descriptions of both normal and abnormal behavior, and the effects of therapy. A full account of a behavioral state would also provide spectral analysis of the endocrine and metabolic processes associated with each of the periodic modes. When such data are available, we predict that we will at last glimpse the design of man in the light of physics.

Postlude

We have sought the foundations for a suitable, general theory of systems that can account for integration of structure and function at the level of the whole organism, as well as for evolution and adaptation. Others also have already begun the work. Foreshadows of the edifice to be built are present in the work of Monod (2) and Eigen (17). In Eigen's brilliant discussion of the evolution of macromolecules, and in the notion that selection for fast processing may itself lead to organization in the forms of closed cycles of catalytic activity, we find a basis for the expectation that such catalytic loops will preserve all their members, and that thermodynamic engines will appear. Our general views and those of Eigen appear to be close, although a sense of the specific details are developed more extensively by Eigen. A different example of a biologist's view of dynamic organization may be found in the review by Kushner (19).

We have published elsewhere a first attempt to develop in detail a biological systems science based upon the principles discussed in this article (Iberall (15); Bloch, et al. (18)). We have there begun to review the increasingly rich literature documenting the existence of periodicities in biological processes. We know that biologists, however imaginative and given to theorizing, are ultimately respectful of experimental results. Therefore, we believe that it is the accumulation of hard evidence that nonlinear cycles are ubiquitous in the biosphere (and, as we have indicated, in the physical universe generally) that will force the development of a biological systems science based on the principles of nonlinear mechanics and statistical mechanics in the direction we have described above. No one disputes that the heart beats, mammals breathe, brain rhythms persist. However, whether or not periodic behavior is part of a general strategic design is the question at issue.

The choice of experiments to be performed in the future requires the making of a decision according to a policy. The policy to adopt a spectroscopic approach to biological systems will either be formed slowly out of the pressures arising from accumulated evidence, or it can be adopted more rapidly on the basis of theoretical considerations such as those presented in this paper. Our hope is that this paper will catalyze the development of that systems science necessary for explanation of integration at the level of the whole organism. If so, it is ironic to note that the authors will have performed the function of - an enzyme. But perhaps that is after all the true nature of life processes, for among the bees it is not workers that beget workers, nor drones that beget drones. Instead, catalysts beget catalysis!

Table I

Behavioral Modes of Man

(Reprinted from Bloch et al. (18))

Mode	Periodic?	Estimated free-running period or frequency
1. Resting	yes	10 min, 2-3 hrs, 5 days, 3 months
2. Eating	yes	2-4/day
3. Drinking	yes	4 hours
4. Sleeping REM non-REM	yes	1-2/day
5. Voiding	yes	4/day urine 1/day feces
6. Grooming	yes	10 mins
7. Changing posture	yes	1-2 mins
8. Using body (exercise, play, gross motion)	yes	90 mins
9. Working	yes	2-3/day
10. Being sexual	yes	3 days
11. Relating to others Loving Caring Cooperating Stroking, touching	yes	4/day

Mode	Periodic?	Estimated free-running period or frequency
Conversing		
Sheltering		
12. Fantasizing	yes	100/day
13. Withdrawing, escaping	no	--
14. Attending	yes	--
Arranging		
Planning		
Problem-solving		
Learning		
Studying		
Creating		
Being introspective		
Reading		
Thinking		
15. Being aggressive	yes	--
Competing		
Striving		
16. Contending	no	--
Fighting		
Hating		
Being hostile		
Being angry		
17. Being acquisitive	yes	--
Being greedy		
Stealing		
Cheating		
18. Envying	no	--
Being jealous		
19. Feeling loss	no	--
Grieving		
20. Fearing	no	--

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VI. REVIEW OF J. MONOD'S CHANCE AND NECESSITY

A number of reviews of this very important book appeared late in 1971 (e.g., Science, N.Y. Review of Books, N.Y. Times). Since the problems raised by Monod were problems similar to those that had confronted us in the kinetics of biochemical processes at the membrane level and in our discussion of the integrative organizational level, it seemed that the best thing we could do was to review the book. (For Search, intended for the July-August 1972 issue. It is now a defunct publication of the Innovation Group, which also published Innovation. They ceased publication, with the review in galleys, as of July 4, 1972.)

Jacques Monod, CHANCE AND NECESSITY, Alfred A. Knopf

The technical thesis of cybernetics, the organism's command-control system acting by feedback, was developed by Wiener, von Neumann, and McCulloch. The aim of bicnics, a technical extension of cybernetics, was to discover whether principles of biological organization might have applications in other areas of technical design. That aim is being realized, and thus there is a growing need for better understanding of biological principles by non biologists. Very few engineers have been willing to undertake the prerequisite multidisciplinary studies.

Monod's book contributes a fundamental cybernetic view of organization of the living system at the primitive molecular biological level. It deals with the concepts of organization in living systems and the implications of a genetic code for all levels of purposeful organization.

His first thesis is that reliable and invariant reproduction precedes purpose in all living systems; purpose being directed, coherent, constructive activity. Purpose then emerges by selective evolution. This differs from the vitalists' view (e.g., Bergson's vital force) and from the implicit animism in dialectical materialism according to which there is a perfect mirror of reality in the mind. The appearance of living organisms was not foreordained by the general laws of nature or by the general evolution of the universe. Their appearance is compatible with but not predictable by such laws.

Monod's second major thesis probes how and why protein is the essential molecular agent of purpose. In principle, he believes any purposive performance in a living system calls for geometric specific interaction. (To suggest an analogue at the management engineering level, it is not the brilliance of the elite manager-engineer that creates the purpose of an organization, but his forceful thrust in seeing to it that all of the essential ordered and directed functions required by his organization actually take place.) Monod starts from the fact that specific shape and handedness of protein molecules in solution permit them to recognize each other and assemble, similar in part to the repetition of molecular crystallization. Structure and function are revealed rather than created by the assemblage. He suggests a similar character for the formation of organs, which ultimately grow out of the same geometric specificity by dynamic, not static, processes.

> In the reviewers' opinion, the second thesis is inadequately defended, since we must conceive models for building all structures out of a few physical forces. We are plagued by intervening details. We could say that purpose lies in the basic subatomic forces that can invariably assemble such specific molecules. They are, just as remarkably, always assembling nuclear particles into molecular systems. But people also assemble systems. Purpose then could be said to emerge <u>ab initio</u> at every reliably reproductive level.

As Monod sees it, a specific molecular action may be described as one in which the state of many inputs will determine an output state, which will itself control a power amplifier. Basically a propositional logic controls the amplification. It may not be only binary, but it is not much more complicated than logic networks currently in use.

> It would appear that we have adopted this notion from the onset of communications engineering (1920's), or feedback (1930's), or of analogue and digital computation (1940's, 1950's). The switch function is also very similar to McCulloch-Pitts neural net modelling. But it has clearly turned out that the nature of mind still is not revealed by such information processing tricks.

> Unfortunately, in our view, this thesis of Monod's cannot flower. Just as Wiener confused feedback with purpose in cybernetics, so Monod confuses purpose with control of a speed of reaction by catalytic switches. Namely to regard a system that compensates for deviat[illegible] by a particular rule as purpose is utterly misleading as to the [illegible]ptive motion of purposeful systems toward a goal, independent of the many kinds of disturbance and independent of the means of taking corrective action. Yet Monod is right about the nature of biochemical reaction rate control via catalytic enzymes. The nature of the primitive step of controlling biochemical specificity throughout the body is validly defended. The stretch to extracting complex organism purpose is not.

Monod notes that the control system uses a purely machine code, a propositional calculus not bound by chemical constraints "which makes each organism an autonomous functional unit, whose performance appears to transcend the laws of chemistry if not to ignore them altogether", i.e., the control system uses a purely formal language. At succeeding levels (e.g., organs, including the nervous system and endocrine system) there will still be dependence on molecular processes based on proteins with geometric specific recognition properties, again with a machine language.

> Once more it becomes necessary to assert that an automatic machine language is not sufficient to define purpose. Some dynamic structure beyond a machine logic is required. Thus, to claim that this elementary "cybernetic network in living beings far surpasses anything that the study of the overall behavior of whole organisms could ever hint at" suggests a lack of sufficient study of complex systems. The reviewers would agree that a vague general theory of systems has little merit, but a well founded dynamical theory of systems would be of great use. The issue raised is not whether living organization can be explained by physical law, but what reductionism is complete enough to encompass purpose. The machine logic of multi-input switch enzymes is not sufficient. As one operational mechanistic scheme, it certainly is basic and important. The physicist too could claim that purpose emerges from elementary forces and the specificity of a few particles - electron, proton, neutron, and photons. When one applies statistical mechanics to ensembles of active entities only a few measures emerge for the assemblage. These measures are the so-called summational invariants.

As his ultimate reduction Monod points out that the genetic code begets the genetic code, i.e., the 4 unit nucleotide language of DNA codifies the linear amino acid chains, which fold themselves into geometric specific globular proteins, which furnish the geometric specific enzymes, which govern the chemical direction of life processes. Furthermore the code provides the very highly specific nature of life's invariant reproducibility.

But the code is changed only by chance, by mutations. The experimental content of life provides a selection pressure for evolution. To prepare for the transition to the problem of living organization at the level of man, Monod points out that at higher levels of organization (e.g., the organism) two frontier problems still persist: the origin of life, how the code itself could have come into existence; and how chance and selection pressure could lead to the comple·ity of the higher nervous system. Differing with the current empiricism of science, Monod proposes that purpose is not directly or innately codified in the genetic code, but is only a patterned program of performance that unfolds through experience. With no experience there is no unfolding. The full import of that will have to become explicitly clear to would be manager-engineers. You don't learn sex or selling from a code book, you learn it by a sequential experience which permits you a readout at the right error rate. All processes including language, learning, and cognition, Monod believes, emerge this way. But cumulative experience is only wrung out by chance.

The first two thirds of the book are concerned with outlining Monod's molecular thesis. How the genetic code expresses itself is elegantly told.

Then the last third of the book explodes with the germ of ideas all latent in Monod's view of the genetic code. Evolution comes into being as an irreversible process. Species react to their environments. Their purposive performance places a selection pressure on their gene pool. Inevitable chance mutates the DNA of the genetic material. Selection pressure, 'necessity', selects the course of emergent species evolution.

Selection pressure on the upstanding australopithecines, on a cortex structure whose evolution for ideation barely kept ahead of physical evolution, finally forced articulate symbolization. Language was born. Thence culture was born. This in turn created the selection pressure and survival value of intelligence. While in lower animals coordinative and representational activities take place in the brain, in man the cognitive functions of registering and grouping events and incorporating experiences into them, and of simulating events and programs of action are added. There can be and is an innate cognitive frame of reference in the genetic code. Though human behavior involves elements acquired through experience, they are acquired in the social cultural milieu by a program. That learning program is man's genetic heritage. It is the simulation function which is the unique characteristic of man's brain. On this language rests.

Cues for man's social behavior are discussed in Monod's last chapter. Simulation and language made man master of his domain. They created pressure toward group behavior. But having mastered his environment, man's own species became his only adversary. Tribal warfare became the important evolutionary factor. Now cultural aspects push man. Intelligence, ambition, courage, imagination are the current factors of personal success. These ultimately select the genetic direction.

Peers among the human species are now faced with selecting wisely. Tribal evolution created the need for explanation and myth. They provided an ontogenetic program for man, and stabilized his societies. Man otherwise hasn't the simpler genetic stability of the social insects, whose program of inheritance is automatic, chemical. He requires myth and religion, an idea easily connected with animism - whether religious, Marxian, or utilitarian. We face the choice of objective truth, science or knowledge versus a selection of values. But ultimately objective truth must be based on a theory of value. "Authentic" discourse or action is the junction at which knowledge and value combine. It is an ethical judgment that makes a man act to acquire knowledge in accordance with objective truth. Man and man alone can make that choice. It substitutes for animism. It makes man a lonely creature, devoid of myth.

Thus Monod has raced from the protein molecules to the policies of man's authentic actions in a world with a future over which man may have some say. Is there any other significant construct for organization? The reviewers doubt it. The sketch is there; the details, particularly dynamic, physical, and hierarchical, are not.

VII. ON GLOBAL STABILITY: A STRATEGY FOR ITS ACHIEVEMENT IN VIABLE SYSTEMS

However the problems posed by Monod's book and the aspects of systems not treated in Iberall's systems' book, namely startup of systems, suggested that we try to say something about self organizing systems. The following essay is a first attempt. It also provides a first attempt at a dynamic view of catalysis, particularly as it may be relevant to biology. It is inspired at least in part also by our companion piece on molecular kinetics.

Background Issues

1. In a recent issue of the New York Review of Books there is a provocative review by Stephen Toulmin of Jacques Monod's CHANCE AND NECESSITY (1). The question Toulmin debates is whether Monod's call for the reintegration of fundamental biological theory with natural philosophy and social sciences has properly dealt with past developments in the philosophy of science. Do Monod's details of molecular biology cast any new philosophic light of which intellectuals were not aware (except for these details)? Toulmin says not.

2. This dialectic is made even more significant to any reader who will go to the trouble of inspecting, say, Toulmin's THE ARCHITECTURE OF MATTER (2). One will find therein a very perspective discussion of western origins - how the issues of the physical sciences took shape and form from the Greeks of the 6th to 4th centuries B.C., and how, essentially arguing back and forth, the same threads were pursued in detailed form right up to 'now' (1962 at the time of his writing).

3. The present author is a physicist-mechanical engineer who has developed his interdisciplinary science capability by working in many scientific-engineering fields. An outgrowth of that interdisciplinary outlook is contained in a recent book (3) in which the task of developing a technical paradigm for complex systems overshadowed the issues that Toulmin raised, namely that science must be philosophically based and philosophically sound. Recognition of that issue at this time has served as the trigger for this article.

4. The modern day scientist is generally ashamed of his philosophic thoughts. Like sex in Victorian times, it strikes him as a distasteful subject to discuss in mixed company (of layman and scientist). Yet one might note that, in every scientific discussion, the discussant's philosophic slip is almost invariably showing. (To carry the analogy one step

further, a perceptive male or female generally has great difficulty in carrying on a purely intellectual discussion with a member of the opposite sex who is handsomely and sensually endowed, according to the participant's cultural standards. In primates, the usual simple discharge of such an engendered tension is a copulatory act, not prolonged verbal discussion.)[1] However, one of the difficulties in achieving some kind of status for interdisciplinary effort is the developing of keen appreciation of the subtle postures of outlook and the required amenities of discourse.

5. It was not clear to the author, during the early years of his career, that interdisciplinary science was a taboo area. In fact he was encouraged, in best Horatio Algerian fashion, to undertake interdisciplinary science by the host of problems he was confronted with in 30 years of performing and directing research. But he can state with dogmatic certainty that interdisciplinary science (i.e., engaging in interdisciplinary scientific research) is not a marketable commodity today, and likely never has been. The specialist is always ready to tear interdisciplinary practitioners down. He has also learned, but much more recently, that the same conclusion is true with regard to the reaction of academic 'peers'. (The vested interests of the academic, as keeper of scholarship for example, never allow him the open luxury of permitting such strange free roaming beasts.)

What is wrong with the specialist's criticism? It is simply that the specialist is never right indefinitely. Thus more than one outlook ought to be tolerable. "Ah, yes, but -" the specialist would reply, "those outlooks that are debated out of turn, either before their time or after their time, just confuse current issues and understandings." So what? Particularly if some broader integration of outlook is possible.

6. The author is quite conventional in most ways, with his own hangups and difficulties, but he has a major point for which he is making a plea, to specialist colleagues and other educated persons. His concern is not with scoring intellectual points but in influencing thoughtful men of action.

In a well ordered world, he sees the need for the following hierarchy

[illegible] author intends nothing vulgar in his dual identification of intellec- [illegible] and sexual posturing The socially secure scientist is generally un- [illegible] the full formal ritualistic nature of his presentation. By rais- [illegible] issue and making him somewhat aware of the form it takes in another [illegible] - where he can see the dramatic phylogenetic differences in a primate, as viewed in Jane Goodall's I[illegible] THE SHADOW OF MAN or in turkeys, well described in Scientific American (June 1971) - the intent is to persuade him to examine his own rituals. Also the perception is not being offered by an 'outsider' (though the specialist may deny this) but by a human being who belongs to the same order, namely 20th Century Scientificus Americanus.

of intellectual activity, all leading, in turn, to action:

a) There is a need for scholarship of the past. This is a purely academic role. It generally behoove. others to have some greater or lesser idea of history.

b) There is need for free philosophic-scientific speculation. This is in the main an academic role. Taking time out from 'doing' activities is otherwise a luxury, often requiring some kind of 'withdrawal', perhaps but not necessarily to an 'academy'.

c) There is then need for directed research. This, in the author's opinion, is not an academic role, although academics could step out of their other roles to perform this function.

d) There is the subsequent need for applied research and development.

e) Beyond that, hastening to end the line, is the need for development engineering, production engineering, marketing 'engineering' (and all the other managerial engineering tasks), product testing and evaluation and maintenance engineering.

Since a management manual is not intended, but only a light introduction to scientific-technical function, no further details are offered.

The essential point is that there is a line of scientific-technical functions which starts from the philosophic and leads to the practical, that those functions cannot be performed by one person (or one type of person), and that there is uncertainty as to where the philosophic-technical integration might take place. To fill in this gap, one must pursue this line of needed technical function with some discussion of contemporary problems.

7. Heretofore in human society, men were dealing with so-called non-interacting problems. The coupling between institutions and the modes of behavior of man were very limited. Individuals, local communities, countries could fairly well solve their own problems themselves. They were masters of their own fates. With the growth of an industrialized society, beginning in 1918 with Henry Ford's mass production line (interchangability of parts, an essential ingredient, had begun 50 years earlier; while the explosion of powered machines had begun 50 years earlier than that), the institutional means of dealing with men's problems changed. Society began to be interacting. In 50 years, the consequences of that interaction has fallen upon us. We are now faced by the economic problem. Economics, in its modern definition, is the competition for scarce resources by which men deal with the production and distribution of those goods which represent man's needs. (Man's needs are indefinite; they evolve and grow in time.) Economics thus represents a rate limited problem of dynamic interaction among many factors. This is technically a dynamic systems' problem, and

it happens to be the technical fact that man doesn't yet know how to deal technically with such complex interacting systems' problems, either with regard to their design, analysis or synthesis. It is still a few years premature to say so, but the economic costs of maintaining our future society have not yet hit us.[1] It is the increasingly urgent requirement for understanding the design and analysis of complex systems which prompts this article.

The need to write such pieces becomes even more urgent when the technical practitioner realizes that 'suddenly' our society no longer gives a tinker's dam(n) about science and intellectual endeavor. It will exacerbate the discussion, but the reader should note that there is a sharp division in technical circles between those who think that the academic and a particular industrial complex oversold the roles of their scientists and technologists in the post-World War II period and those who don't. Let this remark stand for the social-political aspects of the problem.

Some Previously Discovered Principles

1. In mid-19th century, Claude Bernard came to the following, now classic, view of the biological organism. "It is the fixity of the milieu interior which is the condition of free and independent life", he wrote. "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". J. S. Haldane stated "No more pregnant sentence was ever framed by a physiologist". Fifty years later, Cannon denoted this central principle of living systems as homeostasis, the maintenance of near constancy of the operating internal variables of the living system after being subjected to external disturbances. In technical terms, one would say that the system regulates its variables.

2. Starting in 1940, the author began to make thermal, respiratory, and metabolic measurements for what were originally limited mechanical objectives. How shall a man's respiration be supplied so that he can survive in high altitude flight; what garments or coverings could one put on a man to permit him to operate in the vacuum of deep space, with regard to mobility, respiratory sufficiency, hot and cold temperature extremes, and low gravity? These measurements began to reveal something that is conceptually obvious in a technical abstract sense.

3. If a complex biological organism (we will generally imply the human as a prototype) is to be prepared always, to undertake autonomous

[1]See, for example, a note that the author put into a recent Congressional hearing on water. It is estimated that about a $10 trillion investment is needed over the next 30 years to provide a number of basic social-ecological necessities that heretofore were free or of low cost, (e.g., water, air transportation, defense, education, material resources, health).

action, then it must be internally powered by engines. If the complex biological organism has an autonomous life (as opposed to being constantly hauled back to the workshop in which it was created for recharge, or in someone else's garage and repeatedly tampered with to make it work), then it most likely must preserve its identity from epoch to epoch within its lifetime by some sort of internal coding These two principles, one might assume, have a sound and common physical and metaphysical (i.e., philosophic) basis.

4. Consider the first concept. In physics, the overriding principles are embodied in the laws of thermodynamics, i.e., one requires that processes are consistent with thermodynamics. Now, in thermodynamics, two kinds of processes can be visualized. In one, degradative thermodynamic processes, the disorderliness of its energetics increases. That is, the system undergoing the process loses energy, generally in the form of heat, to the rest of the universe. In the other, a cyclic process, called a thermodynamic engine process, can be brought into existence. This process, too, is lossy and degradative in its energetics, but it can do something about it. While its operation also places a charge on the orderliness of energy in the universe, the system can pay for that loss but keep some of its aspect variables in sustained cyclic motion. Forever? No, only for the life of the system. To run the system for a long time there must be a large stockpile of stored, highly ordered energy, and the engine simply acts to convert this energy in a rate governed cyclic process. Another limitation on the system's 'life' is that its working parts eventually wear out or disappear. The mathematical process that describes the system's normal operation is known as a limit cycle. If too little or too much energy is fed into the engine per cycle, the engine increases or decreases its energy intake in such a way as to maintain - always as the limit - some form of cycle. This so-called nonlinear mechanistic scheme is a regulator of sorts; it is best described as a cycle or frequency regulator.

5. Consider the second concept. If there is no external tampering and the system comes to a near equilibrium (which means that somehow it arrives at a state where on the average it puts off as much as it takes in, namely such quantities as size, shape, other primitive characteristics reach near to some 'final' state), then one must surmise relatively fixed structures to achieve the near constancy of function. Again the same thermodynamic consideration arises. It is most plausible too that these ongoing functions (of maintaining form) are achieved by thermodynamic engines. Since these are not being incessantly tampered with, when near equilibrium, even the structure of the engines cannot keep changing. Thus form or formal processes once again suggest frequency regulation.

6. In the early part of the 19th century, the French mathematician Fourier, proposed a remarkable theorem. He pointed out that any functional form (namely any functional variation in time) can be represented by a unique sum of simple periodic functions. The particular form of these

functions is known as simple harmonic motions, namely the kind of simple back and forth variation or oscillation that you get if you watch the bob of a swinging pendulum. There are various niceties about Fourier's theorem which are too specialized to discuss. Simply put, any variation in time, unless it is much too wiggly at any point, can be represented as a sum of simple periodic variations. If the variation in time is itself periodic, then the sum is made up of a countable series of such periods;[1] if not, the number of such simple periods forms a continuous spectrum.

Now this is of course a very abstract idea, but the concern here is the relation between the abstract mathematical idea of representing function by periodic phenomena or oscillations, and the idea that physical function must be achieved by thermodynamic engines, cyclic processes, or oscillations.

7. Measurements made in biological systems (of metabolism, temperature, oxygen consumption, respiration gas volume, blood fuels, red cell number, hormones) gradually revealed a discrete spectrum of oscillations. When these observations were added to the obvious periodic variations in behavior (living things sleep, eat, void, copulate, reproduce, grow - all processes showing largely repetitive character) it was finally realized that the thermodynamic engine process must be the foundation for all essential actions of the living system. This discovery has been epitomized as a principle, the principle of homeokinesis.

8. One must note that the principle of homeostasis carried with it no concept of its realizability. According to homeostasis, a system must maintain its identity in both its form and its variables. But how? Individual processes are noted, but the question is not answered in a general way by physical principles. All through these arguments the issues of philosophy and physics interact.

In 1965 (4), the principle of homeokinesis was put forth. "The exploration of the dynamic characteristics of the biological system, of the fundamental role of homeostasis, and of limit cycle oscillators, particularly for regulation purposes in the biological system, led to a much broader generalization that <u>all internal systems in the biological system consist of limit cycle oscillators, and that the system is governed both chemically and electrically by moderating the stability of these oscillators.</u>" This principle is essentially a dynamic extension of the principle of homeostasis. It provides the operational thought that the preservative functional characteristics of the living system emerge via thermodynamic engine cycles.

[1] Namely you can count them off as 1, 2, 3, and so forth, whether a finite number or even an indefinitely large number of periods is required.

To some extent, the principle of homeokinesis has been gaining acceptance. To illustrate, the author is involved with a group of highly regarded biological collaborators who are engaged in fashioning a biological systems science (5). They have been willing to accept homeokinesis as an operational principle, as a basis for a modified paradigm for biology.

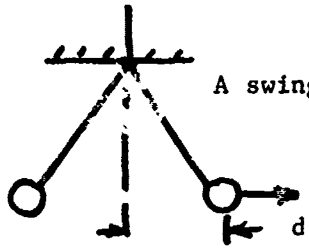
The discovery of the concept of homeokinesis in 1[illegible]5 was tied to the realization that the same nonlinear nonequilibrium thermodynamics[1] which led to limit cycle oscillators also lies at the same base of all viable dynamic systems. Thus the author also proposed in that report "General systems dynamics. The problem posed of decoding the biological system, namely of finding a physical foundation, other than the general laws of physics and chemistry, for viewing the dynamic complex that is the macroscopic human animal, has led to a new concept of the regulation and control dynamics of physical systems in general. The central formulation of control theory, as a general problem in non-linear mechanics, is to analyze and synthesize those physical systems that can be represented or designed for within a narrow slit perpendicular to the 'displacement' axis in phase space, regardless of disturbances, both static and dynamic. (This definition is for the simplest case, the analogue of the positional servo.) This formulation is meant to replace the formulation of comparison of output with a reference at an error summing node, and the operational amplification of the error to take corrective action. The former is more general, and includes all dynamic problems that are associated with regulation and control. The brevity of formulation should not be mistaken either for naivete or simplicity. (For example, the general physics of dynamic systems may be characterized as dealing with the exposition of systems that can be represented anywhere in the phase space.[2] Control systems are only moderately more restrictive.) Characteristic behavior that emerges is the dynamics and stability of both static and dynamic regulators; control dynamics both as a near-linear decay toward the control equilibrium, or as a non-linear limit cycle oscillation, as in 'bang-bang' control."

What that mouthful means is that whereas most engineers have been caught up in the web of feedback as the basic cybernetic principle by which systems work, here another basis was offered. It was not simply a matter of feedback that maintains life processes by comparing an output

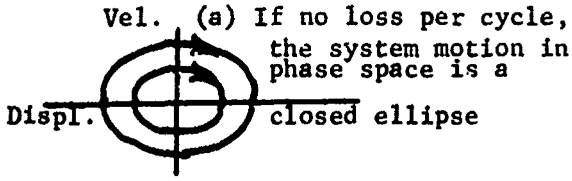
[1]A note: The problem of thermodynamics and engine cycles, as many authors, including Toulmin, have expressively put it, was brilliantly opened by the engineer Sadi Carnot in the early part of the 19th Century. The currently favored theory of nonequilibrium thermodynamics capable of dealing with all such issues, both of degradative processes and sustained engine cycle processes, was developed 100 years later by Lars Onsager (who recently received the Nobel prize in chemistry for that work).

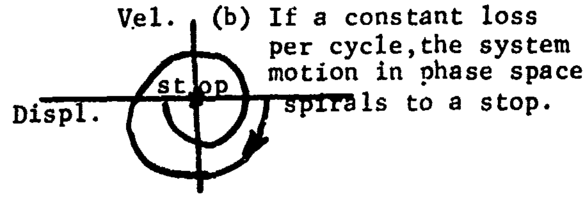
[2]Note: See the following figure. Phase space is the geometric representation of the velocity and displacement of each degree of freedom of a system.

Figure 1.



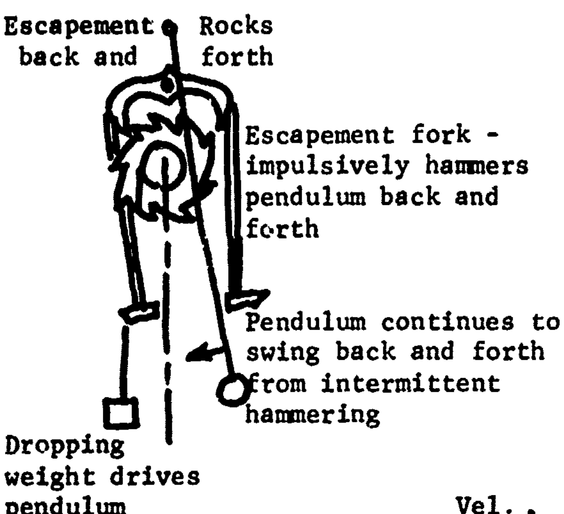
Illustrating a Dynamic System (i.e.,its displacement from a rest equilibrium)



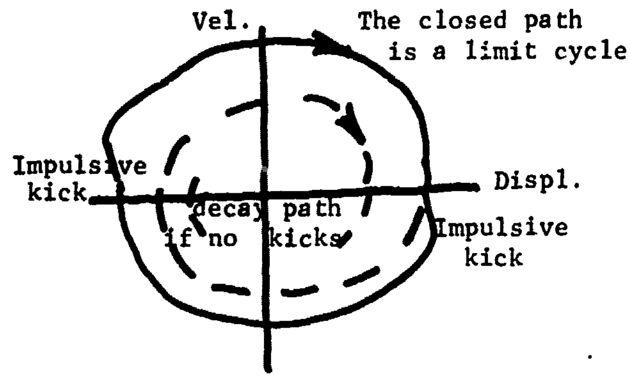


Each ellipse is a cycle starting with different velocities or displacements

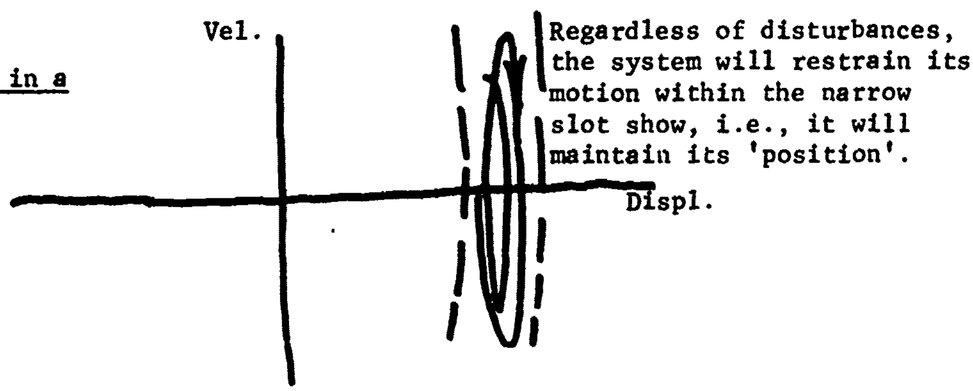
Its Representation in Phase Space (a plot of velocity versus displacement)



A Dynamic System in a Limit Cycle



Its Representation in Phase Space



The Phase Space Representation of a Control System (e.g., equivalent to a positional feedback servo) with a prescribed set point and taking corrective action, but the entrainment of ongoing processes as oscillators trapped within a very narrow but deep chasm in the geometric picture by which dynamic process can be depicted, - 'phase-space'. An exposition of phase space and this concept of control is shown in the figure on the previous page. (What difference does one paradigmatic mouthful make for another? It changes the basis on which you try to design systems, a very significant point.)

9. By 1967 the author was collaborating with Warren McCulloch (6) in a description of behavioral homeokinesis. Just as internal physiological processes were yoked together by links in a cyclic chain of performance (at this point science might consider its indebtedness to Rube Goldberg who, with the most delightful whimsy, but in the best spirit of great exposition, showed imaginatively how chains of destined performance might be yoked), so were behavioral chains with their external links of motor performance. The thought was expressed that these behavioral chains arose from the organism[1] by the same fundamental process of thermodynamic engine cycles. Specifically, this means that not only do the internal physiological processes take place periodically, but that the daily-weekly-monthly-yearly modes of behavior, the modes of classical 'emotions', also pass over the individual in periodic fashion. How else would your spouse, friends, enemies, or acquaintances (including your psychiatrist) know you, if you didn't repeat your performance? While this might be regarded as a facetious question, it is not really. Underlying it is the profound Gibbs' hypothesis, the ergodic hypothesis. Active systems of atomistic entities which are gathered into ensemble (i.e., an 'assembled' system of many component entities) cycle through all modes of behavior that are available to them, and you cannot tell the difference in performance from time to time or from ensemble to ensemble. The purest form of the ergodic hypothesis is not realizable, but it becomes the best guide to rough measures of performance (You can't tell much difference from one day to the next; from one country to the next; from one person to the next; all of you [men, women, Chinese, kids, blacks, adults, Jews, Greeks, etc.] are alike, etc., etc., etc. These are the cliches used over and over in so many contexts.) Coupled with the Fourier theorem, one finds that the individual fills his time slots with the same characteristic performance over much of his adult lifetime. This was the message that McCulloch and the author attempted to put across in 1967.

[1]The descriptive word for the process is epigenesis. On one hand there is some fundamental replication and growth processes coded at the genetic level. This has been the province of molecular biologists, e.g., Monod, Watson, but also including the dynamic concepts of Brian Goodwin (TEMPORAL ORGANIZATION IN CELLS). The interaction of the genetically unfolding organism with its environment and experience becomes coded in memory and command-control areas as performance sequences and is known as epigenesis or epigenetic coding.

10. But there was still a missing ingredient. The organism is an evolutionary system emerging from many separate lines of development. Imagine all of the factories of the Western world. They were not all built at the same time, with the same design and managerial philosophy. Yet hopefully they were each built to survive, to perf... function for an indefinitely long 'life' time. The question that the author took up in 1969 with his colleague, S. Cardon, was what philosophic design characteristic could be seen in the bioorganism by which its ultimate regulated life process would take place. The principle proposed was hierarchical regulation (7). If a system existed (in an evolutionary sense) and had solved some regulatory problem, nature's designer (namely the same self organizing forces that led to the previous self operative thermodynamic engine) could add another level of regulation to one or more of the regulated processes. Thus in any currently operative plant (e.g., man), one would find a complex nested sequence of regulating mechanisms or chains by which some particular characteristic homeostatic performance would emerge. That story was developed around specific illustrations. Body core temperature and cardiovascular performance were used as examples.

11. A book then followed (3) and provided a general extension of these ideas from the bioorganism to all viable systems. The author views the characterization of a 'viable system' as consisting of three phases. First, a system has a start-up in some workshop. It can be the womb, the factory, or nature's crucible, e.g., in water, earth, or air, with energy from the nuclear fires of a distant sun. (Note the echoes of the same themes raised by the ancient Greeks. If one starts to quibble, "But what is earth?", say, it is a somewhat moot point. The detailed answers of whether earth is one or many forms, or 100 atomisms, or two nuclear substances proliferating into 30 and then 100 fundamental particles which really are processes, or the hunting of three 'quarks' all illustrate that historical-physical modes do not change the philosophic conception. Is it that our Western thought has been ghost ridden from the start by the Greek philosophic construct and that we remain enchanted by it, or is theirs the closest approximation to absolute truth that sense perceiving man can achieve? These questions are posed here to help those who stumble over what is nature's crucible. The physics is very difficult, and we scientists don't yet have good answers but, as the reports have always had it, we're making good progress. Both aspects of that statement are true - the satire and the sincere belief.)

Beyond start-up, there emerges the life characteristic and phase of a viable system. The system essentially maintains form and function for a long period. Energy and water are taken in and released by thermodynamic processes. The system has the autonomous capability of roaming an environment and drawing upon such fluxes and operating for a long time in the face of many disturbances. (Some living systems may run out their lifetime with a single store, e.g., a sun.)

The 'life' characteristic is not solely the sum of those processes which preserve life's functions in the narrowest sense. It also includes the organism's 'purposes' or 'goals' (8), e.g., an industrial system not only has to 'survive', it has to do it by being productive industrially. That is, purposes or goals are functions which have to be performed or sought or attained by the organism as part of its life processes.

Ultimately, because of larger scale issues, the system runs down through a degradative phase: parts wear out, material departs, processes precipitate deleterious ingredients.

12. It is hardly possible to dwell on the fundamental issues being discussed here without sensing the strong relevance and interrelation of both philosophy and physics. All of our arguments are aimed at finding a philosophic vantage point from which to view the specific issues and then finding a physical path which is consistent with the philosophic. In the background, of course, stands one's metaphysical structure (or structures), which Kuhn has referred to as one's paradigm.

13. The referenced book (3) is about the life phase of systems. It is about how the cosmological degradation promised by the second law of thermodynamics is consistent with the existence of self forming systems based on cyclic thermodynamic engines, and about how such systems' organization come into being and persist at every level. In general, it was shown that these systems alternate in levels, between atomism and a continuum character. Thus, a continuum instability[1] would create the next higher level stable atomistic system.[2] A collection of atomistic systems would become unstable in their assemblage and create a stable superatomistic system, etc.

Now in this article a new issue is faced. It is concerned more with gaining a philosophic vantage point for understanding the start-up of viable systems than with the detailed physics of start-up. Yet 'practical' men - designers, organizers, builders, engineers, executives, politicians, maintenance men - should not regard this paper as merely philosophic 'chaff'. It is meant to be a basic design guide to the design, synthesis, or maintenance of long-lived functional systems. However, rather than being a detailed handbook, it provides the guide in the same sense as Carnot attempted thermodynamics.

[1] A system is unstable, loosely, if it won't stay put, but goes into motion.

[2] Atoms, ions, and molecules collectively form the continuum of matter (e.g., the air, or sea water, or rocks around us). In extended size, this continuum collection forms gross atomistic structures (e.g., the air mass cells that govern our weather, the grains that make up the polycrystalline structure of solid matter, or in fact cellular life itself).

On A Strategy for Long-Lived Systems

1. Aristotelian logic and philosophy gave us a calculus of propositions and relations. The Platonic ideal, and later the Hegelian-Marxian dialectic provided a different kind of foundation, in which being and becoming represented an alternate view of reality and realization. The Cartesian view, on the other hand, was a mechanistic scheme for bringing Aristotle up to date and continuing his philosophic impact. Within this century, novel attacks on these amorphous concepts (which also include those of Kant) might be said to have been provided by Charles Peirce (see for example (9)), and subsequently Korzybski.

While reference to these particular individuals may appear somewhat idiosyncratic, the thrust developed by the line of men named is not so much with all the philosophy of science as with the view of reality and how the scientist might regard reality. Thus from an early polarization in the concepts of Aristotle and Plato to a parallel reformation in the views of Descartes and Hegel and Marx, we move on to a more modern form of the argument.

In the 1970 Korzybski Memorial Lecture (10) Gregory Bateson, in trying to determine the character of the mind-body problem, explored the Korzybski thesis that one must understand that a map on a piece of paper is not the same as the territory which it represents. Thus, he asks should one relate the quest for understanding of the mind-body problem on the substance of the mind or to its pattern? This question is typical of a classic dichotomy in western philosophy - substance and pattern (being and becoming,etc.).

These issues indicate the need for a three parameter (or triadic) quest, for there is the territory, the map, and the mind. Such triadic questions have been explored by Warren McCulloch and his colleagues (11), who obtained their clues to these issues from Peirce.

2. This citing of names and problems is not our present concern. They are added to the pot to indicate the sources of ingredients which must go into the cooking of a philosophy of science. An enlargement of the names and traditions may be gathered from sources such as Popper (12), Cohen (13), and Nagel (14).

Finally, we are up to our thesis. Just as it is necessary to distinguish being from becoming (form from function), and the territory from the map from the mind, so we wish to introduce another set of distinctions: it is necessary to distinguish the principles of operation and the mechanisms of operation from their embodiments and, above these, from the strategy of a working viable system.

As an applied scientist-engineer, the author has been concerned with actual embodiments of mechanism (aircraft instruments, home appliances, industrial process hardware, nuts and bolts, industrial instruments, development of materials, personal equipment including space suits and clothing for hot and cold.) In his engineering training, the author was indoctrinated into mechanisms and their behavior. In his earlier scientific training, he was indoctrinated into the principles of thermodynamics, of electricity and magnetism, of mechanics, of nuclear, atomic and molecular behavior, of chemical change. Building upon this foundation largely laid by 2500 years of earlier workers and thinkers, and upon his own experience and training in the arts, social sciences, and humanities, the author attempted to provide an interdisciplinary scientific world outlook on the operation of viable systems (3). That modelling has not provided an adequate foundation for the strategy of bringing viable systems into being, in particular long-lived viable systems. That is what we propose to discuss now.

4. There seems to be two strategies for bringing a viable system into being. Both are based on fundamental thermodynamic principles: energy is conserved, but it may be transformed; as a result of natural processes, there is a loss in the ordered form of energy via degradative physical mechanisms; it is possible to provide sustained cyclic and periodic flows of energy as long as there are reasonably contiguous sources and sinks of energy (i.e., two sources - one at higher 'potential' than the other, e.g., higher temperature).

In one strategy, a cycle of performance is arranged which will bring the initial state, through a series of transformations, back to a state that cannot be distinguished from the initial state. Mechanisms are provided which will physically and temporally perform those transformations. By these transformations, a large energy source is drawn from, and transformed into power. (Power, it should be emphasized, is the flow of energy per unit time.) It must be recognized that losses will be encountered; but some escapement or other mechanism must be conceived of which will replace most of the losses per cycle. The engine system is assigned a limited range of tasks to perform. <u>It is otherwise quite isolated in its environment</u>. Once started up, by whatever means are necessary to take it into its limit cycle of performance, it will then continue to run for a 'life-time' of performance (namely till parts wear out, etc.). A gasoline engine endlessly rotating a pump illustrates such an engine (or the previous figure of a clock escapement).

The key limitation to this system, a simple thermodynamic engine, is the underlined phrase: besides performing the simple task that it carries on, the system is otherwise quite isolated from its environment.

5. We are concerned with another strategy, one appropriate to complex systems which are globally stable within their environment. The strategy discussed above is not adequate: the first severe disturbance from which

the system is not protected will topple the system.

6. Although not relevant to the direct line of the argument, a few examples of very simple limit cycle oscillators may provide useful insight. (They are all of the first type.) If a small rectangular strip cut from a card is dropped in a gaseous atmosphere (i.e., it operates from the grav itational potential of height), it does not drop like a stone, or waft like a leaf, but rather it goes into a spinning mode. It forms a very simple 'sustained' cycle. It is the simplest thermodynamic engine that the author has been able to find.

A second example is a product of our complex modern society. If one goes out to a deserted shopping plaza on a windy Sunday, a person may find there a flagpole with a long chain attached to the top. A sustained clang-clang-clang will be heard, as the wind sways the chain outward and the chain falls back to make its persistent mournful sound. (It is the potential of the constant wind which is thermodynamically entrained in this limit cycle engine.) Of course many readers may recognize an older form of the same engine, i.e., the Aeolian harp, the note drawn by a fiddler's bow, or the tone piped by the devotees of Pan. But all of these are devices from an older more rustic environment.

7. These examples serve to illustrate that conceptually, in the evolution of systems, a first requirement is that some cyclic chain of events come into being. It is apparent that a cyclic chain can emerge from systems already in the environment. The cycle may be not only self created and self maintained, but it also may be coupled to some other self maintained cycle process. In that case, we would regard a cycle to be cued, rather than self developed (autonomous). A cued cycle requires only some kind of coupling; an autonomous cycle requires linear[1] instability and some suitable kind of nonlinear character which can provide nonlinear limit cycle stability.

Most often such a limit cycle system will be sensitive to changes in the environment and its 'life' will be quite evanescent. But there is the possibility that the system might affect its own environment and 'wear in its own path'. In that case the processes involved are likely those concerned with evolution. In the potential surface on which this pseudo-living system finds itself, a broadened range of regulatory paths develop. The concept of regulation is used (always) to denote the keeping of motions within narrow bounds independent of disturbances. That is, for many direc-

[1]The concept of linearity in a dynamic sense has not been defined here. Loosely it is contained in the concept of superposition. If behavior in time is not dependent on the concentration of players (namely the same effects would be seen if concentration of players were A or B or their 'linear' sum), then the system is linear. Else not.

tions of disturbances, on the plane of existence (the potential surface on which the system operates) the system can maintain or regulate its operating state. Thus it is no longer so sensitive to disturbances.

The basic fact seems to be that it is (a) the evolutionary change of a thermodynamic limit cycle engine operating on a broad regulatory hyper-surface (b) on which the engine operation is insensitive to many disturbances (the various dimensions of the hypersurface), (c) so that the system can persist for a long time in changing environmental conditions, which provides one (and perhaps the only) global strategy for long-lived systems which have fully interacting capabilities with their environments.

Evolution, in this frame of reference, is not a pressure that is constantly and closely engaged in testing survival value. Many augmentations and accretions can take place to a system, before a next accretion that 'suddenly' provides a new 'engine' mode that has increased survival value.

8. Here we have expressed the key thought which suggests a strategy for systems, rather than principles or mechanisms. The idea can be adapted by any scientist, engineer, or administrator and used as the basis for analysis, synthesis, operation, or maintenance of a system.

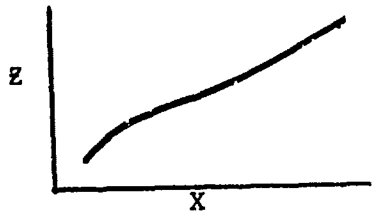
We will attempt to illustrate these ideas by a number of examples so that the reader might gain a better idea of what this means.

9. It is not clear where a system will start (i.e., develop some rudimentary thermodynamic cycle). In nature, it may be from a falling leaf; in man, it may be from a passing idea (e.g., "Why don't I start a business?"). However, for some incidental reason a number of mechanisms are assembled which can achieve a persistent periodic character. Their operation include means or modes for drawing locally from (essentially) time independent potentials and putting that energy into cyclic form. The potentials are adequate both to feed and overcome the losses in the process and to provide whatever energy is otherwise extracted during the cycle (e.g., as in performing work). If the process is robust, then it will persist despite a considerable variation of external disturbances in the surrounding environment, including changes in the supply potentials. ('Robust' may be given a more technical definition; perhaps the concept of the nonlinear stability margin is most suited.)

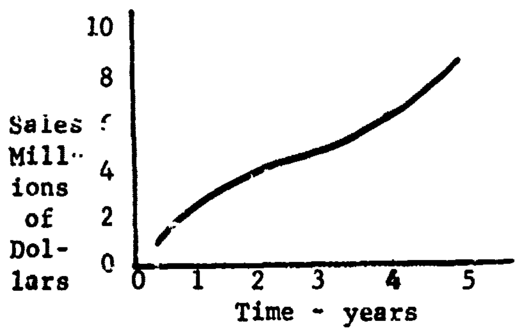
10. At this point it may be useful to define a regulated process. While the concept is essentially mathematical, it can be presented geometrically, thus rendering it more easily comprehensible (and hence more palatable)[1].

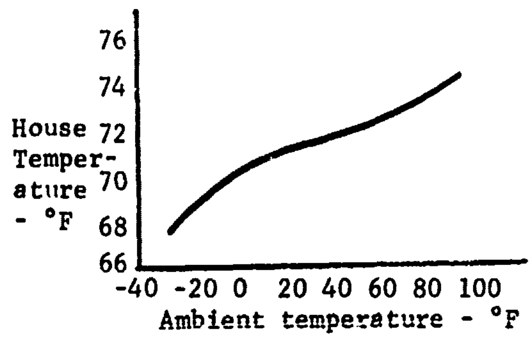
[1] An article by the eminent French mathematician René Thom, in the Nov.-Dec. 1971 American Scientist, discusses this point very well. Those who wish to get up in arms about the too high degrees of abstraction, in say the 'modern math' that their children bring home from school or in technical descriptions that are too highly abstractly algebraic, will enjoy that article.

Suppose we wanted to achieve a certain functional characteristic

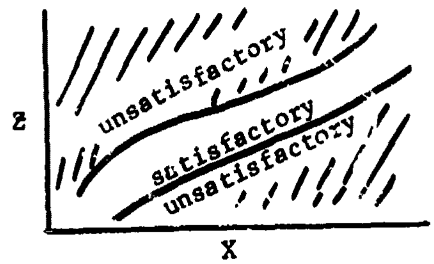


This might be or

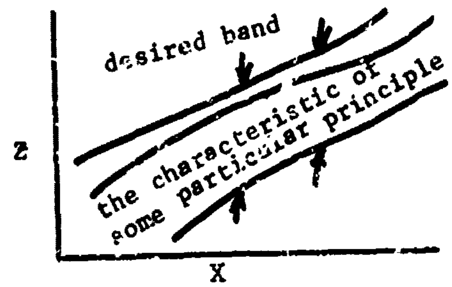




Since 'perfection' is not our goal, but adequate performance, we might settle for a particular performance band:



There may be no physical principle which provides that exact shape of response, but we can find some (e.g., one) that fits within the band:

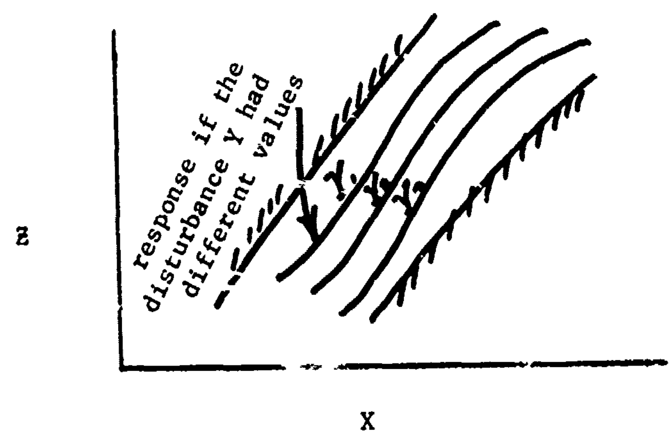


Then that particular mechanistic embodiment is said to provide a satisfactory regulated property Z for a certain range of the 'disturbance' variable X.

If we can build that embodiment into a system so that it helps to achieve satisfactory performance for the entire system, then we can say that the system is regulated. Consider temperature in a house.

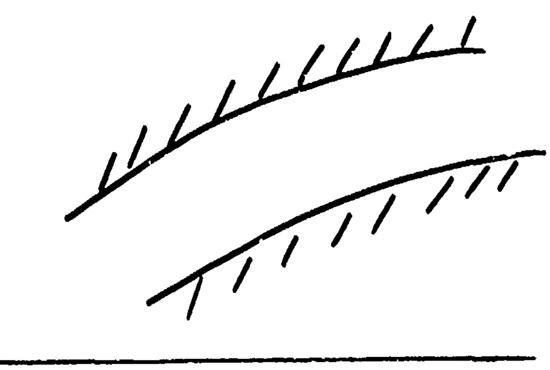
Thus, for example, we might find something that responds to outside temperature by bending (or straightening itself out). We might heat our house with a constantly running furnace, and have that 'something' alternately open or shut a door to let in more or less outside air and maintain desired temperature. That illustrates a regulator. Or we might let the 'something' control the action of some auxiliary power source (i.e., some other engine) which might regulate the house temperature even closer or faster. This type of regulator is known as a controller. We will not illustrate such typical 'Rube Goldberg' mechanisms. The technical field of automatic control is concerned with such devices.

Another important extension of the basic concept of regulation is that there may be more than one source of disturbance. (In the case of the house temperature, it may not only be the outside temperature that 'disturbs' inside temperature, but also outside wind velocity) The regulation problem might still remain to hold the regulated property Z within the desired regulation band in spite of all disturbances (X, Y, etc.):



This is as much mathematical argument as we shall present.

11. A primary characteristic of the global strategy of a system is that the elementary engine cycle must have a strong regulative characteristic with regard to its cycle periodicity (or frequency - the number of cycles that it performs per unit time).



To illustrate this characteristic: Over a man's lifetime, independent of the vicissitudes of temperature, state of health, mental stress, etc., he must eat a few times a day. He must sleep nearly once each day. He must exhibit a nearly fixed number of REM incidents in sleep each day. A woman must ovulate about once a month for a large part of her adult life if a sufficient number of progeny are to be produced. These processes are determined by complex frequency regulators.

12. It is doubtful that the first developmental prototype of any primary regulated 'engine' rhythm is strongly regulated. However it must have an evolutionary regulative character. While this is not an operationally meaningful phrase, the concept of an emergent evolution is operationally meaningful. By whatever 'accidents' are necessary, the engine develops ancillary compensating or regulating characteristics so that it becomes less sensitive to disturbances (i.e., it can increase its nonlinear stability margin, thus becoming more immune to transitory disturbances).

How is this done? We don't know! The concept of emergent evolution represents a strategy for global stability, not a prescription for mechanism. We do not believe that the first few steps in any emergent evolution are necessarily advantageous. They are what they are, but they stay around. Ultimately one additional ingredient in the chain is captured, and 'suddenly' a viable advantage emerges.[1] Nature, the mind, man, society - any of these may interact with a perishable operating system, and discover a way to strengthen its grip on life. Why? Because the fundamental process or processes continue to beat and as a result, manage to stir up other pro-

[1] Strategically, we don't know. Tactically, we do. If we have built a system that works poorly, initially, we are not surprised. We 'debug' it, namely by 'systematic' search we ultimately stumble on factors that depreciate performance and remove them or augment them.

cesses into repetitive patterns.

13. Why can this strategy work at all? Because there is a vicissitudinous milieu surrounding the system. The energetics of the very hurly-burly, the signalling, the ongoing noises, the ever-present passerby, may become entrained with the primitive system. This will build up its regulatory character.

14. However, the system does not work by developing the regulatory character of only that one primary frequency regulator. It may begin to entrain other frequency regulators, and to start up new engine cycles. These new cycles will also have evolutionary problems. Now, however, the primary rhythm may help to stabilize the emerging process more rapidly.

15. As time goes on, a full emergent evolution may occur, one which may in fact shift as conditions in the environment change. Thus there is a gradual emergence of more and more directions in which the system is immune to failure. By the time we consider the living system, with perhaps 3 billion years of development, we must acknowledge that its selection of directions of regulation and compensation has been manifold.

16. However, in time the system may fail. Its channels may choke up with unwanted constituents; or by changing its stability, it may shake itself into another kind of failure. (Its internal processes may no longer be 'cooperative'.)

17. Those of us designing systems (e.g., working equipment, families, societies, corporate institutions, etc.) still have limited experience. The strategy of designing for global stability is still too new and unexplored to be used as a do-it-yourself kit. Yet it has often been an underlying thesis of great thinkers. (The history of the American Constitutional Congress provides a remarkable example of men struggling to design a strategy for a stable society.) We would hope that this more formal introduction to the concept may help readers to appreciate its generality and thus further its application in diverse fields.

18. One final note may serve those who wonder why systems can come into existence at all. It is a global topology that emerges from the limited number of forces available to bind our atomistic entities together. At the very lowest level very strong forces bind particles together. Fine, why don't they bind all particles together? They do, but the forces saturate and the system becomes unstable in larger size. From residual forces, the ensemble seeks a pattern by which the weaker forces can stabilize. They do. The process now grows outward, bound together by still weaker forces. These saturate and the system becomes unstable in larger size. And so forth.

Thus, bonds link nuclear particles. These form atoms. They form molecules. Molecules grow in linear chains. The arrangement becomes unstable. It forms a helix structure, in which weaker side chains bind. The arrangement grows out further and becomes unstable. It balls up under weaker forces. At this level, these weaker forces can be organized into cellular life. Cells grow forth and form colonies by still weaker forces. And so forth.

At each level, whatever residual forces are left over, they are sufficient to develop a binding structure of sufficient size. Structure emerges. The forces saturate. But again there is enough force left over for the next patterned level of organization.

Epilogue

1. We can illustrate our thesis (and give the reader a little more to think about) by discussing some rudiments of the design of two systems:

the foundation for a living system
the foundation for a viable corporate system.

2. Consider first the primary mechanistic requirements of a living system. As we know them now, some minimal requirements are the following:

a) a lipid bilayer which surrounds some water and which can incorporate moderate amounts of protein within the bilayer. (The primary characteristic proposed here is a basic instability which will permit various small molecules to pass through this membranous covering. The covering provides enough surface tension to form a near spherical closed surface. Further, the energy associated with the surface is not great, so that material can enter with moderate ease. The transport is not passive; the transport is an active process requiring a small amount of energy to accomplish it. On the other hand, large molecules are not transportable - or at least not transportable with any ease. Thus, passively, the membrane acts as a semi-permeable membrane to large molecules, and permeable to small molecules and ions.)

b) an internal encoder which can take small molecular bits from inside the internal liquid environment and build them up to protein. (Protein thus synthesized has the 'remarkable' property of maintaining a colloidal osmotic pressure difference (of about 25 mm Hg) across the membrane. Actually this 'remarkable' property of protein emerges simply from its molecular size and its solubility or near solubility. Yet this property furnishes a fundamental engine process for life. It, as well as the encoder, are both remarkable mechanisms. Equally important is the fact that protein is also utilized within the membrane layer to help act as part of the dynamic engine 'gate' for small molecules.)

c) a dynamic 'gate' which can also grow in size while retaining its function, and which can possibly divide by surface instability. An in-jest-divide engine process is thus conceptually feasible for the enclosed cell.

Note that protein acts both as a structural strengthener in the membrane and as a material which helps make up the engine.

There are a number of things wrong with the model engine. First, it is necessary to account for the energetics which will support the production of encoder (either the protein production process produces free energy available to the interior constituents, or a separate energetic engine - oxidative or some other - exists in the interior.) Second, this model process has not suggested a way for making a growing lipid layer.[1]

One possibility is that the original of this process was not reproductive, but that first there was a stationary cellular process that was repetitively formed in the environment by some chemical instability. Another possibility is that a number of incomplete processes were initially formed, each of which may have had a partially successful engine characteristic, or some useful regulatory process. Only when a number of these partial systems coalesced did a more fully viable system come into being. It is useful thus to think of these other partial engines.

3. An alternate system might have contained:

a) a lipid bilayer which surrounds some water and can incorporate moderate amounts of polypeptides within the bilayer. Again there is postulated a basic instability which permits small molecules to pass through the membranous cover. There are two ways in which the membrane could permit such passages. In one, an everchanging mosaic of dynamic pores could come into existence because of the instability of surface tension. Diffusion or flow through those pores could take place. In the other, a combination of approaching molecular complexes interacting with the membrane wall could produce the instability.

b) an internal 'catalyzer' (the previous encoder may not be much different) in the form of an enzyme.

The fundamental idea in either system involves a relatively large molecular complex (i.e., one possessing large internal energy storage in many internal modes, and thus relatively slow motional characteristics) which is able to deal with small molecular complexes in its vicinity and to modify

[1]It was interesting that subsequent to the first draft of this sketch, this subject has just surfaced on the agenda of biology. At the April 1972 Federation (FASEB) meeting at a special membrane conference held at that meeting, the nature of growth and 'synthesis' of membranes was discussed by P. Overath, of the University of Cologne.

their reaction rates, thus acting as a catalyst. The large complex is relatively fixed but it also has all kinds of interesting dynamic 'wall' characteristics. Together these properties make the scheme useful for entraining functional chains. The detailed ways by which geometric and dynamic force structures can perform their functions are beyond our present speculation. Suffice it to say that others have successfully suggested examples (e.g., of how to make catalysts).

However, for the scheme to work, the system must be protected from a too open environment. Thus it needs a surround, i.e., the membrane. Further, the scheme must include preservation or self replication of the catalyst. Thus again we face the problem: how does self reproduction of gross structure take place? Both the instability property and the production of lipid are required.

4. It may be that many such schemes (e.g., synthesis of protein, carbohydrates, lipids, potassium communications, sodium 'pump' characteristics) can come into existence, and that 'life' does not form until the self reproduction process takes place. At this point in our thinking, we have epitomized this as the problem of the growth and division of the lipid layer, although it may actually have been some other problem.

Perhaps there was required one protohormone (rather than simply an enzyme, and just acting by a mass action equilibrium). If, for example one or more engines had the dual characteristic of producing both a little polysaccharide in an engine process and, say by a chain or fork, also a little lipid, then a dual instability could come into existence. Ingest, produce internal constituents, grow, become unstable, divide.

5. Many of these processes seem to be in some difficulty if conceived of as having emerged entirely in liquid. It may be relevant to consider that processes may have emerged at gas-liquid interfaces. An advantage of such a scheme is that it can include forced convective processes which may act as a sustained source of reactive chemical ingredients. Thus, chemically reactive substances produced deep in the earth or high in the atmosphere could be transported into the watery phase and then the formation of films or various 'cellular' processes could take place by virtue of hydrodynamic forces. Such a concept has become more plausible with the dating of the origins of life increasingly close to the 'hot' birth and early life of the earth (e.g., earth age 4.5 billion years, life startup 3.2 billion years ago as currently dated). Many gas-liquid-solid processes likely occurred for the first time during those early historical epochs. (They had no earlier history, but were unique to a particular cooling down phase of the earth. For example phase transitions would be expected processes.)

6. An 'earth' phase, prevalent as an energetic process source of chemical reactivity and phase change, would have brought a number of parallel engine processes into existence. Those that were most resistant (regula-

tory) in their autonomous life would have survived. (For example, some products of 'engine' processes discharging near the end of a pipe bubbling physical-chemical 'reactive' components into a liquid medium might last only out to a radius of 0.01 inch; others 1/4 mile; finally some might be able to 'motor' around the surround 'indefinitely' - as long as conditions in the surround were right.) Those long-lived ones might then combine with other ingredients to become more self-regulatory. Many such combinations may have been necessary before an 'adaptive' combination was achieved which could self produce. (To illustrate, a bubble that incorporated a surface strengthener might last a much longer time than one which didn't. The point is not trivial: the limited range of protection of red cells against hemolysis is an excellent example. A red cell has the deforming toughness of nylon. If it had the characteristics of some earlier 'polymer', it might not be suited to the life processes.)

7. From this point of view, the detailed chemistry of the process is not so important as long as chemistry (i.e., chemical combination or patterns of conformation) was available. That becomes mechanism. The self-regulatory properties are more important. These include:

- coalition
- periodic processes
- motor ability, or mobility, or mobility range
- super-coalition without loss of identify
- multiperiodic processes
- internal motility
- reproduction

For example, photosynthesis is ordinarily considered a basic ingredient for the life process. It could be so in two different ways. In the first place, photosynthesis might have been the fundamental process by which a basic stream of chemical reactive product was made available. In the second place, similar to the other mechanisms suggested, it may have provided one additional energetic step in catalysis (e.g., it might be the energizer for some particular catalytic molecule).

8. The essential ingredient, as discussed in our earlier systems' science reports, are the two somewhat mystical structures of the 'wall' and the 'elite'. We now bring them closer together.

A characteristic motion of a particle which reacts like other particles is being swept as a Brownian motion throughout the throng of other particles. Chain reaction forces can also propagate from the outside and bring coalition into being. But if a particle has internal modes and a somewhat higher bulk viscosity[1] than the other particles, it does not relax its internal

[1]The bulk viscosity is a measure of how energy is partitioned in a system into other than its translational momentum (moving about motion). It relates to energies tied up in other internal forms. Examples are rotation, vibration, or conformation.

energies as quickly and its time response is different. (It has 'hangups'.) Thus, to some extent, it acts as a wall for other particles. (This furnishes a requirement that the biophysicist, Howard Pattee, has suggested as necessary for reproducibility as a hereditary process. Pattee has required time delays and 'non-holonomic' constraints[1] for his molecular entities. Pattee had no model for the process; here we have suggested one.) Chemists know of a variety of such polymeric structures which they can make, which will create delays in motion.

The number of forces by which the atomistic (here atomic) substructures are built up are few. The atomistic entities of the wall are in faster (limited, e.g., vibrational) motion. When particles approach the wall, local wall atoms will transform them. The authors of a Scientific American article on "Catalysis" (December 1971), using example of heterogeneous catalysis (the specific type doesn't really matter), state that there are five stages in the mechanism: first, a diffusive approach of the atomistic entity to the 'wall' of the catalyst; second, a tie-up of the entity (by "chemisorption", namely by a process involving an energy change); third, a chemical reaction at the surface; fourth, an untying of the reacted products; and fifth, a diffusive motion away from the wall. Basically, the catalyst or elite has 'chemically' transformed the entity; that is, it has changed the entity's constellation. Elite - wall - bulk viscosity are the keys. Not every wall transform is catalytic, but some may be.

The second half of the system is the isolated local (internal) environment within which the elite or catalytic process can take place in a relatively secure backwater.

9. For a mechanism by which the catalytic wall transformation might take place, we would suggest that the mechanics must be very close to a limit cycle. Namely, although the process is aperiodic (there is a chemisorption and desorption - an aperiodic phase), the lockup is so near a limit cycle that the details of its initial starting conditions of entry are lost. Instead the constellational transformation takes place.

The chemist might say that this is only an awkward way of stating that a surface chemical reaction has taken place. We beg to differ. In the role of physicist, we would depend on the chemist to suggest the kind of surface reaction involved, but we would point out that the acts of ab- (or ad-) sorbing, reacting, and desorbing create a combined chemo-mechanical process. The chemist/physicist could only hand-wave his explanation without the physicist/chemist.

[1]'Non-holonomic' is a technical term in physical dynamics that relates to how variables may be related to other variables. If their constraining relations are integrable they are holonomic; otherwise not. The gears in a train are holonomically related, a spinning and rolling billiard ball is not holonomically related to the pool table.

Thus it is a basic dual process which is required. But it is only near orbital lockup of a limit cycle that has the required mechanical properties.

One can see in this limiting process the kind of problems which the chemist often encounters with catalysts. Some catalysts can poison, i.e., the near limit cycle is not quite aperiodic and in fact locks up more permanently, or becomes locked up more permanently with other than the desired end-products. Other processes can use up catalyst, i.e., in the near limit cycle, some of the material of the catalyst can be removed (e.g., by being ripped or broken off) so that the catalytic structure, such as its large surface area, is degraded.

10. At this point it is appropriate to switch to the foundations for a viable corporate system.

a) A viable corporate system needs an elite structure, a catalyst - that is, an individual who has enough bulk viscosity to withstand the rapid relaxational buffetings to which everyone is subjected. His atomistic extensions - hands, feet, muscles, brain - must be capable of interesting transforms. (For example, he must be willing to do a lot of walking and talking.)

b) The surround of the elite must be sufficiently non-stormy that he can provide transformations of other atomistic particles brought into his vicinity by diffusion. (He may add tentacles, pseudopods, etc. to increase the local diffusion rate.) The surround is often built by money or labor.

c) A basic performance engine cycle must be developed. (A man bakes a pretzel, runs out and sells it, buys more dough, makes another pretzel, ...).

d) It soon turns out that there are a number of functions which the system must perform. They involve

production
design
plant maintenance
sales
fiscal control

In the beginning the elite performs all these functions, and must provide formal structures for their achievement. (Later they may be split apart.) The ability of the elite to manipulate his extensions by formal transformational rules permits him to structure the sys The ability of the elite to bring into coalition other individuals and uctures to help to compartmentalize the emergent corporate functions furthers the development of a viable corporate entity. Gradually this operational coalition becomes aware of those further regulatory functions which have to be developed to make the system more independent of its environment (e.g., to become the source of its own raw materials so as to be more independent of changing market conditions).

The purpose of this paper is not to provide a managerial manual, but rather a statement of a broad principle. Thus, we go no further with these examples, and proceed to a final summary statement.

In order to persist, a viable system must adaptively develop, by evolutionary change, a broad shallow plane of regulatory immunity against the disturbances which may come from many directions around its horizons. In an energetic sense, a viable system must truly have a low profile.

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VIII. ON THE PHYSICAL BASIS OF A THEORY OF HUMAN THERMOREGULATION

As a result of an ongoing extensive review, we have modified and extended our original report on this subject, which was presented in NASA CR-1806 (June 1971).

It may be of interest to indicate the reviewers' outlooks toward our efforts. The following comments were received from a well-known thermal physiologist who is chairman of a division of life sciences in a medical school at a large university.

"August 9, 1971

" ... I found Part I of your NASA CR-1806 report an interesting and provocative presentation of the thermoregulation problem. I am asking our students interested in this area to read it."

The following letter to a review chairman of an engineering journal includes a first round of reviewers' comments and our replies.

"August 17, 1971

Dear Dr. ___:

Enclosed are revised copies of our paper, "On the Physical Basis of a Theory of Human Thermoregulation" ... We feel that the changes made should answer all of the reviewers' valid criticisms. Other points which we, on second thought, felt were not sufficiently explained are now given more attention. Also appended are replies to the reviewers' specific comments. This letter contains a few general remarks.

The reviewers' comments that ours is "not a theoretical paper", that it is only "description and speculation", that our results for heat transfer coefficients are "trivial", and that we are "considerably behind the state of the art" imply that we are neither qualified nor competent to undertake the proposed task. Since we do not believe that such attacks are ever answerable, we choose to use this letter as a vehicle through which to respond to answerable criticisms.

1. Our paper is aimed at bringing experimental data within a theoretical construct. The sources of data are referenced and readily available. At the prodding of the reviewers, we have added more recent references, but the content and conclusions reached in our Figs. 1-3 remain unchanged.

2. While the reviewers imply increased average metabolism in the cold, we have provided more background to show that there is no large metabolic response to the cold on the average. Shivering simply is not an adequate source of heat. We made this point a long time ago, and data presented as long ago as the thirties and as recently as the 1968 Symposium at Yale support this statement. We feel that it is incumbent on the reviewers, if they still disbelieve us, to provide suitable references to equilibrium measurements to support their contentions that average metabolism at rest in the cold increases 2-5 times the value at a neutral temperature. (We caution those who take up this challenge to consider carefully the requirements for equilibrium and not to be deceived by the normal 2:1 cycling variation in metabolism which occurs in all temperature regimes. We are concerned only with the equilibrium mean values.)

3. The statement of one reviewer that ours "is not a theoretical paper" conflicts with our idea of what (a theoretical) science is supposed to be. On the basis of the data we reexamined current thinking, we exposed inadequacies in present concepts, we proposed new concepts as hypotheses which resolve some existing problems. The new ideas remain to be tested. They may be wrong. Yet if they contribute to progress in the field by encouraging us or others along rational courses of research, then they are significant.

4. One reviewer claimed that "the finding that h is constant over the temperature range considered is trivial, no one will contest it or expect anything different. It is the authors who through faulty understanding and reasoning arrived at h = 3 at $T_a = 5^oC$". (How "trivial" one considers the result depends on his respect for the complexities for the Navier-Stokes equations. We have had much experience with them in other fields, yet we don't know how to solve them in general and, we daresay, neither do our critics.) We didn't contest the constancy of h or expect anything different. But, wishful thinking aside, the data force a different conclusion. We didn't force any issues as one reviewer implies. The issue was there all along, waiting to be picked up. Indeed, we have now included in our paper the fact that J. Colin and his colleagues (1968 Symposium at Yale) noted the same discrepancy in h, but they didn't know what to make of it, and ducked the issue essentially by wishing it away.

5. In commenting on our discussion of tissue conductance, the reviewers again question our competence and motives: "The entire discussion of equation 7 appears to be an attempt to force the available physiological measurements of tissue conductance into an unacceptable context by making incorrect assumptions." We repeat, our conclusions are based on the data - show us data that refutes them. Impelled by the comments of one referee, we have added a rough calculation, deliberately overestimating the effect of countercurrent heat exchange and showing that the effect is not important to the essential issues of the paper. Although we modified the language, the same "unacceptable blow-up" in calculated tissue conductance occurs, unacceptable to us because it is not explainable by physical pro-

cesses; unacceptable to the reviewers because ... because ... ?

6. The reviewers complained that we are "guilty of unacceptable oversimplification" and that our general description of thermoregulation is "misleading and incorrect". Apparently the reviewers failed to understand the purpose of our paper. As stated in the title, the paper is, most fundamentally, a reassessment and reformulation of the physical basis of a theory of human thermoregulation. To that end, we have treated a deliberately simplified case of nude, resting human in a steady state. This was stated several times in the paper (it is now stated several more) and renders irrelevant reviewers' comments that only steady-state equations are developed. At this point we were not interested in the complicated kinds of computer modelling performed by Wissler, or Hardy and Stolwijk. They, in their own ways, have made simplifying assumptions to evade issues they didn't understand.

We thank the reviewers for pointing out a number of typographical mistakes and making two useful criticisms. First, we realize that $\bar{T}_s$ does not exceed T_r in equilibrium in the heat, although it is not clear to us how close they approach each other. However, this does not relieve the difficulty with a theory for tissue conductance. Second, we appreciate that we used the term "sweat gland" too loosely in the paper and so we have modified our terminology. However, our hypothesis of a subsurface evaporation remains the only apparent means of reconciling experiment with physical theory. It is our purpose to stimulate others to a better explanation if they can find one. The question of the pertinent physiological structures and mechanisms will require much future work to resolve.

Sincerely yours,"

"Reviewer No.

General Comments

1. The manuscript as presented, is considerably behind the state of the art. It contains errors of fact and concept which should be corrected before publication. If the authors would consult more modern literature, they might wish to reconsider their present manuscript. Specifically helpful might be chapters by Cunningham, by Stolwijk and by Wissler in "Physiological and Behavioral Temperature Regulation", J. D. Hardy, A. P. Gagge and J.A.J. Stolwijk, Eds., Charles C. Thomas, Publs., Springfield, Ill., 1970.

Specific Comments

Page 2

The authors are misinformed about two important points:

2. Scrutiny of Russell Sage calorimeter work (see, e.g. Hardy and

DuBois, J. Nutr. 15, 477 (1938)) will reveal steady state data with increased metabolism in the cold. At an ambient temperature of 5°C there will be much more than a 20-30% increase in metabolic heat production and fig. 1 is physiologically unacceptable. To interpret the 20-30% rise to cardiovascular work in the cold completely ignores shivering as a means of heat production.

3. At high body temperatures the rise in metabolic rate is partially due to increased cardiac work, but most of it can be ascribed to the Q_{10} effect.

Page 3

4. Line 3 should be $T_a = 45°C$.

5. Line 4 - local skin temperature is not the sole or even the most important determinant of sweating and the authors should avoid giving the impression that it is. E at rest is not 18 Kcal. m^{-2}. hr^{-1} at $T_a = 25°C$ but closer to 10. The authors should avoid the notation Kcal/m^2/hr which is strictly incorrect. To describe thermoregulation as beginning on line 11 is very misleading and incorrect. Again, skin temperature is not the sole determinant. How about heavy sweating at a skin temperature of 30°C during exercise? The authors are guilty of unacceptable simplification.

Page 4

6. Eg. 1, and 2 should be limited to the steady state or a storage term should be introduced.

7. Fig. 4 contains a fallacy: M is not constant but increases in the cold, and the figure is calculated without allowing for storage of heat. The data points are acceptable and are different from the calculation at h = 7 because -

a) metabolism was elevated through shivering

b) body gives up heat to the environment on a net basis (i.e., no steady state reached) -

or a combination of a and b.

Page 9

8. This reviewer is under the impression that in engineering practice the higher of forced and free convection is to be preferred over vectorial addition. The finding that h is a near constant over the temperature range considered is trivial, no one will contest it, or expect anything different. It is the authors who through faulty understanding and reasoning arrived at h = 3 at $T_a = 5°C$.

Page 12

9. Second paragraph - The authors seem to be misunderstanding the function and result of vasomotor activity. In terms of heat transfer the importance of vasomotor activity is not the water content of the tissue, but the convective heat transfer between interior and periphery.

10. Third paragraph - The anatomy of the skin makes it impossible to accept the concept of evaporation below the skin surface as a meaningful one. Even if all the evaporation took place at the bottom of the sweat gland the effective length of the conductive path from core to skin would hardly be affected."

Reply to Reviewer No. 1

1. Review of 1968 symposium denies the first sentence. We have turned every page in the Hardy, Gagge, Stolwijk book looking for any crumbs, helpful or contradictory. We have added them. They change nothing.

Cunningham. Her data on forearm skin conductance show the same high unacceptable conductance on the basis of just M instead of M-gE. While local 'steady' heat transfer was noted, one doesn't have the faintest idea what the tissue equilibrium might be. It really takes hours of immersion to set up an equilibrium, not 9 minutes. Thus the tissue conductance really being measured is not known.

Stolwijk. As he states, it is not his intent "to propose any one quantitative concept of thermoregulatory controller". The paper is a computer simulation of a nonequilibrium transient. We fail to see its relevance to our paper.

Wissler. Wissler has been offering the same piecewise breakdown of the body for the past 10 years. (We had occasion to review one of his papers a long time ago.) We have no quarrel with breaking the body down into a complex of pieces, but the only thing Wissler is going for is a simple first order model of a 1/2-1 hour transient. One may note that the IEEE Spectrum Biomedical Engineering paper by Fan et al. (BME-18, 218, 1971) fairly reviews his paper. We do not find it relevant to ours.

2. Item 1 clearly indicates that the reviewer, by the work he referenced, has not come to grips with issue of equilibrium data. It is stated that at 5°C (the range was up to 23°C) there would be more than a 20-30% increase in heat production. This is simply not true. Irving at 0°C clearly showed that a 10 hour average was only 20-30% higher. Since 1938 Hardy and DuBois (and now the present reviewer) have mixed up this issue. One can clearly see in the studies made by the ASHVE group that an equilibrium is reached without storage. Gagge, at the 1968 symposium, might idiosyncratically propose to test thermodynamic equilibrium by "a 'new' linearity criterion for partitional calorimetry". We prefer the old-fashioned way. Wait long enough till the transients die down and measure time averages.

3. The Q_{10} effect would give less than a 10% rise in M between T_a = 25°C and T_a = 40°C. Thus, we are still left with increased cardiac work as the major cause of the rise in metabolic rate.

4. Misprint.

5. The 18 was a misprint in the text; it is shown as 10 in the graphs. Our notation is not incorrect; in fact, it is quite conventional in engineering circles. The breakdown into three zones of thermoregulation was quite customary (e.g., in Davson, 1964; in Ruch and Patton, 1966). We were not discussing sweating during exercise. We were not discussing exercise at all. We were discussing sweating at rest in a particularly calm environment. We have no physiological theory for sweating. We do have a physical theory for the end of sweating; Kerslake's psychrometric process.

6. The equations were limited to steady state.

7. Fig. 4 contains no fallacy. M is constant in the cold, a[illegible] .ere is no storage when averaged over 3-5 hours.

(a) Metabolism is always cycling and includes shivering and non-shivering. In the cold it is not elevated more on the average than 20-30% above its average value in the warm.

(b) This is our point; the metabolic data used is at and near equilibrium; the temperature data is not. The issue we are raising time and time again is that of the temperature at equilibrium.

8. The reviewer has the wrong impression. For near equal heat transfers, a vectoral addition would be preferable. At the 1968 symposium, the Colin study also found a lower value (their Fig. 7-4). They did not recognize the real issue and fumbled away the opportunity for a rational reduction.

9. The measure of vasomotor activity as it affects us here is the effect on heat transfer. We do not seem to misunderstand vasomotion on that score. How the vasomotion might take place has been the subject of microvascular studies on our part; thus we are aware of the anatomical changes taking place. But the issue remains a physical one. What is the change of effective 'conductance'. The boundary layer between skin and core doesn't seem to change much in thickness. Thus we are up to modelling specific conductance.

10. We are proposing a physiologically tough issue to resolve, but it really poses the nub of the problem. We would very quickly welcome a better thesis. Ours is at least plausible.

"Reviewer No. 2

General Comments

1. The manuscript by Drs. Iberall and Schindler presents physical models of human heat balance in cold and warm environments. The modifications which the authors propose for the physical processes of effecting heat balance are interesting and provocative, but since they are based on errors of fact they cannot be taken seriously. The authors calculations of the skin to air heat transfer coefficient is acceptable as long as they are considering physical principles but their assumptions for comparison with physiological data are in gross error and lead to what the authors term "an unacceptable blow up". Similar errors are scattered through the manuscript.

2. A second point of concern is that the physical bases of heat transfer for humans have been treated in great detail and much more extensively than the authors' attempts. That is, their treatment of the problem is some years behind the research and development front. Whether or not the lively imagination of the authors in proposing alternatives can make up for these deficiencies is, of course, a matter for decision by the Editorial Review Board.

Specific Comments

Page 1

3. Third paragraph - "effective temperature" combines dry bulb and wet bulb temperatures - not dry bulb and wall temperatures.

Page 2

4. Second paragraph - The authors should be aware of the fact that long term temperature regulation (days or longer) in any but nearly neutral environments is achieved by behavioral rather than physiological means. This statement applies rather generally to both homoeothermic and poikilothermic species.

5. Figure 1 - There is something wrong here unless the author is speaking of the first few minutes of cold exposure or the putting on of additional clothing in the cold. The references do not support the authors' figure 1. For example, ref. 11 - the male subjects were not in thermal balance even at 26°C and measurements were carried only to 22°C. The author must be careful about experiments of 1-6 hours exposure to cold air. Thermal balance is achieved only by periodic bursts of shivering causing metabolic rates of 2-5 times resting levels. There are clear differences between primitive tribes who generally go about naked (even in near freezing weather) and allow marked decreases in body temperature before shivering and the white man who tends to maintain body temperature at the expense of more frequent bouts of shivering.

Page 3

6. Sweating usually begins when skin temperature is about 33.5 - 34°C for resting man and at about 35°C for resting women. In the cold evaporative heat loss is less than 10 kcal/m^2.hr.

7. The author chooses to ignore changes in internal body temperatures as affecting temperature regulation in resting man. Such an assumption is not in agreement with the facts.

Page 4

8. The authors' assumption that the "function of the thermoregulatory system" is to maintain the metabolic rate and the internal temperature is not strictly correct. The metabolic functions of the body are largely independent of thermoregulation.

Page 5

9. No observations of the heat transfer (skin to air) coefficient are as low as 3-4 Kcal/m^2.hr.°C. Most values are 7-8 with some as low as 5-6 for the man lying on a net in still air. In the cold, h has a larger value due to shivering because convective losses are greater than in neutral or warm air. The values of free convection shown in fig. 5 may be low for the 5-10°C environments.

Page 10

10. The remark about the inconsistency of the experimental values of h and the calculated values is unconvincing to this reviewer. As noted above, no values of 3-4 kcal/m^2.hr.°C are acceptable except for the clothed man. Values of 6-15 have been reported for the nude man depending on activity and air velocity.

Page 11

11. The experiment in the "open but shaded space" cannot be seriously considered. The author should really be more familiar with work in this general area and I would refer him to the book recently published by Chas. C. Thomas, Springfield, Ill., entitled - "Physiological and Behavioral Temperature Regulation". There are many references to older work as well as engineering calculations of values of heat transfer coefficients in air, O_2 - helium mixtures, etc.

Page 12

12. $\bar{T}_s > T_r$ occurs from time to time for short periods during body heating, for example in a warm bath at 40°C or under a radiant heat load.

There is nothing remarkable or "nonphysical" about these situations in terms of calculations of tissue conductances. However, equation 7 is valid only in the steady state. The entire discussion of equation 7 appears to be an attempt to force the available physiological measurements of tissue conductance into an unacceptable context by making incorrect assumptions. There is no reason to assume that sweat is vaporized below the skin surface, and to use such an idea would require a skin structure far different from that known to exist. For conditions of work or heat exposure, the addition of sweat evaporation as an important heat loss term under physiological control is well known and has received much study. There is no "unacceptable blow up"."

Reply to Reviewer No. 2

1. Errors in fact? Gross error in comparison with data? We have exhausted the available data. We don't see such errors.

2. Not really treated in more detail. The Rapp Study and the Colin Study in 1968 symposium are about at the same level that we have been doing for the past 10 years. We don't quarrel with them; the results are essentially the same. Our lively imagination may confound the reviewer, but we would have hoped that he might have responded with insight rather than insult.

3. We have not made a distinction between "effective" or "operative" temperatures, etc. Our T_a is a function of air and wall temperatures and humidity. The point now noted is physiological.

4. The reviewer should be aware that physical equilibrium can be achieved in non-neutral environments, i.e., 5-40°C. This statement applies to humans.

5. There is nothing wrong with Fig. 1 except to show solid data for the estimated ends. It was necessary for ASHRAE studies to redo the Hardy et al. and Winslow et al. studies to find out the equilibrium results. Also we repeated them in 1955 and 1965. The data, except for scatter, are shown in Fig. 1. In 1968 Nielsen (p. 207) shows results over the 5-35°C range at about 1.5 lpm oxygen uptake. The only question is the temperatures at which system breakdown would ensue; in the cold or in the heat. We have done 5 hour experiments in the cold down to 10°C nude and made measurements breath by breath. Has the reviewer? The Irving data show little difference between nude tenderfoot and acclimated Indian.

6. We find no difference in our statement. The 18 was a mistake. It was 10 as in the figure.

7. The internal body temperature at rest doesn't change (1968 symposium, p. 206, Fig. 14-2). It changes from 37 to 39°C with exercise.

8. The sentence was misleading and has been changed. We agree.

9. At the end of 1-2 hours it still looks like h = 3-4, i.e., the body is not at equilibrium. The issue we have been raising is what is the equilibrium. We submit that a lowered surface temperature, not a raised metabolism, has to be demonstrated. h is not larger in the cold. It is the same theoretical value as shown by Colin (p. 95, 1968).

10. The same point. h = 3-4 is either not equilibrium, or it has been faked out. We prefer to believe it not equilibrium.

11. We are familiar with the book. If the convective pattern is suppressed, we submit that an h less than 7 is obtained. We showed this in 1965, and it may or may not be true for Colin (1968). As the work of Ralph Kennard in interferometry showed, it takes a considerable height to get a fully developed convective cell going. Very few study rooms can afford the luxury. It all has to be carefully thermostatted.

12. We are talking about steady state. We concede that T_r may remain somewhat larger than $\bar{T}_s$ (say 1-2°C) due to evaporative cooling. The issue comes to a head when the tissue vasodilates and the surface becomes wetted.

Then either $$M = CA(T_c - \bar{T}_s)$$

or as we think $$M\text{-}gE = CA(T_c - \bar{T}_s)$$

The issue is whether a C can exist which will make up for the small temperature difference in the heat. If it cannot, then a subsurface g could account for the difference. In this paper, we argue that the increased C is not achievable and therefore propose the second alternative as a new hypothesis. The reviewers are free to write their own papers and prove an acceptable large C.

"Reviewer No. 3

Remarks

1. This paper is a combination of description and speculation. It is not a theoretical paper. The descriptive portion is a review or rephrasing of a rather standard accepted idea in thermophysiology. The speculation is related to the authors' previous interest and reports on the time constants of the system and also to some interesting, but unsupported, hypotheses related to circulatory shunting and evaporative losses. The frequency response analogy to the carotid baroreceptor is not justified.

2. Only Section III, the Physical-Physiological Problems - Some New Thoughts, contains any new material and this is properly labelled as thoughts rather than facts. The thoughts are interesting and can be tested. The paper would be acceptable if it were a presentation of support for these

hypotheses and conceptually, then, would be a valuable addition."

Reply to Reviewer No. 3

1. All we can do with his assertions is deny them. Neither the assertion nor the denial have any weight without the paper's being fairly reviewed. This the reviewer has not done. (Sentence 1) A combination of description, speculation, and physical theory makes a theoretical analytic paper. (Sentence 2) Therefore the paper is a theoretical paper. (Sentence 3) While the paper reviews in part certain ideas of thermophysiology, it shows contradictions and proposes new hypotheses. (Sentence 4) Most papers relate to their authors' earlier interests. The time constants discussed relate to equilibrium time constants. Data have been selected with these time constants in mind. The authors offer hypotheses. They offer experimental data to support physical reasons for the hypotheses. The burden is now on physiologists to prove or disprove the physiological mechanisms. This is a standard procedure in systems parameter identification. (Sentence 5) It is a difficult thesis to attack or defend. The physiological literature is no more clear on what determines the regulation of average pressure level (i.e., 100 mm Hg) in the mammal than it is on what determines the 'thermostatted' 37°C, which is proposed over and over again to be a 'set point'. Both the carotid sinus response and the hypothalamic response seem related to the autonomic system, and lesions in specific structures (i.e., the carotid and hypothalamus) abolish the high frequency response without abolishing the longer and slower responses.

2. (Sentence 1) Section II identifies and resolves discrepancies between the theory and measurement of h. This is the first time that this has been done. (Sentence 2) The new ideas proposed can indeed be tested. The tests involve difficult physiological measurements of local skin temperature, of tissue temperatures down to the muscle layer, and of heat fluxes down to the muscle layer.

"Reviewer No. 4

Remarks

1. I found the paper difficult to follow and may have misunderstood it. If the points raised on the following can be clarified it would be acceptable.

2. The paper turns largely on problems arising from the consideration of published results presented in Figs. 1-3. Five sources are quoted but sources for the individual figures are not identified. There are considerable differences in physiological response between different subjects, and unless the curves in these figures are derived from the same (resting) subjects and indeed from the same experiments, the discrepancies demonstrated in Fig. 4 should not be given much weight. In those days skin temperature measurements were perhaps not as reliable as one might wish. The thermo-

couples were often covered with adhesive tape.

3. The value of $h = 7$ kcal/m^2 hr ^{o}C for 'still' air deduced in section II has independent experimental support. See for example Gagge & Hardy, J Appl Physiol 23 248-258, who review the work and propose a value of 6.0 for sitting-resting subjects. The value would be somewhat higher for the standing or lying posture.

4. Section III is difficult to follow. T_s does not exceed T_r in man in equilibrium, although it may in animals which rely on the respiratory tract for their evaporative heat loss.

5. Para 2, p 12 deals with the conductance of the body shell tissues. It is not clear to me why the upper level of conductance should be limited by the conductivity of blood. This appears to neglect transport of heat by blood flowing along the temperature gradient. The maximum conductance is apparently independent of the blood flow, depending only on the quantity of blood in the tissue.

6. Para 3, p 12 introduces the concept of sweat evaporation beneath the skin surface. This is plausible, but the sweat glands lie within the top half millimetre of the skin. I do not see how g can exceed about 0.025, since the tissue to which it applies is 2 cm thick.

7. There appears to be a discrepancy between the deductions summarized in Fig 7 and the experimental observation on P 11. According to Fig 7 at an ambient temperature of 19^{o}C f is about 0.6. In still air the value of f.h would be about 4, consistent with the experimental points in Fig 4 but not with the result cited on p 11."

Reply to Reviewer No. 4

1. We have tried to clarify his points.

2. We have further identified other sources of skin temperature data. The main response of Fig. 4 depends on the experimental h. Thus the issue, basically, is to find self-consistent data taken for a given free convective arrangement. The discrepancy at low temperature cannot be whistled away. It is clear in a number of people's data.

3. That is why we now have reasonable confidence in the near $h = 7$ value. True it can change somewhat with attitude or wind, but the issue is that it should be near constant in any wide range experiment.

4. We have fixed Section III. $\bar{T}_s$ may not exceed T_r, but it comes quite close. This drives the conductance value up very high.

5. We have attempted to outline further the argument of countercurrent heat exchange.

6. The difficulty of getting a plausible subsurface refrigeration held us back from ideas for 6 years. The concept, purely hypothetical, of subsurface evaporation is physically plausible. We bring it up now to get the 'show on the road'. It will take considerable controversy before the issue of how this extra heat flows is settled. There is no trouble with panting animals, but to get such evaporative augmentation from the human seems more difficult.

7. In Fig. 7 we have a theoretical result for f and g as functions of T_a. Fig. 4 shows $\bar{T}_s$ vs. T_a for assumed values of h. Since Eq. (1) is

$$M-E = hA(\bar{T}_s - T_a),$$

independent of f, it is not valid to consider fh as an effective h in Fig. 4.

An effort was made to solicit comments from one or more 'objective' thermoregulational physiologists (namely ones having no vested interest in a particular position). The following reply was obtained from a well-known European thermoregulation physiologist to our raising the question as to the possible validity of subsurface evaporation.

"August 25, 1971

Dear ___:

Thank you for your letter of 2 August. We probably understand one another fairly well, and you are not surprised that I should produce an anatomical objection to an otherwise inoffensive and useful coefficient. You must also be aware that this is a likely reaction from others. Although you may prefer to retain your own quasi-anatomical concept of this coefficient, it would sell more easily to people like me if you were to make the interpretation either more obscure or more flexible. You might, for instance, just use the coefficient on the ground that it works, and offer no explanation. This might be a sound black box attitude, but would not match the paper very well. Alternatively it might be possible to interpret the coefficient as a ratio of conductance to sweat rate or something of that sort, which needs to be mathematically identical with your depth of evaporation, while sufficiently plausible or irrelevant anatomically to excite no objection.

I am sorry you are up against ..., particularly as they must control most of the outlets on your side of the water. A journal ... is ... published by ... . The current number ... contains a fairly acrimonious exchange on the subject of heart rate and work capacity. The proportion of physiology papers is not very large, but this might in fact encourage the editors to accept your work since they like to try to cover all the disciplines concerned with their subject. Publication there might tempt your critics into the open.

Yours sincerely,"

A second round of reviews were received, dated April 14, 1972. They are responses from four people who presumably work in the physiology of thermoregulation.

Reviewer No. 1

"The authors have done a thorough job of presenting an interesting theoretical approach to establishing models for temperature regulation in humans exposed to environmental extremes, limited to those conditions within which man is capable of reaching and maintaining a state of equilibrium. They have established the limits to which their approach is applicable and have honestly pointed out the shortcomings and some of the unanswered questions.

The authors have indicated that their experiments have yielded lower $\bar{T}_s$ values than reported by others, yet Fig. 2 gives higher values (e.g., at T_a = 20°C, the fig 2 value for $\bar{T}_s \approx$ 29°C, their value for $\bar{T}_s$ = 26°) perhaps their experimental values should be included in Fig. 2."

Reply to Reviewer No. 1

As pointed out in the text, Figure 2 represents a summary of the previously published data which this paper attempts to interpret via a suitable model of thermoregulation. Thus Fig. 2 should not include later data which we were obliged to obtain in order to resolve some discrepancies between theory and experiment.

Reviewer No. 2

"I find the paper more interesting than most. It contains several ideas which are new to me, and although I do not find it possible to accept them all, for the reasons outlined below, I should welcome publication on the ground that controversial material of this sort stimulates thought.

I remain troubled about the upper limit set on the mean tissue transfer coefficient. If there is a large circulation of blood very near the skin surface, heat transport to the surface will be predominantly due to this, and could greatly exceed that to be expected from conduction through the underlying tissues. (Countercurrent heat exchange between the vessels supplying the skin would reduce the efficiency of the skin circulation as a heat transport mechanism, but this effect is hard to quantify). For this reason I find it hard to go along with the subsequent arguments about the quantity g.

Arguments about f are unaffected by this, and it seems an admirably simple way of dealing with the often neglected matter of regional vasomotor responses to cold."

Reply to Reviewer No. 2

On pages 16-17 and in footnote 36, the issue of concurrent heat exchange was treated. Not having a convincing model for that phenomenon, we simply estimated (in fact deliberately overestimated) an upper limit for that effect. This overestimated value indicated that the countercurrent heat exchange effect was not large to resolve the problem raised in the second paragraph on p. 17. Thus, we could safely neglect it for the rest of the paper. Inclusion in later calculation would tend to reduce the values of f in Fig. 7 (i.e., see Eq. (12), p. 20). The effect is small, about 10%.

Reviewer No. 3

"This reviewer finds the authors not responsive to the comments made before in the first review; it is clear that their response does not lack for aggressiveness.

It does not appear useful to repeat the objections from the physiological viewpoint.

As a specific example of the increase in oxygen uptake due to shivering we would like to present: Raven et al, Compensatory cardiovascular responses during an environmental cold stress, 5°C. J. Appl. Physiol., 29 (4): 417-421 (1970). These authors find a sustained increase in oxygen uptake in a 5°C environment from about 250 ml/min in a neutral environment to about 700 ml/min after several hours in the cold.

The assumption of the manuscript that such increased metabolism does not occur is quite central to the argument.

In general the authors and the editors have a considerable responsibility to their audience to make sure that the physiology contained in a paper such as this is beyond any criticism. The audience is not only uncritical, but is also more likely to adopt the ideas presented, since they are presented in a familiar manner. The result could be that large numbers of engineers would end up with a view of thermoregulation unacceptable to their physiological colleagues."

Reply to Reviewer No. 3

Reviewer says I was not responsive to past comments. I regret that he would not repeat his physiological objections. We attempted to answer all objections previously raised sentence by sentence. Thus this choice is a copout. The reviewer is entitled not to have any desire to continue this tedious painful process, but not simply to hide his objections by vagueness.

Thus we approach his reference, Raven et al, J. A. P. 29 (4), 417, 1970, which deals with the question of an increased metabolism (oxygen consumption) in the cold. We will grant the following: that paper shows the following responses (average for a group).

O_2 uptake	260 ml/min	at	28°C	
	510 ml/min	at	5°C	first 1/2 hr.
	580 ml/min	at	5°C	second 1/2 hr.
	680 ml/min	at	5°C	third 1/2 hr.
	710 ml/min	at	5°C	fourth 1/2 hr.

I am pleased to see the data. It does contradict our conclusions. But that brings me back to 1956-1960. The situation was contradictory then and remains so now. I will try to reconcile the issue. But first a comment. If I, an engineering type, were reviewing that J.A.P. paper, I would have rejected it for its one-sided presentation of the issue. One side is presented well, but the other side is not. I was taught that in technical quandries, both sides should be presented. For example, the test methodology is quite similar to mine of 10-15 years earlier. That work should have been referenced, since it clearly influenced the 1970 study. But the main point of my 1960 report was that data have to be reconciled at equilibrium. That was the same point of my 1972 paper. Their 2-hour data are not at equilibrium. In fact, if one wanted to judge the course from the data tabulated above or their Fig. 2 (on one subject), one could even draw the conclusion that the metabolic rates were still climbing at the end of two hours. Extrapolated one might find levels as high as 1 to 1.3 lpm oxygen uptake (see figure in text). But the fact is that I, Goodman, Lenfant have shown dynamic cycles, and I have shown that it is necessary minimally to carry data on for at least 3½ hours, more like 5 hours. Further, this study does not show temperatures. I submit that temperatures would have shown that the body hasn't achieved equilibrium.

Also these are unacclimatized subjects (over which I am not making an issue) but they are perhaps inexperienced subjects. Did they remain free of motion for the entire test period. Recent J.A.P. studies have indicated that at least 50% increase in metabolism can and does take place over almost imperceptible motions of a so-called rest state. This is further tested by the Raven report that blood flow and oxygen uptake increased as for normals, namely when oxygen went up 710/260, blood flow went up twice (5.1/2.6 lpm per m^2/lpm per m^2). The point that the rise in blood flow was not from heart rate but stroke volume is an interesting and important piece of cardiac design, but not so immediately relevant to the thermoregulation issue. Blood perfusion, needed for metabolism, and oxygen uptake stayed together. Was this really a cold response, or was it 'imperceptible' increased motion for an untrained subject. Irving's data (J.A.P. 1960) taken over 10 hours at 0°C showed most clearly that sleeping subjects did not provide any exceptional rise.

Thus we agree with the reviewer that whether "increased metabolism does not occur" or does occur is crucial. However, the point of our paper was that there is a difference of opinion, and we are willing - now anxious - to add the Raven reference with an additional last footnote. But we insist that our opponents, many of whom tend to be detractors rather than simply admitting that there are issues worthy of more explanation, permit us to publish within our own literature. They are quick to point out our responsibility to engineers within engineering literature to give papers that are acceptable to physiological colleagues. But are they willing to accept the counter responsibility? I have 25 years of record that indicates they have never been willing to permit engineering commentary in their literature. The last very formal request I made in 1971. I would take their last paragraph more seriously if I could find any evidence that they permitted us that privilege. They could put it under any label of controversiality that they choose, as long as they permitted me access to their journal for my views.

Reviewer No. 4

"This is not a very interesting paper and contributes very little. It discusses issues that have been of interest to thermoregulatory physiologists for years. Iberall and Schindler seem to confuse functional relationships and correlations. The point about the overall heat transfer coefficient being in error due to insufficient free air is quite possibly true but there are other sources of error due to the averaging for $\bar{T}_s$.

Reply to Reviewer No. 4

This is nonsense. The sentences say that our paper which discusses issues of interest to physiologists is not very interesting. I find the sentence contradictory. O.K. don't read it.

A third set of reviews was received June 15, 1972. Two are from engineers and two from physiologists. We quote without comment. No authors' replies are attached because we dictated a one-hour verbal tape in rebuttal.

Reviewer No. 1

"This paper is rather poorly written exposition by authors who apparently know very little about either heat transfer or physiology. A large portion of the paper is spent trying to justify the variation between a computed h based on simplified geometrical model and an average h based on a measured metabolic rate. It should be apparent to the authors that in both the free and forced convection models used that the h is based on an isothermal model and that the local h can be much different than an average h. The human skin temperature is obviously not isothermal. In addition the h in protected areas (between the legs, between the arms and trunk, and in the neck area as well as the shoulder areas) is obviously much smaller than unprotected areas resulting in reduced heat transfer. The seemingly frantic search of the authors to find an explanation for this discrepancy ignores these basic factors.

Again, in the discussion of the mean tissue coefficient, the authors seem to avoid the problem presented by the large variation of the thermal conductivity of fatty tissue vs. muscular tissue. The argument concerning the importance of the convection of blood made as a foot note is very unconvincing since articles by Wissler quoted by the authors point to a much more sophisticated model which indeed indicates that blood perfusion plays an important part in skin temperature.

The factor f used by the authors to denote the fraction of the body surface which has undergone complete vasoconstriction is indeed artificial. It is well known that the blood flow in the extremities of man and other mammals is at least in part controlled by the body as a thermoregulatory function. This is accomplished at moderate environmental temperatures where even in moderate conditions the temperature of the hands and feet may approach ambient temperature.

The authors' denial of the function of the hypothalamus in the control of the core temperature is not substantiated by their work. There have been numerous experiments reported in the literature with both man and other mammals which verify the conclusion that the hypothalamus is indeed the portion of the nervous system which controls the general thermal regulation.

The authors have not presented any theory of thermoregulation as they claim. At best, they have presented a "fudge" factor without any physical or physiological basis in an attempt to get better agreement between very crude heat transfer predictions and equally crude total body calorimetric results.

This is essentially the same paper which was presented by the authors at the 1971 Symposium on Temperature Measurement and Control sponsored by the National Bureau of Standards and the Americal Physical Society. Since the proceedings of that symposium is being published, the Journal may wish to check and see if this paper was accepted for publication in those proceedings to avoid republication in the event other reviewers recommendations are opposite of this review."

Reviewer No. 2

"The authors of this paper have done little more than cover an important subject with a vail constructed from the flimsy fabric of ad hoc assumptions, most of which are either unnecessary or unjustified. As such, I do not recommend it for publication in the ... .

Several specific comments are in order. One is that there exist a number of valid models in which the various terms are clearly defined and can be related to observable quantities. It seems to this reviewer that progress in the area of human thermoregulation will result from the continued development of these models, rather than from the development of new, ill-defined models. The subject of thermoregulation is really concerned with the relationship between factors such as blood flow rates, metabolic rates, and sweat rates and factors which determine the thermal state of the body. Unfortunately, the authors do not discuss this matter, but instead mention it as an unresolved issue. Finally, the authors commit such errors as suggesting that heat transfer coefficients for free convection and forced convection should be added vectorially, and stating that heat transfer by free convection can be studied by standing the subject in a shaded spot. Competent engineers should know better."

Reviewer No. 3

"This is a very stimulating paper, in large part because of the large gaps it reveals in our knowledge of the mechanisms involved in human thermoregulation. It hopefully will provoke some physiologists into providing some more insights into these mechanisms, so that a more complete theory will be possible in a few years."

Reviewer No. 4

"The engagingly written manuscript ... by Iberall and Schindler entitled, "On the physical basis of a theory of human thermoregulation", is a bold one both in its contention that the current theory of biological thermoregulation is inadequate and also in its proposal of subsurface evaporation. One may agree with the contention but find it difficult to accept the proposal. Nevertheless this sort of breezy original thinking is refreshing and the new idea should be exposed to public scrutiny instead of asphyxiation by a referee. Hence I am recommending that it be published. I hope you will find my reasoning acceptable."

It seems clear that some physiologists see a different status for human thermoregulation theory than some engineers.

And still another review was received July 21, 1972.

"The manuscript by Iberall and Schindler has been studied carefully by three different individuals in this Department including myself. All of us have had considerable experience in the physiological aspects of temperature regulation although none of us are trained engineers. Your final judgment should take these facts into consideration.

We are in basic agreement that the presentation contains ideas and information of merit and worthy publication, but it would seem that such repetitious material should be deleted with emphasis upon the conceptual ideas and the new data. Much of the introductory material is repetition of well known facts arising from existing literature. In our judgment, the concepts proposed can readily be established from this body without describing its background and origins except to credit responsible authors. Evaporation from regions below the skin surface is an interesting and plausible idea--I happen to agree with the concept and believe we have observed evidence for it. As one of my colleagues states (see below) Dr. Iberall should be able to calculate the approximate quantities to be lost this way if his other estimations are valid. In sum, we believe parts of this paper are worth publication, but it will require condensation and "tightening" before this is warranted.

The specific suggestions and criticisms of one of my colleagues are listead as follows:

1. Although the role of the hypothalamus has been somewhat overplayed, little evidence is given to support this contention and statements in the summary section #7, page 29 should be withdrawn.

2. References which consist of collections of various authors' works, 3, 4, 7, and 19, are useless because the reader does not know which author is being referenced.

3. Many of the references are unedited and not generally available and, hence, of little value to the reader, e.g. almost all NASA or military type publications.

4. Section II seems to be OK.

5. Section III (see page 16) the basic assumptions of Bazett and McGlone hold until shivering occurs. This shivering heat production could account for a 20-30% increase in heat production which would not be accounted by the simplified version of the mean tissue coefficient equation (see equation 7). This is due to the fact that the shivering heat production would not be measured by the T core. Thus, apparent "conduction" would be in error during shivering.

6. The last paragraph of p. 16. Where do the expected "conductivity" values come from? Do they account for the near 100 fold changes in cutaneous blood flow that can occur?

7. I agree that evaporation can occur in the skin and, hence, it can vary the calculated "conductivity" calculation? The authors should calculate the amount of water which would be evaporating in this manner and then ask the question.

8. Page 18 and also figure 6. Isn't it misleading to say that g would only reach 0.33 value when, in fact, the C could reach 25 and thus g would be even smaller than 0.33?

9. Pages 19-21. The calculation of a weighted mean skin temperature corrects for "f". The authors consider areas of the body with low temperatures as being not part of the regulation system. How can this be implied when one considers the fact that the skin temperature of these areas are at least 10°C higher than the environmental temperature? The body is obviously losing a great deal of heat by these areas and cannot be neglected.

10. Parts of this paper are worth publishing, but not the whole article.

Our combined advice would be to return the manuscript for some condensation in length, taking into account the specific questions posed. A clearer picture of what aspects of current hypotheses are acceptable to Dr. Iberall needs to be distilled, a concise presentation of how he would change specific items, and finally, a carefully organized scheme which incorporates his suggested alterations. Since he has not contributed very much new experimental data himself (at least he does not present them in this paper although he speaks often about them) he must clearly separate fact from fancy and work all of them into a well integrated schema which the reader can evaluate."

We accepted the spirit of this review but countered its specific comments in detailed ways that are not of great importance. Perhaps at this point it would be much more interesting to the reader to read the present form of the paper, which follows, to provide his own judgment.

Abstract

Thermoregulation is commonly described as hypothalamic 'feedback' control of a servomechanical 'set point'. Review of steady-state data (nude, resting human, low wind and humidity, 5°-45°C ambient temperature T_a) does not support this concept. Instead careful study of the physics and physiological physics is suggested to clarify the role of the hypothalamus. The following illustrate unresolved problems.

Reported mean skin temperatures $\bar{T}_s$ vs. T_a are incompatible with the physically determined skin-to-air transfer coefficient of about 7 kcal/m^2/hr/°C. At low ambient temperature, either mean metabolism M must be higher or $\bar{T}_s$ must be lower, or the physical conductance must be rejected. One experimental test suggests that $\bar{T}_s$ is lower than commonly quoted (e.g., $\bar{T}_s$ = 26°C instead of 30°C at T_a = 20°C). We believe that such discrepancies arise if free convective transfer is suppressed or if experiments are not carried on to equilibrium. We thus emphasize the test requirements for equilibrium of the body. The mean metabolism may reach its near equilibrium value in about 20 minutes after initial exposure. However, heat storage and changes in tissue temperature are significant for closer to 2 hours, and it takes at least 3 hours of sample data to obtain accurate equilibrium temperature measurements. Also, there is no solid evidence for low tempera-

ture metabolic (so-called chemical) regulation; in the cold equilibrium M rises only 20-30%, not 200-300% as proposed by some workers. A second problem, at high ambient temperature, is that the usual definition of mean tissue conductance $[\bar{C} = M/(T_c - \bar{T}_s)]$ leads to nonphysically large $\bar{C}$ when $\bar{T}_s$ approaches deep-body temperature T_c.

To resolve these difficulties we offer two hypotheses: (a) the body self-regulates to maintain a vital 'regulated' core; peripheral regions cool, e.g., extremity surface temperatures drop toward ambient; the regulated core 'contracts' longitudinally; (b) a significant portion of the evaporative heat loss may occur below the skin's surface, possibly in the sweat glands. Adjustment of two parameters emerging from these hypotheses allows a consistent modelling of steady-state thermoregulation. They are offered for physiological study. It is suggested that hypothalamic control is one component of regulation operating at higher frequency (with 7 minute period) than a steady-state self-regulation (3 hour period).

Introduction

In this paper we undertake an examination of the physical factors that may lead towards a theory of human thermoregulation.

We shall show that there exist discrepancies between predictions of generally accepted theory and results of generally accepted experiments. The objective of this paper is to identify those discrepancies, explain why they have arisen, and propose some new ideas for their resolution. For this first effort, in order to make our major points as clearly and simply as possible, attention is restricted to the steady-state (equilibrium) characteristics of the nude, resting human. (Thus complexities, which would otherwise confuse discussion of transient effects or of the effects of exercise or of the effects of clothing, are deliberately avoided.) This represents the mathematically and conceptually simplest real case in which all relevant physical facets of the problem can be examined.

There has been inadequate discussion and controversy concerning the stringent requirements to achieve a true equilibrium of the human thermoregulatory system. On the basis of previous studies and reports (1), we will regard a physical steady-state to be achieved when it has existed for a few multiples of 7 minutes and can be sustained for more than 4 hours with only negligible variation in all time-averaged parameters. There is evidence that 7-20 minutes is sufficient settling time for oxygen consumption, blood flow, pH and carbon dioxide equilibria, but that a minimum of 4 hours is the time required to achieve an accurate open thermodynamic equilibrium.

These numbers were obtained experimentally over an ambient temperature range of 15°C to 35°C, at rest or at exercise. To summarize the findings: any change in sustained conditions (e.g., ambient temperature or activity level) leads to an initial transient which completely dominates all other effects for the first 7 minutes. Even after the first 20 minutes, a system is still under the influence of the initial transient. At all times there is a high frequency cycle (2 minute period) in metabolism and a low frequency cycle (7 minute period). After 20 minutes the average metabolism is determinable with an accuracy of about 10-15% by taking 2-10 minute averages of sample data. There is thenceforth little subsequent change in metabolism. However, the taking of sample data averages is required for the next 3-5 hours to determine the average metabolism to 1-2% accuracy. In the case of body temperatures (or 'storage') a much slower transient exists. There are lower frequency cycles (30 minute and 3½ hour periods), and a time on the order of 60-90 minutes is required for the initial transient to die out. After that the mean temperature at any station would not change very much, but the cycles would continue. Thus a minimum of 4 hours are needed to achieve equilibrium in temperature and to avoid storage (2).

In its simplest form the problem of equilibrium thermoregulation can be formulated as follows:

There are essentially two independent variables, a maintainable activity level of the subject (e.g., resting, walking, running) characterized by his metabolism M, and a measure of the environmental conditions summarized by an "ambient" temperature T_a. In this paper, for the purpose of emphasizing the sharp physical issues which emerge, we consider only one sustainable activity level, the resting state of the nude human. The ambient temperature represents a combination of the air temperature, the radiative wall temperature, and the relative humidity. The air and radiative temperatures shall generally be taken to be the same. The relative humidity is not important at low ambient temperatures, but plays an important role at high temperatures (3).

Given the two independent experimental variables, one seeks to model the observable dependent variables: deep-body or 'core' (e.g., rectal, tympanic membrane, cranial) temperature T_c, mean (over the body) skin temperature $\bar{T}_s$, and evaporative heat loss E. The essential physical requirement for equilibrium is that the metabolic energy produced within the body must be conducted or convected to the body's surface and thence conducted, convected, or radiated to the environment. There may be heat storage during the (transient) approach to equilibrium, but in the steady-state there can be no time-averaged energy storage in the body. Failure to satisfy this condition implies continuing changes in time-averaged body temperatures, and thus a non-equilibrium situation. (Appreciable change in deep-body temperature is incompatible with life.)

Examination of published data thought to be relevant to thermoregulation reveals that much of it is short time scale (less than 1 hour) 'dynamic' data. Other investigators, forming their conclusions largely on the basis of such dynamic data, have generally proposed or implicitly assumed putting the burden of thermoregulation on the hypothalamus, with that structure acting essentially as a thermostat with a specified 'set-point' (4-9). While this proposition may be valid for short-term regulation, one must keep an open mind as to possible roles for the hypothalamus or other structures in long-term equilibrium regulation (10, 11).

One must search the literature rather carefully to find true equilibrium data (12). A brief summary of available equilibrium data (1c, 5, 13-19, 29) which must be accounted for by a model of steady-state human thermoregulation is provided in Figures 1-3.

1. Deep-body temperature T_c is nearly constant, independent of ambient temperature, for a given activity level. For a resting nude human, it is near 37°C and varies only about 1°C as T_a varies from 0°C to 45°C. At equilibrium, or near equilibrium, the variation of deep-body temperature appears to be that described by Nielsen (20, 21) and Lind (22).

The question naturally arises as to whether the near constancy of T_c represents autoregulation of the system or the existence of a 'set-point' temperature to which some feedback controller continuously adjusts the system. With regard to this question, Hardy (6) correctly reviewed our 1960 point of view (1a) in the statement that "the equations for heat transfer from the body and for body temperature equilibrium together with the control systems equations should provide the necessary material for a complete systems analysis of the physiologic temperature regulator. However, there is not sufficient information concerning the details of the regulator [of the set-point] to make this a worthwhile effort at this time". In spite of an endless repetition in the literature of some graphs which purport to show evidence for a controlled 'set-point', we have no reason to change our original opinion (23). We did not then and we do not now have any completely satisfactory basis upon which to account for this fairly well-regulated temperature.

In recent years there has been much discussion of the relative merits of rectal, esophageal, or tympanic membrane temperatures as measures of a deep-body temperature. However, the experimental data of Nielsen (21) and Saltin (24) show little difference in results for esophageal and rectal temperatures, the former being a few tenths of a degree lower than the latter in the range 5-30°C. Likewise, tympanic membrane temperature differs little (25, 26). Thus, we make no distinction and simply refer to a deep-body or core temperature T_c.

2. At a given activity level, the metabolism is nearly constant over most of the ambient temperature range compatible with life (Fig. 1). At either end of that range there is an approximately 20-30% rise in metabolism and then an abrupt drop, leading to death. We interpret those rises as energetic charges placed on the cardiovascular system, to provide the blood flow in a peripherally vasoconstricted state at low temperatures, or to maintain profusely discharging sweat glands in a highly vasodilated state

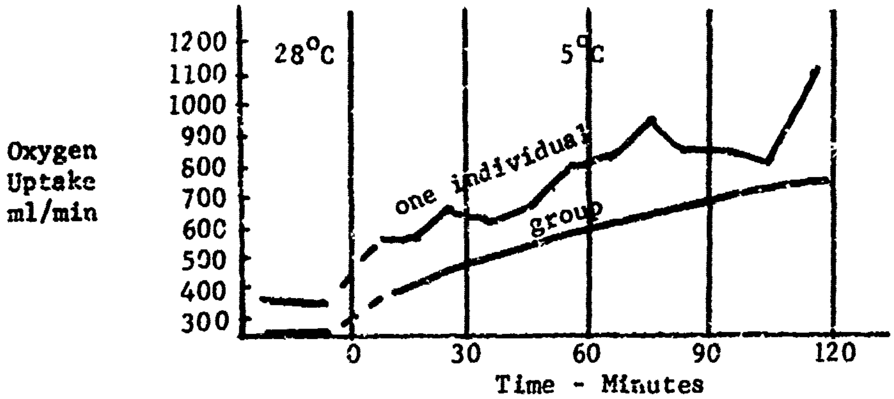
at high temperatures. Increase in activity level shifts this curve upwards and toward lower temperature. However, in this paper we will be concerned only with the resting state.

We specifically point out and emphasize that a 20-30% change in metabolism is the most that can be expected in the steady-state in cold environments. There are larger transient changes, and also continuing cyclic changes, but the time-averaged mean value of M stays within about 30% of its value at 'thermal neutrality' (i.e., minimum M for a given activity level). Such limitations in variations of M have been measured by us and can also be found in the literature (1c, 5, 12, 17, 29). One exception to this is a study by Raven et al (49) who show a metabolism at 5°C double that at 28°C at the end of ½ hour, and nearly triple at the end of two hours. If anything, the study might be faulted for not having been carried on long enough. There is the suggestion in their data that metabolism might have 'leveled off' to an equilibrium value four to five times greater than at 28°C. However, it demonstrates that there still remains room for further experimental study to determine equilibrium results.

Data from Raven et al (49)
Step function from 28°C to 5°C.
Average for group of 11.

	Heat production kcal/m^2 hr	Oxygen uptake ml/min
End of 28°C exposure	40	260
Step to 5°C		
End of first ½ hour	78	510
second ½ hour	88	580
third ½ hour	103	680
fourth ½ hour	107	710

One Individual Profile



In our case, we were impelled to our 1964 experiments (1c) because of unreliability in interpreting the then existing data. For example, Hardy and DuBois (15) had left the impression that the body shivers in cold and perhaps doubles its metabolism. The fact is that, at all temperatures, metabolism continually cycles by a factor of nearly 2:1 (1c, 27, 28), which has nothing to do with shivering. In the cold there may be transient shivering and continued bouts of shivering, but measurements show the same harmonic spectrum of metabolism. In the time-average, taken over a minimum of 3½ hours, metabolism does not change much after the first 20 minutes. The time-averaged mean metabolism shows only a moderate rise for the same activity (e.g., rest) at 0°C as compared to 30°C (Iberall (1c), 5 hour data; Irving et al (29), 10 hour data).

3. Mean skin temperature (an area weighted average) as a function of ambient temperature is shown in Fig. 2 for a resting human. The observed range is from $\bar{T}_s = 22°C$ at $T_a = 5°C$ to $\bar{T}_s = 37°C$ at $\bar{T}_a = 45°C$.

4. When (local) skin temperature reaches about 32°C, sweating begins and, by 35°C, sweating is profuse. The heat lost as evaporation by a resting human (low humidity, low wind) is shown in Fig. 3. At rest, E ranges from 10 kcal/m^2/hr at $T_a = 25°C$ to perhaps 130 kcal/m^2/hr at $T_a = 45°C$.

It has been customary (5, 6, 9) to describe thermoregulation in terms of three distinct physiological mechanisms and approximate temperature regimes, a 'metabolic control' for $\bar{T}_s < 32°C$, a 'vasomotor control' (the vasodilation or vasoconstriction of the tissue vasculature) for $32°C < \bar{T}_s < 35°$, and a 'sudomotor control' (i.e., sweating) for $\bar{T}_s > 35°C$.

In proceeding toward a model of steady-state thermoregulation, we move in accordance with the following constraints. First, the model must be consistent with physical law; ad hoc hypotheses are not permissible. Second, the model must conform to experimental findings. Many physiological issues are still uncertain. Thus, in reexamining conventional physiological wisdom for consistency with these constraints we have some freedom to develop new ideas and hypotheses which might help to illuminate the underlying regulatory mechanisms.

We will attempt to formulate the thermoregulation problem in a way which clearly separates its physical from its physiological aspects. The function of the thermoregulatory system is to maintain a near constant deep-body temperature T_c. Thus, in the steady-state, the heat produced within the body (i.e., the metabolism M) must ultimately be transferred to the environment. This transfer can be thought of as taking place in two stages: transfer from a core, where most of the heat is generated, to the surface, and then transfer from the surface to the environment. Clearly, the first transfer requires determining physical heat transfer coefficients in terms of physiological mechanisms, for example, blood flow, its local distribution, sweat mechanisms, etc. The second transfer, into the environment, is essentially a physical problem, with transfer coefficients depending on geometric factors, surface and ambient temperatures, the properties of air, the wind velocity, and whether the surface is wetted.

Surface-To-Air Transfer - A Physical Problem

Heat is transferred from the surface to the environment by radiation, conduction, free (i.e., no wind) or forced (i.e., a wind) convection. The total heat transfer coefficient h is some combination of the coefficients for these separate processes. For the steady-state, it is defined by

$$M - E = hA\,(\bar{T}_s - T_a) \qquad (1)$$

where A is the total surface (i.e., DuBois) area. (As a minor point, we mention that about 10% of the metabolism and of the evaporative heat loss are lost by evaporation in the breath. Thus M and E above (and henceforth) actually approximately represent (M - .1M) and (E - .1E), i.e., only the transfer across the skin determines the coefficient h.) Rewriting (1) gives

$$\bar{T}_s = T_a + \frac{M - E}{Ah} \qquad (2)$$

In Fig. 4 $\bar{T}_s$ vs. T_a is plotted for various values of h and compared with the data (dots). (Here $A = 1.8m^2$, a typical value.) With the defining equation (1), empirical values of h vary from about 7 kcal/m^2/hr/^{o}C at $T_a = 45^oC$ to about 3-4 kcal/m^2/hr/^{o}C at $T_a = 5^oC$.

In pursuit of a satisfactory theory of human thermoregulation, one must be able to predict these values of h or, more broadly, one must be able to correctly predict the mean skin temperature $\bar{T}_s$ as a function of ambient temperature T_a. Thus, our first efforts must be directed toward developing a theory of h. We hasten to point out that this is not the first time that this is being done. We and others have done it before (5, 30, 31, 32). A more useful recent review is presented by Colin et al (32). However, in this round special attention is paid to important details about the components of h which were overlooked in previous evaluations of the theoretical results.

The contributions to h of radiation and free and forced convection are now evaluated. These can be found in standard references (33, 34).

Radiation. The heat transfer coefficient due to radiation is estimated in the following way. The skin is assumed to be a perfect black body - its emissivity is 0.99 (5). According to Stefan's law, the body receives $s\,\tau_a^4$ kcal/m^2/hr (with $s = 4.94 \times 10^{-8}$ kcal/m^2/hr/(^{o}K)^4 and τ absolute temperature ^{o}K) and emits $s\,\bar{\tau}_s^4$ kcal/m^2/hr. The effective radiating surface is about 3/4 of the DuBois area (5), so that the net heat radiated from the body is

$$H_r = 0.75sA\,(\bar{\tau}_s^4 - \tau_a^4).$$

If we define h_r via $H_r = h_rA\,(\bar{T}_s - T_a)$ then

$$h_r = 3.7 \times 10^{-8} (\bar{\tau}_s^{\,3} + \bar{\tau}_s^{\,2}\ \tau_a + \tau_a^{\,2}\ \bar{\tau}_s + \tau_a^{\,3})\ \text{kcal/m}^2\text{/hr/}^o\text{C}$$

and, putting $\bar{\tau}_s = \bar{T}_s + 273$, $\tau_a = T_a + 273$, we have approximately

$$h_r = 3.0 \,[1 + .0055\ (T_a + \bar{T}_s)]\ \text{kcal/m}^2\text{/hr/}^o\text{C} \qquad (3)$$

With the data of Fig. 2, the contribution of radiation is plotted (Fig. 5); h_r is in the range 3.3 to 4.4 kcal/m^2/hr/^{o}C for $5^o < T_a < 50^o$C.

Free Convection. The value of the heat transfer coefficient for free convection depends on the temperature difference between skin and air and on geometrical factors (e.g., the size, shape, and orientation of the individual, and the size of the chamber in which the experiment is performed).

The analytical solution of free convection problems is very difficult and only the most simple problems have been treated. However, there exists in the literature (cf. the bibliography in Ref. 33) a large body of experimental correlations which summarize the results of free convection experiments in both the laminar and turbulent flow regimes. Three dimensionless numbers are used in correlating free convection data.

The Nusselt number Nu indicates, in some sense, the efficiency of the convection process, i.e., it compares the convective energy transport to the energy that would be transferred by simple conduction. For a body characterized by a dimension D, transferring heat into a medium of conductivity k, for which a heat transfer coefficient h is measured, Nu is defined by Nu = hD/k. Clearly, if one can determine the Nusselt number one can calculate h.

The Prandtl number Pr is a dimensionless combination of some gas properties. For air, Pr is essentially a constant ($Pr = c_p\mu/k = 0.71$, where μ = viscosity, c_p = specific heat).

The Grashof number Gr represents the ratio of the buoyant force to the viscous force on an air 'element', $Gr = gD^3\ \Delta T/\nu^2\tau$, where the acceleration of gravity g = 980 cm/sec^2, the kinematic viscosity ν = .14 cm^2/sec (air), $\Delta T = |\bar{T}_s - T_a|$, τ is the absolute temperature, and . is the same characteristic dimension as in the Nusselt number. An important point is that if the individual is situated such that distances between him and the walls are smaller than D, then one must replace D in the Grashof number by that smaller dimension (ref. 34, p. 181). Since wall proximity tends to decrease the buoyant force with respect to the inertial forces, the free convection may be substantially suppressed.

Dimensionless analysis of the fundamental transfer equations (ref. 33, chap. 23) shows that Nu is a function only of the product Gr Pr. The value of the relationship depends on the geometry of the particular situation.

To illustrate, we consider two cases, the first with an individual in a horizontal position, the second with him in a vertical position. In both cases, for simplicity of modelling, we represent the person by a cylinder of diameter about 1 foot and height about 6 feet. For horizontal cylinders experimental correlations (ref. 34, pp. 177, 180) for h_{free} (in kcal/m^2/hr/^{o}C) are

$$h_{free} = 1.10\ (\Delta T)^{1/3}$$

for $10^9 < Gr\ Pr < 10^{12}$; turbulent flow; $\bar{T}_s > T_a$

$$h_{free} = 1.57\ (\Delta T)^{1/4} \tag{4a}$$

for $10^3 < Gr\ Pr < 10^9$; laminar flow; $\bar{T}_s > T_a$

and

$$h_{free} = 0.7\ (\Delta T)^{1/4} \tag{4b}$$

for $3 \times 10^5 < Gr\ Pr < 3 \times 10^{10}$; laminar flow, $\bar{T}_s < T_a$. (The last result is for a horizontal plate, but there is little difference between plate and cylinder results.)

For vertical cylinders, with D = 6 feet, the experimental correlations (ref. 34, p. 173) are

$$h_{free} = 1.16\ (\Delta T)^{1/3} \tag{5}$$

for $10^9 < Gr\ Pr < 10^{12}$; turbulent flow; $\bar{T}_s > T_a$

and

$$h_{free} = 1.08\ (\Delta T)^{1/4}$$

for $10^4 < Gr\ Pr < 10^9$; laminar flow; $\bar{T}_s > T_a$.

(Note: these correlations were made from measurements on objects perhaps as much as a foot high. Their valid extrapolation to 6 foot heights is not assured.)

Evaluating the Grashof number according to its definition, with τ = 300^{o}K and Pr = 0.71 gives

$$Gr\ Pr = 3.4 \times 10^6\ \Delta T \qquad D = 1 \text{ foot (horizontal)}$$

and

$$Gr\ Pr = 7.3 \times 10^8\ \Delta T \qquad D = 6 \text{ foot (vertical)}$$

Thus, for horizontal positions, laminar regime results hold, while for vertical positions turbulent regime results hold (for $\Delta T \approx 2\text{-}10^{o}C$).

Since the position of the subject is often not stated, or a variety of positions are allowed during the same experiment, the best we can do is to indicate likely values limiting the range of h_{free}. The largest values of h_{free} come from the horizontal laminar results, while the smallest come from the vertical turbulent results. When the skin surface is cooler than the environment, we have only the one horizontal laminar result. The values of h_{free} for the vertical and horizontal cylinders do not differ much, as a consequence of a nominal length to diameter ratio of about 6:1. Thus, since two 'extreme' orientations yield nearly the same values, those values of h_{free} should be fairly good for any orientation. The value of h_{free} averaged between the vertical (5) and horizontal (4a) results is used for $\bar{T}_s < T_a$ and the value of h_{free} from the horizontal result (4b) is used for $\bar{T}_s > T_a$ (Fig. 5).

<u>Forced Convection</u>. When the air in the vicinity of the subject is driven by some potential gradient, the convection of heat from the surface is termed forced convection. For such cases the Nusselt number is correlated with the dimensionless Reynolds number, $Re = DV/\nu$, where D is again a characteristic dimension, V is the air velocity, and ν is the kinematic viscosity of air. If we again assume a body to be representable by a cylinder 1 foot in diameter, then the Reynolds number becomes

$$Re = 95\ V \qquad (V \text{ in feet/min})$$

For flow parallel to the axis of the cylinder (ref. 33, pp. 554-557)

$$h_{forced} = .4\ V^{1/2},\ V < 400 \text{ ft/min (laminar flow)}$$

$$h_{forced} = .07\ V^{0.8},\ V > 400 \text{ ft/min (turbulent flow)}$$

For flow perpendicular to the axis of the cylinder (ref. 33, p. 560)

$$h_{forced} = .34\ V^{.466},\ 0.4 < V < 40 \text{ ft/min} \qquad (6)$$

$$h_{forced} = .20\ V^{.62},\quad 40 < V < 400 \text{ ft/min}$$

$$h_{forced} = .06\ V^{.80},\quad 400 < V < 2500 \text{ ft/min}$$

There is little difference between results for perpendicular or parallel flow. Results of perpendicular flow (6) are shown (Fig. 5) for V = 15 ft/min, a nominal very low forced convection velocity.

A difficult mathematical problem arises when both free and forced convection occur simultaneously. McAdams' recommendation (ref. 34, p. 258) that the higher value be used seems questionable when h_{forced} and h_{free} are of the same order, as occurs in this problem. We would suggest that a 'vector' addition be used and the total convection coefficient h_c be written as

$$h_c = \sqrt{h^2_{forced} + h^2_{free}}$$

The total heat transfer coefficient h is then the arithmetic sum of the radiative and convective contributions. This h is shown in Fig. 5. For low forced convective velocities ($V \approx 15$ ft/min as attempted in many experiments), h nearly equals 6-7 kcal/m^2/hr/^{o}C across the entire ambient temperature range, regardless of the orientation of the subject.

These results are quite consistent with those of previous investigations. For example, we can cite the results of Colin et al (32) who computed h for a forced convection velocity of about 70 ft/min. They obtained a forced convective contribution approximately twice ours and a total conductance coefficient of h = 10 kcal/m^2/hr/^{o}C. For low wind conditions, other workers have also computed h = 6-7 kcal/m^2/hr/^{o}C.

Although these theoretical results may be generally accepted, they are apparently inconsistent with the experimental data obtained in thermoregulating experiments. In particular, Fig. 4 shows that h should vary between 3 kcal/m^2/hr/^{o}C at T_a = 5^{o}C and 7 kcal/m^2/hr/^{o}C at T_a = 45^{o}C. There is thus a need to explain the discrepancy between the value of h predicted on physical grounds and value of h measured by previous investigations of thermoregulation (including ours).

This problem is actually not new with us. It was apparently discovered quite independently by Colin et al (32). They noted that, in the cold, they measured h = 7 kcal/m^2/hr/^{o}C instead of an expected h = 10 kcal/m^2/hr/^{o}C (Fig. 7-4 in ref. 32; recall that their forced convective velocity was four times greater than the velocity on which our calculations were based). However, they failed to consider that their results represented a serious divergence of theory from experiment (35).

Actually, the theory presented here does permit values h $\approx$ 3 kcal/m^2/hr/^{o}C, but only under somewhat artificial conditions. For example, if the free convection were suppressed by closely confining the subject, and if the wind velocity were 'zero', and if the radiative wall temperatures were adjusted to reduce radiation, then one could obtain h = 3 kcal/m^2/hr/^{o}C. However, most experiments reported in the literature were performed under more ordinary conditions, with major efforts apparently being made to maintain the temperature close to the nominal value and to maintain specified non-zero wind velocities. Yet, even given ordinary conditions, there still remains a variety of subtle ways in which the measured heat transfer coefficient can be affected.

The heat transfer coefficients above were computed on the assumption that a steady state was reached; that the subject's body area was maximally exposed; and that free convection was not suppressed. If an experiment in a cool environment is not carried out over a long enough time, mean skin temperature may not have fallen to its final equilibrium value. The value of h will then appear to be smaller than it really is. If the subject is partly or lightly clothed, or if he is allowed to shield himself or protect himself by curling up, or if the space around him is insufficient to allow a free convection flow, then the measured value of h will be less than the calculated value. We suggest that one or all of these effects may have combined to produce values of h as low as 3 kcal/m^2/hr/^{o}C near T_a = 5^{o}C.

Indeed, we strongly suspect that the last possibility, the suppression of free convective flow, is the principal reason that experimental values of h are low compared to predicted values. In reviewing the experimental arrangement of our own 1964 study, we realize that in outlining its theory we had overlooked the fact that we were not and could not have been making measurements with a fully established free convective flow. That would require 20 feet of room height. Instead, vertical free convection was intentionally suppressed. Thus we had measured h = 6.0 kcal/m^2/hr/^{o}C at T_a = 29^{o}C and h = 4.3 kcal/m^2/hr/^{o}C at T_a = 20.5^{o}C. From what we know of others' work, it seems likely that they similarly, unsuspectingly, may have suppressed free convection. The consequence of suppressing free convection is to reduce h by approximately 3 kcal/m^2/hr/^{o}C in the cold (e.g., see Fig. 5).

Why was there no similar discrepancy in warm environments? Figure 5 shows that h_{free} becomes small (it depends on the temperature difference T_a-$\bar{T}_s$) and so, even if the free convection is suppressed, only a slight difference is made in the total h.

We believe that this provides at least an a priori explanation and reconciliation of theory with experiment. To test this one specific issue, we performed an experiment at an environmental temperature of 19^{o}C, in an open (shaded) space, with a male subject wearing only a brief nylon bathing suit. After four hours a mean skin temperature of 26-27^{o}C was recorded. This is about 3^{o}C less than the value in Fig. 2 and it lies nearly on the line h = 7 kcal/m^2/hr/^{o}C in Fig. 4. Thus this datum is strongly suggestive of what we have been driving for, namely that the theory of h established directly from physical principles is consistent with equilibrium measurements. There yet remains a need for further measurements of mean skin temperatures in ambient conditions below 20^{o}C. They should be made under the following conditions: (1) nude or nearly-nude fully extended subjects, (2) a minimum 3-4 hour exposure, (3) low wind velocity (less than 1 mph), (4) open space (i.e., distances to walls should be about 20 feet) around the subject. Only then can there be confidence that the data are suitable for comparison with the theory.

Heat Transfer Through the Skin - A Physical-Physiological Problem - Some New Ideas

The approximate linear associative dependence of deep body temperature $\bar{T}_b$ on average skin temperature $\bar{T}_s$, and deep body temperature T_c at any operative equilibrium, namely

$$\bar{T}_b = aT_c + b\bar{T}_s \qquad (7)$$

and the gross linearity of tissue temperature with depth (see Bazett and McGlone (5)) are generally regarded as sufficient basis for describing a body peripheral zone by a tissue conductance.

The mean tissue transfer coefficient, in the steady-state, is defined as (5, 19, 48)

$$\bar{C} = \frac{M/A}{T_c - \bar{T}_s} \qquad (8)$$

Clearly, this definition is inappropriate as $\bar{T}_s$ approaches near to T_c, as occurs in a hot environment. M is never less than about 80 kcal/hr for a living subject and physically $\bar{C}$ cannot be 'infinite' under any conditions. To avoid incompatibility with the second law of thermodynamics, some other energetic process must intervene. This was intimated in an earlier discussion (1b) without any satisfactory hypothesis being advanced.

A first task is to determine likely approximate physical-physiological limits on $\bar{C}$. The physical expectation for the conductivity of tiss· is a variation from about 18 kcal-cm/m^2/hr/^{o}C when vasoconstricted (i.e., as if it were the conductivity of fat) to about 50 kcal-cm/m^2/hr/^{o}C when vasodilated (i.e., as if it were the conductivity of water, or blood). Thus tissue conductivity is an active physiological parameter. With an average tissue thickness (from the surface to the middle of the muscle layer) on the order of 2 cm (5) the mean conductance $\bar{C}$ would then be expected to vary from 9 to 25 kcal/m^2/hr/^{o}C, (In a warm environment there might be an additional increment to C arising from the countercurrent heat exchange of warm blood flowing near the surface and cooling there. An overestimated upper limit to this contribution is about 15 kcal/m^2/hr/^{o}C (36). Thus, the effect is not important and will be neglected.)

Values of C computed from the data of Figs. 1-3 and found in the literature are considerably in excess of 25 kcal/m^2/hr/^{o}C at high ambient temperatures (5, 37). Thus, we conclude that the definition in (8) is inadequate and that some other mechanism contributes to a consistent determination of $\bar{C}$.

In suggesting a mechanism which is compatible with physical values of $\bar{C}$, we are guided by the following consideration. There are collections of fluid beneath the surface of the skin, for example, in the sweat glands.

Thus, we hypothesize that at least part, and under some conditions, all of the evaporative heat loss may take place beneath the skin's surface. (That is, the subcutaneous tissues may have structures which act as a refrigerator. Whether these hypothesized structures are identifiable with the sweat glands or some other well defined functional unit remains to be determined.) The evaporated water vapor passes out through pores. When the water vapor partial pressure in the pores exceeds the saturation pressure, sweat seeps to the surface and evaporation takes place there. Gagge's concept of a variable wetted surface (5) then becomes applicable.

The subsurface evaporation proposed here is not to be confused with the type of water vapor diffusion originally suggested by Buettner (38). That mechanism was proposed to account for a part of the insensible evaporative loss. The total insensible loss is only about 10% of E. We are suggesting that there is a mechanism which can generate considerably greater subsurface losses. Whether or not that process turns out to be a simple diffusion or some more complex mechanism is not clear.

Thus, we propose that in the definition of $\bar{C}$, M should be reduced by that fraction g of the evaporation E which takes place beneath the surface. (That is, for g = 1, all evaporation is subsurface and the skin is dry; for g = 0, all evaporation is from the surface, perhaps indicating a completely wetted surface.) Then the mean tissue conductance should be redefined as

$$\bar{C} = \frac{(M-gE)/A}{T_c - T_s} \qquad (9)$$

With the data in Figs. 1-3, $\bar{C}$ vs. T_a is plotted for various values of g, Fig. 6. The curve g = 0 corresponds to the previous definition of $\bar{C}$ (8) and illustrates the unacceptably high values of $\bar{C}$. With g greater than zero, the values of $\bar{C}$ can be maintained within physiological-physical limits, at least at high ambient temperatures. In particular, $\bar{C}$ reaches a level near 18 kcal/m^2/hr/^{o}C for g approximately 1/3. As a first approximation, that value for $\bar{C}$ is close enough to the expected limit of 25 to be reassuring of some a priori merit to the model. What the physiological significance of a limiting value of g = 1/3 or thereabouts might be is not known.

The value of $\bar{C}$ measured at low ambient temperatures indicates another difficulty. Here $\bar{C}$ = 3 kcal/m^2/hr/^{o}C is measured (Fig. 6), while the expected physiological lower limit on $\bar{C}$ is apparently 9 kcal/m^2/hr/^{o}C. This difficulty is independent of the validity or utility of our first hypothesis above. That is, the value of g plays an insignificant role in determining the value of $\bar{C}$ at low ambient temperatures, where E is considerably smaller than M.

The usual response to this problem would be to claim that, due to a 'metabolic response' such as shivering, M increases enough in the cold so that computed values of $\bar{C}$ would be at least 9 kcal/m^2/hr/^{o}C. Clearly, M would have to increase by about a factor of 3 (cf. Eqs. 8 or 9) to raise $\bar{C}$

from 3 to 9 kcal/m^2/hr/^oC. However, we have shown that, for a given activity level, M does not change more than about 30% over the survivable temperature range (Fig. 1). (Note that even the doubling of metabolism suggested by some investigators is not sufficient to resolve the issue.) A more realistic mechanism is required.

The following observation opens a potentially fruitful direction for modelling. After 2 or 3 hours in the cold, one's extremities (arms halfway to the elbow, legs halfway to the knee) blanch and their temperatures drop toward the ambient temperature (e.g., see refs. 1b, c). Some longer time scale regulatory mechanism has responded to the cold and redirected blood flows, abandoning the extremities in order to maintain regulation over a vital core. Much less heat is then transferred to the environment across these unregulated areas (the temperature difference approaches zero, evaporative loss is negligible). To represent this idea in the two heat transfer equations (1, 9) let f be the fraction of the total area which remains regulated. The transfer equations become

$$M-E = f\, h\, A\, (T_s - T_a) \tag{10}$$

$$M-gE = f\, C\, A\, (T_c - T_s) \tag{11}$$

where T_s is the mean temperature over the regulated regions and C is the tissue conductance corresponding to T_s. The mean temperature over the whole surface is defined as

$$\bar{T}_s = f\, T_s + (1-f)\, T_a \tag{12}$$

To summarize: The equation set (10, 11, 12) is proposed as representing steady-state thermoregulation of the body. The coefficient h is a physical factor with a value near 7 kcal/m^2/hr/^oC. The coefficient C represents an active physical-physiological mechanism. The parameters f and g are physiological-physical parameters which characterize complex physiological mechanisms, whose effects are summarized quantitatively in this crude way but whose detailed physics and physiology are not yet understood.

The next step is to determine a course of the parameters f and g consistent with observations within the range $5^oC < T_a < 45^oC$. A first requirement is a model of the physical-physiological behavior of C. The transition in tissue conductivity from 18 to 50 kcal-cm/m^2/hr/^oC (39) takes place essentially linearly between local skin temperatures T_s of 28^oC to 34^oC (inferred in part from ref. 5, p. 205, and ref. 1f). With the temperature increasing nearly linearly over the approximately 2 cm from the surface (T_s) to the middle of the muscle layer (T_c) (ref. 5, p. 132) values of C can be derived (Table 1) (40).

Table 1

Peripheral Tissue Conductance vs. Skin Temperature

T_s (°C)	C ($kcal/m^2/hr/°C$)	T_s (°C)	C($kcal/m^2/hr/°C$)
25	13	31	20
27	16	33	22
29	19	35	24

With these values of C and with h = 7 $kcal/m^2/hr/°C$, one can determine the course of f and g. Combining the two transfer equations (10, 11) to eliminate T_s gives

$$f = \frac{(C+h)\ (M-E)}{h\ C\ (T_c - T_a)} + \frac{E\ (1-g)}{C\ (T_c - T_a)} \tag{13}$$

With M and E as known functions of T_a from Figs. 1 and 3, f vs. g is a straight line for a given T_a. A family of such straight lines is shown in Fig. 7. The dashed line indicates the logical likely course of f and g between T_a = 5°C and T_a = 45°C. (There is some uncertainty in the indicated course because the computation in the region T_a > 30°C involves the taking of small differences (M-E) between large quantities (M and E). Thus the dashed curve is somewhat speculative; however, there is little rational latitude for shift.) Figure 7 shows clearly why it is not possible to construct a rational model with g = 0 (i.e., no subsurface evaporation) over the entire range of ambient temperatures. With g = 0, above $T_a \approx$ 30-31°C the body has no mechanism to maintain regulation; after all, f cannot exceed unity.

Thermoregulation in the Cold

In this section the ideas developed above are used to construct a more detailed model of thermoregulation in the cold (T_a < 25°C). The average tissue conductance is assumed to be that of fat ($\bar{C}$ = 9 $kcal/m^2/°C/hr$), i.e., the tissue is completely vasoconstricted. The skin-to-air conductance h is taken to be 7 $kcal/m^2/hr/°C$. Evaporative losses are neglected.

Consider the body to be composed of three regions, a core at a regulated temperature T_c, a muscle layer at temperature T_m, and a skin layer at temperature T_s. Arterial blood enters the muscle layer at temperature T_c and exits at temperature T_m. In the vasoconstricted skin, because of reduced blood flow, there is little exchange of heat between blood and tissue. Finally, to maintain the core blood at T_c, a fraction α of the metabolism must be used to reheat blood returning from the muscle. The energy balance equations for the three layers are:

In the core:

$$(1 - \alpha) M = fAh_{cm} (T_c - T_m) \tag{14a}$$

where h_{cm} is the conductance of the vasodilated core-to-muscle region (typically $h_{cm} \approx 25$ kcal/m^2/hr/^{o}C but the exact thickness of the core-to-muscle region is not certain).

In the muscle:

$$fAh_{cm} (T_c - T_m) + fQ (T_c - T_m) = fAh_{ms} (T_m - T_s) \tag{14b}$$

where Q represents the specific power convected by blood flowing through muscle layers. Typically $Q \approx 60$ kcal/hr/^{o}C. (This may be estimated from a nominal rest perfusion of 5 ml/min/100g times 1/3 of body weight for muscles, e.g., 20 kg, equaling 1 ℓpm blood flow equivalent to 60 kcal/hr/^{o}C.) The coefficient h_{ms} is the (average) conductance of the vasoconstricted muscle-to-skin region ($h_{ms} \approx 17$ kcal/m^2/hr/^{o}C).

In the skin:

$$fAh_{ms} (T_m - T_s) = fAh (T_s - T_a) \tag{14c}$$

For the blood:

$$fQ (T_c - T_m) = \alpha M \tag{14d}$$

Lastly, there is the definition

$$\bar{T}_s = f T_s + (1 - f) T_a \tag{14e}$$

Eqs. (14) are a set of five equations with six unknowns (T_c, T_m, T_s, $\bar{T}_s$, α and f). Lacking a sixth equation, we can continue empirically by assuming that T_c is known as a function of T_a (Fig. 2), i.e., $T_c = 37^oC$ throughout the whole range of T_a. Then, for a resting individual, with (M/A) = 50 kcal/m^2/hr over the range $5^oC < T_a < 25^oC$ the equation set reduces, numerically to

$$f = \left(\frac{M}{A}\right) \left(\frac{1}{T_c - T_a}\right) \left[\frac{1}{h} + \frac{1}{h_{ms}} + \frac{1}{h_{cm} + Q/A}\right] = \frac{11}{37 - T_a} \tag{15a}$$

$$T_m = T_c - \frac{(M/A)}{f\,(h_{cm} + Q/A)} = 37 - \left(\frac{37 - T_a}{10}\right) \tag{15b}$$

$$T_s = T_a + \frac{(M/A)}{fh} = T_a + .64\ (37 - T_a) \qquad (15c)$$

$$\bar{T}_s = T_a + \frac{(M/A)}{h} = T_a + 7 \qquad (15d)$$

Figure 8 shows f, T_m, and $\bar{T}_s$ plotted against T_a. There is fair agreement between these $\bar{T}_s$ and f and those in Figs. 2 and 7; also the values of T_m are reasonable (e.g., compare ref. 5, p. 132).

This model represents a step beyond the first simple model above. Of course, we realize that it is still a considerable oversimplification of the real system. Yet all that is required to 'complete' the problem in principle is an equation describing how the blood is redistributed to different parts of the body, thus indicating which regions are regulated and which are abandoned. That relation would represent a physiological-physical theory for the parameter f.

Others have applied similar ideas to more complex modelling of thermoregulation without having added any further conceptual advance (41, 42, 43). In general, the approach has been not to model the mechanism of the blood flow distribution, but rather to assign values for the blood flow to the various parts of the body. The net result of those assignments is, in one way or another, to effectively assign a value for our parameter f.

A classic direction has been to define an average body temperature $\bar{T}_b$ (47)

$$\bar{T}_b = a\ T_c + b\ \bar{T}_s \qquad (7)$$

Hardy points out that $\bar{T}_b$ is of considerable interest in the study of thermoregulation in the cold (6). However, there is still apparently no satisfactory theory for the parameters a and b. Proposed empirical values of (a, b) range from (.5, .5) to (.9, .1), depending on ambient temperature with more usual values (.65-.8, .35-.2). We can apply our results towards a theoretical attack on this problem. Consider the body to be a cylinder with a diameter d_2 of about one foot (30 cm), an unspecified length, a core of diameter d_1, and a core-surface thickness $[t = (d_2-d_1)/2]$ of about 2 cm. Assume that a fraction f of both core and surface length is regulated at temperatures T_c and T_s respectively, and that the unregulated fraction (1-f) is near ambient temperature T_a. Then the volume-averaged temperature T_b is easily calculated (assuming a linear temperature gradient between core and surface) to be approximately

$$T_b \approx f\ T_c \left(1 - \frac{2t}{d}\right) + \bar{T}_s \frac{2t}{d} + (1-f)\ T_a \left(1 - \frac{2t}{d}\right)$$

Here we have used $d_1 \approx d_2 = d$, $d_2^2 - d_1^2 \approx 4\ dt$, $d_2^2 + d_1^2 \approx 2d^2 + 4dt$, and

$\bar{T}_s = fT_s + (1-f)\ T_a$. Using numerical values above gives

$$T_b = .87\ f\ T_c + .13\ \bar{T}_s + .87\ (1-f)\ T_a$$

Thus we can identify

$$a = .87\ f$$

and, with $\bar{T}_s$ and T_a related by (14d),

$$b = .87\ (1-f) + .13$$

(There is a slight adjustment to these values because $\bar{T}_s = T_a + 7$ in (15d). However, that adjustment will be neglected here.) From Figure 7 we can get f vs. T_a and then tabulate a and b vs. T_a (Table 2).

Table 2

Coefficients a and b vs. Ambient Temperature

T_a (°C)	f	a	b
> 33	1	.87	.13
30	.82	.72	.28
25	.65	.57	.43
20	.58	.52	.48
15	.50	.44	.56

We note that in warm environments ($T_a > 32$-33°C, $f = 1$) the limiting values of (a, b) are (.87, .13) while in the cold the values change to (.5, .5) at $T_a = 20$°C, $f = .6$. These theoretical values are in reasonable agreement with the empirical values being used.

Thus, while not asserting the ultimate validity of our modelling, it is clear enough that plausible relations between f, a, and b can be estimated.

Thermoregulation in the Heat

The modelling of the preceding section can be applied to thermoregulation in the heat ($T_a > 30°$). An equation set similar to (14) still obtains. However, now the whole surface area is regulated ($f = 1$), the peripheral tissues are completely vasodilated so that blood flow is divided between the muscle and skin layers, and the evaporative losses are divided between surface and subsurface evaporation. Thus,

$$(1 - \alpha)\ M = Ah_{cm}\ (T_c - T_m) \qquad (16a)$$

$$Ah_{cm} (T_c - T_m) + Q_m (T_c - T_m) = Ah_{ms} (T_m - T_s) + gE \qquad (16b)$$

$$Ah_{ms} (T_m - T_s) + Q_s (T_c - T_s) = Ah (T_s - T_a) + (1 - g) E \qquad (16c)$$

$$\alpha M = Q_m (T_c - T_m) + Q_s (T_c - T_s) \qquad (16d)$$

where $Q_m \approx 60$ kcal/hr/^oC (i.e., an unchanged muscle blood flow) and $Q_s \approx 75$ kcal/hr/^oC (i.e., skin blood flow might rise above 1 ℓpm when vasodilated) approximately represent the blood division with maximal flow to the skin, and where $h_{ms} \approx 25$ kcal/m^2/hr/^oC throughout the vasodilated tissue. Adding (16a) through (16d) yields a three-set (with A a nominal 2 m^2)

$$(M/A) = 7 (T_s - T_a) + (E/A) \qquad (17a)$$

$$55 (T_c - T_m) = 25 (T_m - T_s) + g (E/A) \qquad (17b)$$

$$25 (T_m - T_s) + 38 (T_c - T_s) = 7 (T_s - T_a) + (1-g) (E/A) \qquad (17c)$$

with five unknowns: E, T_c, T_s, T_m, and g. If we assume that E and T_c are known functions of T_a, Figs. 2, 3, then we can solve for T_s, T_m and g. The need to take small differences between large quantities which are not too precisely known leads to unreliable calculations for g. At this point we are left with a better description by the simpler model in Section III.

For ambient temperatures above about 40^oC, the skin is completely wetted and now evaporative losses are determined by physical and geometrical factors. The simplest derivation of evaporative loss is based on the similarity of the heat and mass transfer equation sets when those transfers take place in the same hydrodynamic field, that is, when the process is psychrometric. Pertinent details on psychrometric processes are reported elsewhere (refs. 33, 44). The important result is that the heat transfer coefficient for convection h_c (i.e., heat transfer = h_c x temperature difference) and the mass transfer coefficient h_m (i.e., mass transfer = h_m x water vapor partial pressure difference) are related in the indicated units by

$$h_m \text{ (kcal/m}^2\text{/hr/mm Hg)} \approx 2 h_c \text{ (kcal/m}^2\text{/hr/}^oC)$$

Figure 5 shows that, for small wind velocity V = 15 ft/min, h = 2 kcal/m^2/hr/^oC and thus the expected value of h_m is 4 kcal/m^2/hr/mm Hg (45, 46). The maximum possible evaporative heat loss from a completely wetted surface depends on the water vapor partial pressure difference between skin and environment, determined by the ambient temperature, skin temperature, and relative humidity. Demands on the body for heat loss in excess of this limit cannot be met, and the result is heat prostration.

Thus, in warm environments there is a shift in regulation from subsurface cooling to surface cooling, with a physical psychrometric process determining the ultimate limit to a capability for evaporative cooling.

Summary

1. Some of the usual assumptions and definitions in thermoregulation have been reexamined for consistency with physical theory.

2. The theory for the skin-to-air heat transfer coefficient was shown to be consistent with properly carried out equilibrium measurements. The criteria for proper measurements were specified. It was shown that failure to satisfy these criteria had, in the past, led to discrepancy between theory and experiment.

3. Computation of the physiologically reactive skin conductance was shown to be inconsistent with equilibrium measurements at both high and low ambient temperatures. Two hypotheses are proposed to bring computations of effective skin conductance into accord with measurement and physical-physiological requirements.

4. First, it is proposed that a significant part of sensible evaporative heat loss may take place from below the surface of the skin. This process takes place on a scale much greater than that of the insensible water vapor diffusion proposed many years ago. At this time, no firm attempt is made to specify the structures which might maintain this process.

5. Second, it is proposed that, in a cold environment, the body can and does direct blood flow away from a significant fraction of its surface area in order to maintain its deep-body temperature. The temperatures of these unregulated regions drop toward ambient. Since there is no large rise in metabolism in the cold, this appears to be the only available survival mechanism.

6. A simplified model of thermoregulation was presented to illustrate how these hypotheses help establish a consistent theoretical foundation. To avoid involvement in complex, unknown physiological issues, a semi-phenomenological approach was adopted. That is, we did not hesitate to use experimental data to help fill in gaps in the theory.

7. This work is principally aimed at developing the physical basis of thermoregulation. The hypotheses put forth here may be considered highly speculative. We do not contest that. Rather, we point out that current ideas are not adequate to resolve several serious problems. It is our desire and intention to provoke thinking along lines which might lead to a physically and physiologically consistent theory of thermoregulation. Still, our hypotheses clearly are not devoid of merit. The preliminary modelling in this paper indicates that significant aspects of the problem of equilibrium thermoregulation may be shifted away from the internal mech-

anism of hypothalamic control, and that a consistent theoretical foundation can be developed if a substantial burden of thermoregulation is placed on the peripheral tissues.

8. There are many issues unresolved by this first simple modelling. The major one, still elusive, is how (or why) the body maintains an internal temperature near 37°C. A corollary problem is that of the mechanism which regulates vasomotor responses and blood flow subdivision. Work is continuing in these areas.

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   (b) Iberall, A., Cardon, S., NASA Contractor's Report CR-141, Jan. 1965.

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2. These data were reported more than a decade ago (ref. 1a). Unfortunately, later workers have not paid sufficient attention to them.

3. The precise definition of an 'effective', 'operative', or 'standard operative' temperature has been a source of endless research in this field. For the progress which has been made, see, for example, papers by A. Gagge at the 1939 and 1971 Temperature Symposia. A more precise definition of our 'ambient' temperature than that implied here is not relevant to the point of this paper.

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10. That such a remark should not be regarded as misleading (or heretical) one may point to an analogous case in pressure regulation in the cardiovascular system. While the carotid baroreceptor may be involved in short term 5-15 second regulation of blood pressure, it is not the determinant of long-term pressure regulation.

11. While the issue of dynamic vs. equilibrium data has been discussed more fully in our 1965 NASA Report (ref. 1b), it still remains subject for debate. For example, in a recent review, on the basis of his own data, Benzinger (Figs. 14, 15, 16 in ref. 9) finds the apparent existence of a "discordant" relation between sweat rate and skin temperature to be "paradoxical" and "antihomeostatic", although he finds sweat rate and hypothalamic temperature to be "concordant". He point out, "In spite of the trite observation that man in a warm environment has a warm skin and sweats, an opposite relation was presently seen." We have argued (ref. 1b) that Benzinger's data can be understood only as part of a dynamic model. Metabolism and evaporation are fundamentally tied together, not by a 'static' value for hypothalamic temperature, but by some large scale self-regulatory chain, with about a seven minute time scale. Interpreting Benzinger's data as dynamic, rather than equilibrium data, resolves the paradox.

12. Except in the case of our own work (ref. 1c) and that of a few others, we have often had to rely on shorter term (1-2 hour) data. For such data, metabolism may be inaccurate by 5-10% and body temperatures by even more. Part of our objective is to show that our description is consistent with others' non-equilibrium data and that, thus, we can say something about their equilibrium even if it is not reached.

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23. There is a rise in deep-body temperature from near 37°C at rest to about 39°C at a peak aerobic oxygen uptake of about 3 ℓpm. The variation in between is essentially linear. We regard T_c as being a regulated (i.e., compensated) variable, not a feedback controlled 'set-point' variable. On the other hand, there is essentially no variation in T_c with ambient temperature in the range 5-30°C ambient. There is a much poorer degree of regulation at higher temperature. (The flat regulation also tends to break down at lower temperature at higher work levels.)

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35. They tried to extricate themselves from the difficulty by throwing the burden of the discrepancy upon the storage term in their equation. They then argued that the discrepancy in h simply allowed them to correct assumed value of the parameters used to evaluate the mean body temperature. However, that argument is not convincing to us. Their data was taken after a two-hour exposure and thus should vary only indifferently from true equilibrium data. Therefore the storage terms are negligibly small and the real issue remains: Why is their measured h less than their predicted h?

36. To include countercurrent heat exchange one would write (7) as

$$M = A\left[\bar{C} + \frac{c_p\,\Delta Q_b}{2}\right]\left[T_c - \bar{T}_s\right]$$

where c_p = specific heat capacity and ΔQ_b = increased blood flow to the skin. Thus there is a parallel shunt flow of heat which increases the effective tissue conductance because the hotter core blood is cooled in its transit through the capillary bed. (The Graetz number is low so the exchange is complete even in the very short capillary distance, ref. 33, p. 461.) The heat exchange is proportional to $(T_c - \bar{T}_s)$; the coefficient 1/2 arises from taking the average temperature difference in the boundary layer.

The increased boundary layer blood flow ΔQ_b is due to the cardiovascular charge for increased metabolism in the heat. A rise of 30% in metabolism may be correlated with a rise of about 10% in blood flow (ref. 1e). At about 5 ℓpm total blood flow, it would be difficult to assume more than 0.5 ℓpm for the increased tissue flow. However, preferring to overestimate the effect, we will assign ΔQ_b = 1 ℓpm. The heat capacity is essentially that of water. Thus in the warm, we could expect at most an effective tissue conductance of 25 (from conduction) plus 15 (from countercurrent exchange) kcal/m^2/hr/^{o}C. Thus countercurrent exchange does not relieve the dilemma and will be neglected.

37. Cunningham, D., chapter 22 in ref. 19. Even though these experiments were done on the forearm where the tissue thickness is likely less than 2 cm, the same disturbing conclusion obtains. If with her Fig. 22-4 we use an estimated tissue thickness of 1 cm (assuming that at an application temperature of 25-30^{o}C there is only heat transfer by simple conduction), then we would expect at most $\bar{C} \approx 50 + 15 = 65$ kcal/m^2/hr/^{o}C (see ref. 36). However, her figure shows $\bar{C}$ as high as about 120 kcal/cm^2/hr/^{o}C.

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39. Here we neglect the possible effects of blood flow along the temperature gradient. They are small (ref. 36).

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$$T = T_s + \frac{1}{2}\,\frac{T_c - T_s}{t_s + t_m/2}\,t_s$$

where T is the average temperature over the skin thickness t_s. Writing $N = t_m/t_s$ gives

$$T = T_s \frac{N+1}{N+2} + T_c \frac{1}{N+2}$$

N represents an anatomical quantity - the ratio of muscle thickness to skin thickness. Typically N might range from 1 to 3. In any case the larger contribution (at least half) to T comes from T_s. Thus the vasomotor response is quite sensitive to T_s.

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45. This result can be compared to the experimental results of Kerslake et al. (Kerslake, D., Waddell, J., J. Physiol. 141, 156, 1958; Clifford, J., Kerslake, D., Waddell, J., J. Physiol. 147, 253, 1959). They used a velocity of 50 ft/min and so their value of h_m should be $4(50/15)^{1/2}$ = 7.3 kcal/m^2/hr/mm Hg. They actually measured 7.8 ± .2 kcal/m^2/hr/mm Hg.

46. A similar theoretical calculation was done by G. Rapp (chapter 6 in ref. 19). However, in his final calculation of h_c/h_m, he apparently overlooked the point that psychrometric calculations apply only to a completely wetted surface (where the heat and mass transfers take place in the same hydrodynamic field). As a result, he slightly overestimated h_c/h_m by assuming a mean skin temperature of 33°C, too low for a completely wetted surface.

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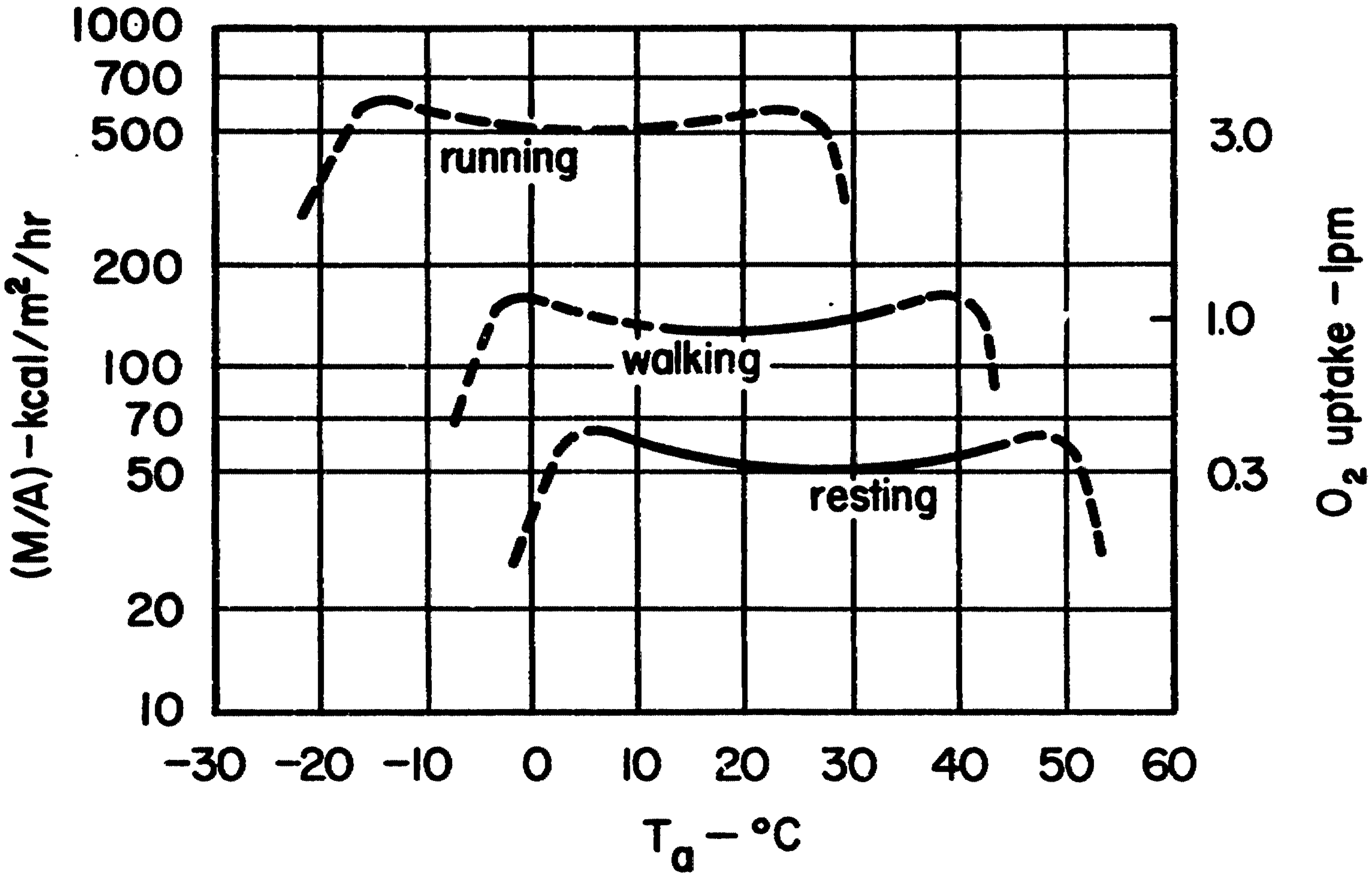

Figure 1. Metabolism and oxygen uptake vs. ambient temperature for various activity levels. The dotted portions represent reasoned guesses at the limits of survivability.

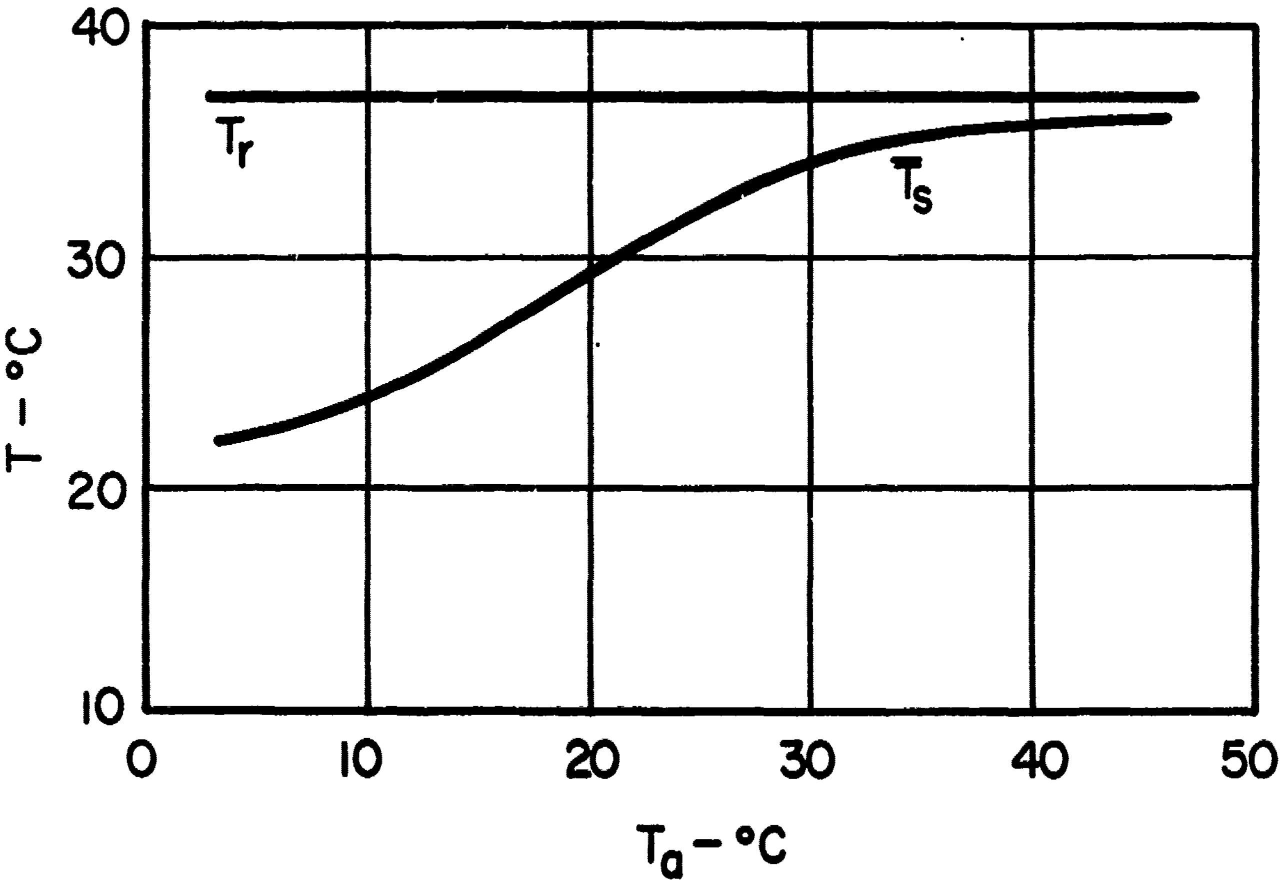

Figure 2. Deep-body (T_r) and mean skin ($\bar{T}_s$) temperatures vs. ambient temperature for a resting individual.

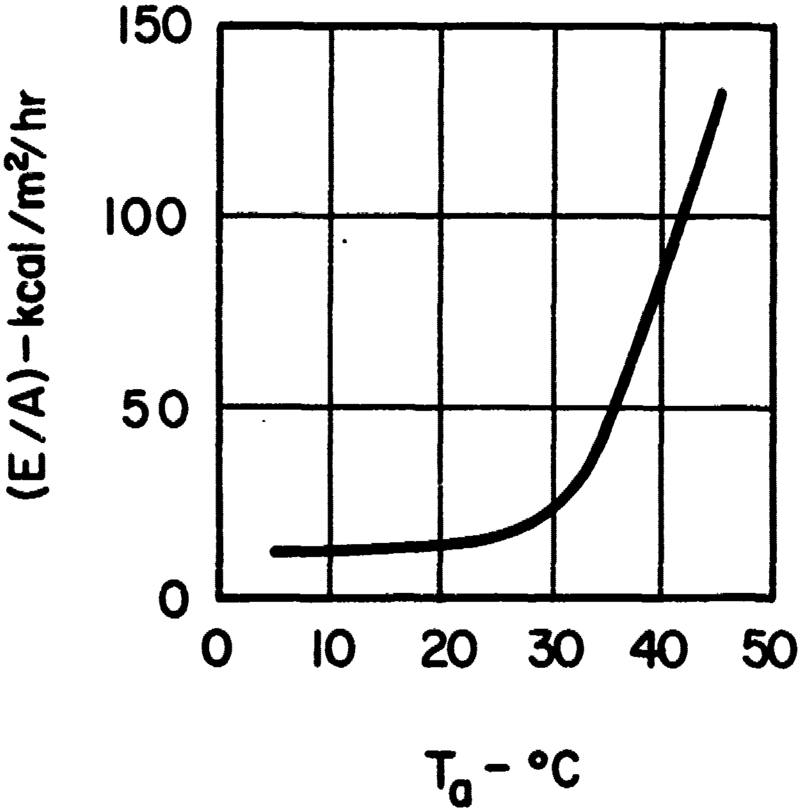

Figure 3. Evaporative heat loss vs. ambient temperature for a resting human; low humidity and low wind.

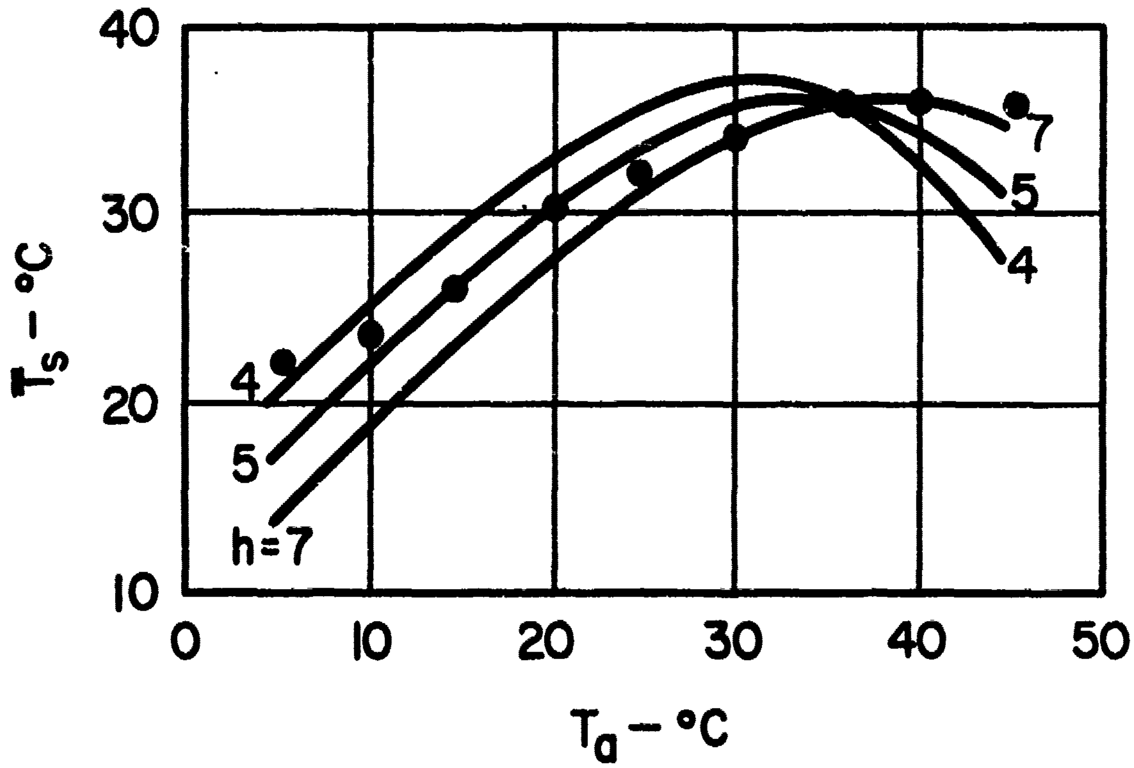

Figure 4. Computed values of $\bar{T}_s$ (solid curves) compared to experimental values (dots) vs. ambient temperature for various values of h (in kcal/m^2/hr/°C).

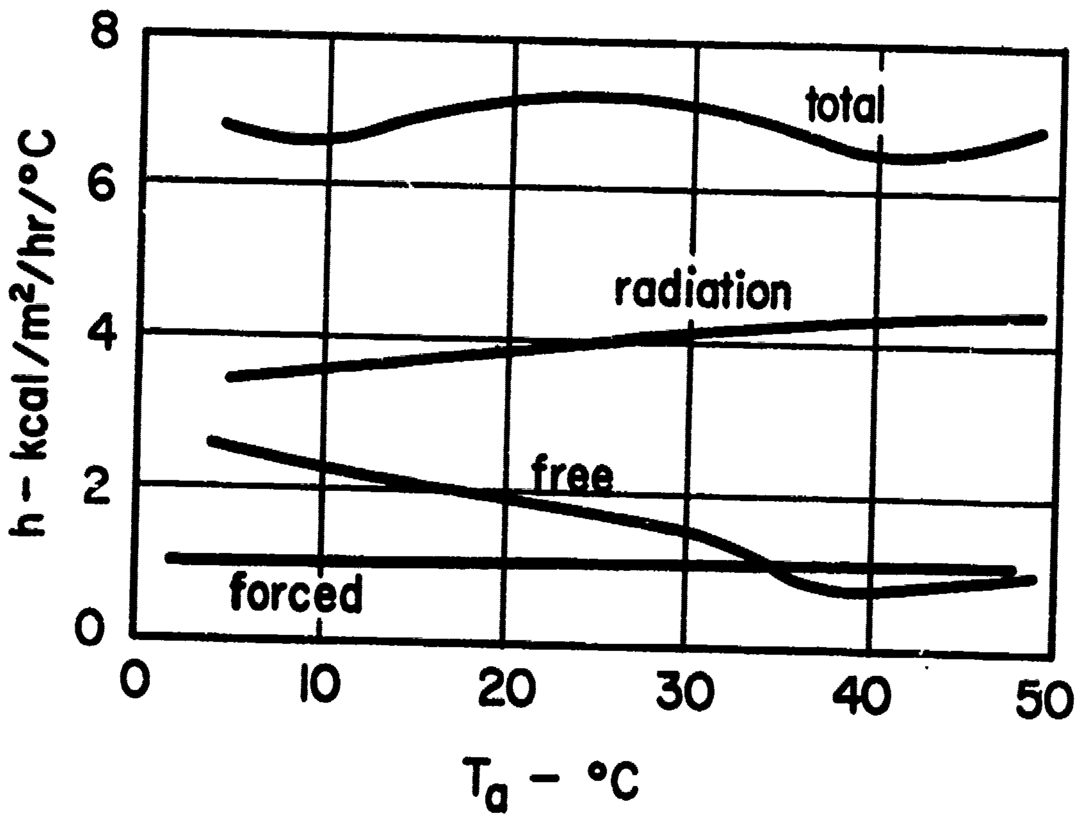

Figure 5. Contributions to h from radiation, free convection, and forced convection as functions of ambient temperature.

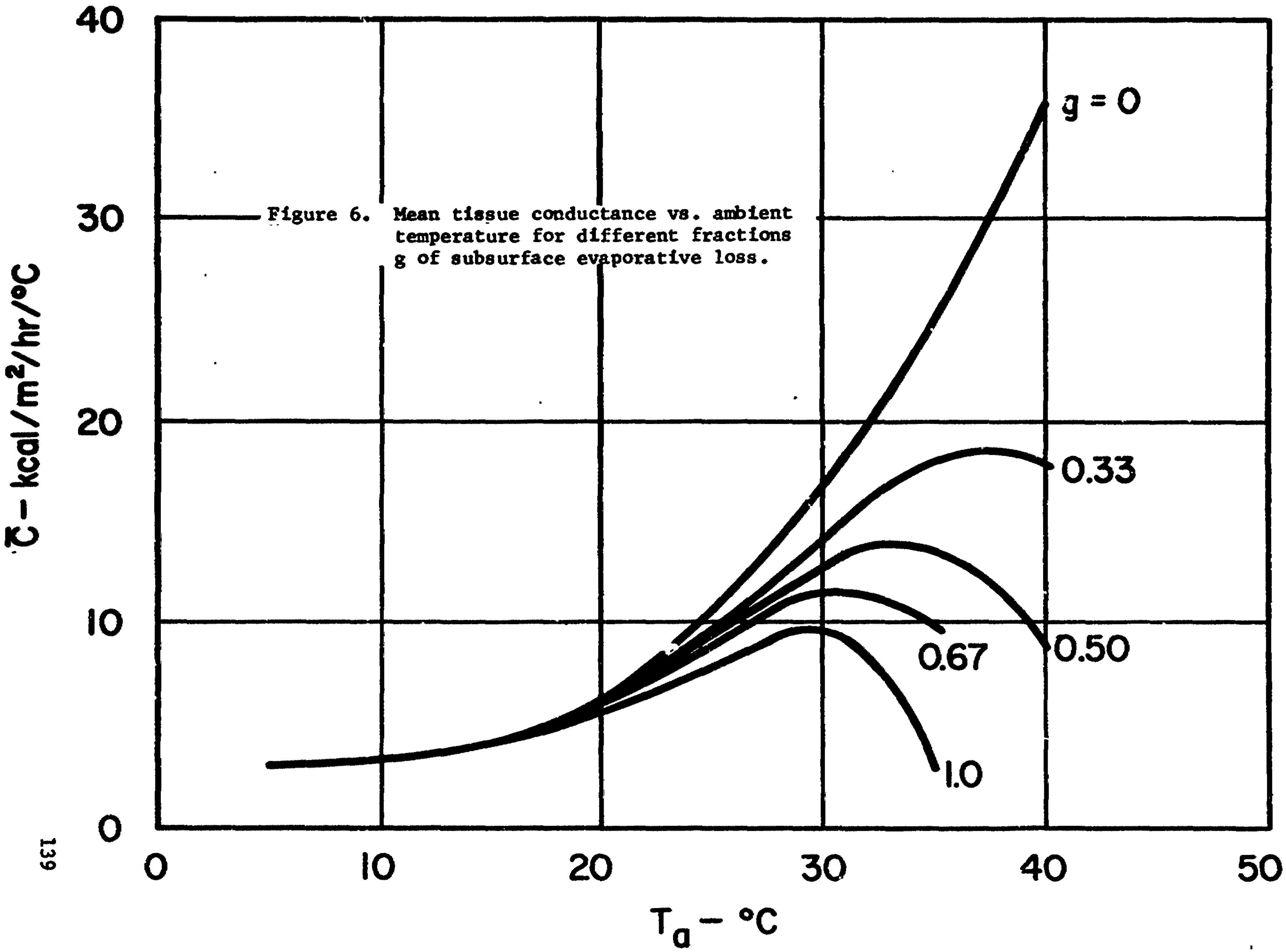

Figure 6. Mean tissue conductance vs. ambient temperature for different fractions g of subsurface evaporative loss.

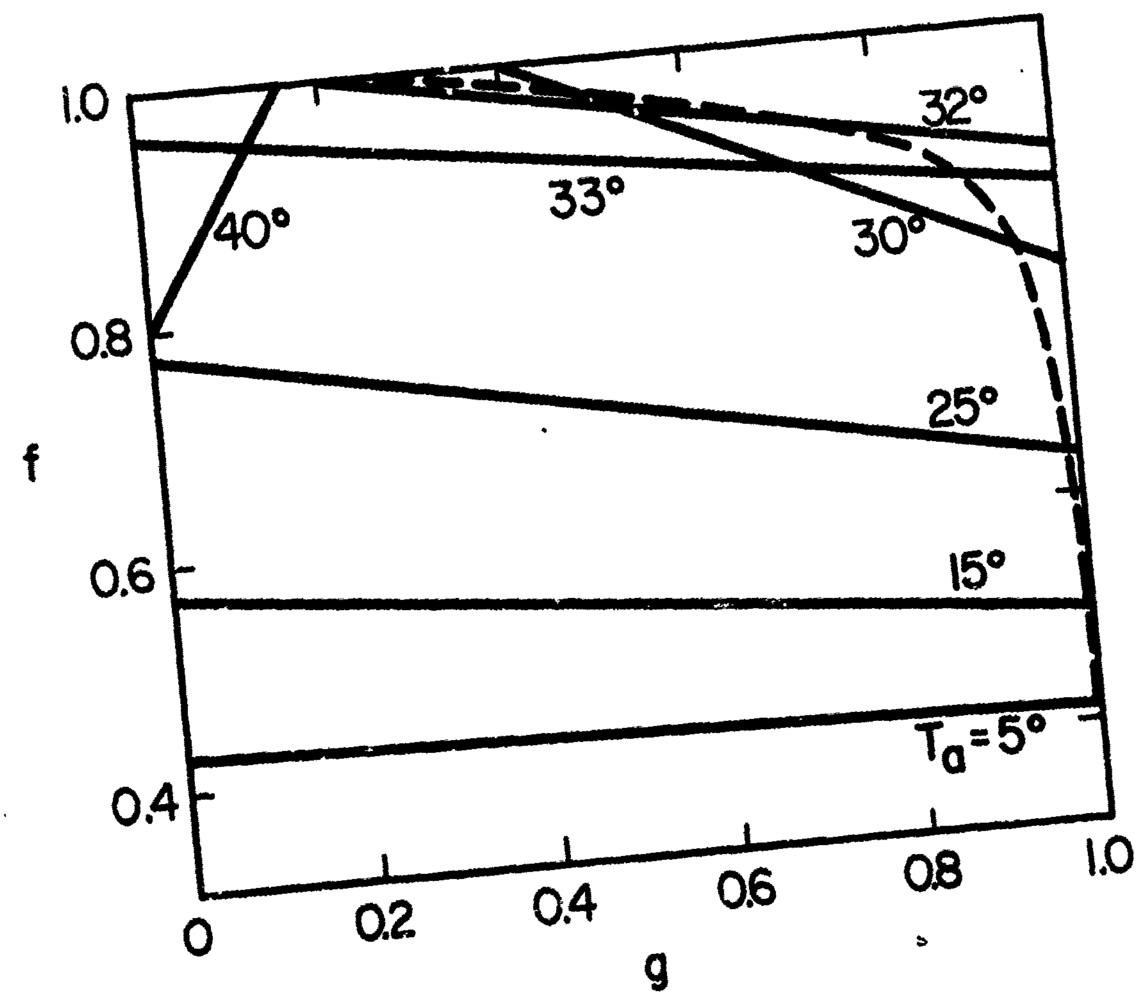

Figure 7. Likely progression (dashed line) of f (fraction of body area regulated) and g (fraction of subsurface evaporative loss) vs. ambient temperature.

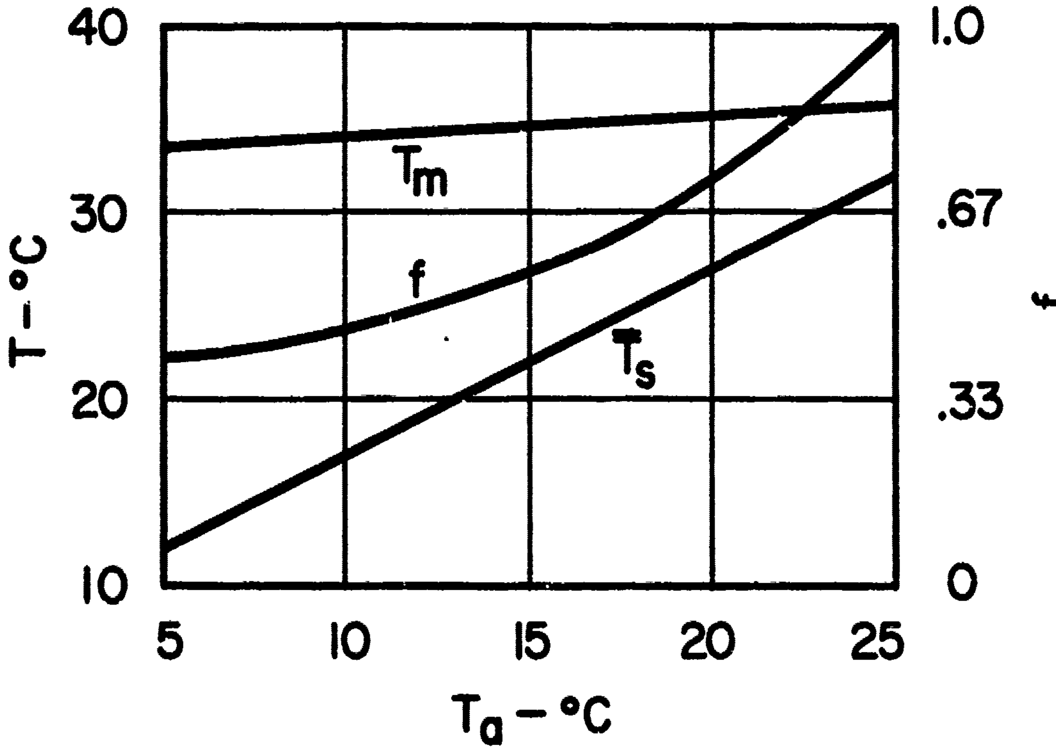

Figure 8. Computed muscle (T_m) and mean skin ($\bar{T}_s$) temperatures and fraction of area regulated f in a cold environment.

Within the confines of our own report, we feel entitled to a parting shot with regard to how the current review process treats originator or maverick. We draw our text from S. Drake's DISCOVERIES AND OPINIONS OF GALILEO, Doubleday, 1957.

"With the publication of the Letters on Sunspots the period of Galileo's most famed discoveries drew to a close, to be succeeded by one in which his even more famous opinions became the subject of violent and widespread controversy. Ostensibly this battle was waged over the Copernican system; in reality it was fought over the right of a scientist to teach and defend his scientific beliefs. The real issue was perfectly clear to Galileo at all times, as it was to some of the theologians who were soon to decide the contest against him. But by his avowed enemies in the church it seems never to have been understood at all. To their minds Galileo was attacking the church; to his own mind he was protecting it from the commission of a fatal error. In place of the contempt Galileo felt toward his adversaries in science, he showed rage and indignation against his religious opponents. Ignorant men were powerless to injure science, but they could seriously damage the church. In order to prevent such a calamity Galileo undertook a struggle which involved him in grave personal danger, while his enemies acted not only in complete safety but even with a prospect of gaining glory."

Illustrative of his opinions, Galileo's letter to Christina, the Grand Duchess of Tuscany opens:

"Some years ago, as Your Serene Highness well knows, I discovered in the heavens many things that had not been seen before our own age. The novelty of these things, as well as some consequences which followed from them in contradiction to the physical notions commonly held among academic philosophers, stirred up against me no small number of professors--as if I had placed these things in the sky with my own hands in order to upset nature and overturn the sciences. They seemed to forget that the increase of known truths stimulates the investigation, establishment, and growth of the arts; not their diminution or destruction."

IX. FLOW AND PRESSURE REGULATION IN THE CARDIOVASCULAR SYSTEM

In our earlier systems' report (8), we presented a Guytonian model of the CV system. This view has been spreading throughout the community of CV researchers, significantly, because of Guyton's little book of almost a decade ago (6). Quite recently, Guyton has developed his modelling further into a very large scale version (9).

Guyton places large emphasis on function curves, and it is to his credit that he has made the most complete effort to cover all of the essential coupled compartments into a sufficient unity to embrace the CV system. As he validly concludes, this will force the field of circulatory physiology and change from a series of disconnected speculations to that of an engineering science. This objective also sits beyond Forrester's and his colleagues' modelling of business, urban, and global economic dynamics.

However, with a physical scientific bias (as expressed for example in Chapter V), it has seemed useful to propose - at least in part - another foundation for modelling. In a large sense, we would consider it 'thermodynamic'.

A brief statement of the difference in outlook can perhaps be expressed by the following illustration:

1. Man as poet - artist of abstraction - can describe a system (e.g., a loved one) of interest to him by an indefinite outpouring of words. But does this capture the total unity, the essence of the system or person?

2. Man as engineer - abstract clinician of how a thing works - can take such 'poetic' or 'loose' descriptions and boil it down to what he can see or visualize as its necessary entities and connections.

3. Man as scientist - abstractor of 'essences' - can seek a reduction to the minimum number of ad hoc assumptions. This is what we are looking for in the long run.

At this point in history, the author must clearly indicate that he doesn't possess Guyton's far superior and intimate knowledge of the CV system. Thus we can make no claim for any completeness. But we offer it as an amendment, written earlier than Guyton's latest summary, but certainly audacious, considering that Guyton's large scale piece (9) has emerged. We offer it in the sense and spirit of attempting to call attention to a way of putting forth 'principles' for the biosystem, and in fact for all complex viable systems. A fuller structure of analysis, e.g., a scientific systems CV description, is the ultimate objective.

Abstract

The human body is a complex factory that performs a great many internal and external functions. A fundamental requisite for its viability is the maintenance of its thermodynamic engine action for two basic purposes - to power its movement, and to thermoregulate its interior. It will likely be of great interest to those in the process control field, both with mechanical and chemical engineering interests, to get some idea of how these functions are achieved. It is quite remarkable that the functions are basically achieved by a two flow control, by the blood as a carrier and heat exchanger, and by an oxygen stream. Fuel and combustion by-products are also carried by the flow streams, but they will not be considered. An engineering systems description of these two flow streams will be proposed that differs in many respects from the current physiological view.

As an organizational overview: the bio-organism is self-organizing. Form and function are genetically programmed; attributes emerging from the interaction of the developing organism with its varying local environment. If the variation is too large the system does not emerge. But internal form is maintained more as function rather than passive structure cast for life. Body materials are in transit with widely differing turnover times.(1) Homeostasis (2) is the summation of processes by which internal conditions are maintained within the viable body independent of external variations. This principle does not account for an organizing program; it affirms that regulation and control chains are essential ingredients in the maintenance of form and function. Homeokinesis, (3) a more dynamic form, is a doctrine that by means of self-sustained internal oscillator chains (thermodynamic 'engines'), internal conditions are regulated by changing the operating points of these chains, principally by inhibition and release. Experimentally a common scheme of the mechanisms seems to be dynamic regulating, governing, or compensating relations. (4) The oscillator chains show marginal stability, which is often mediated by parametric change.

An attempt is made to provide insight into these regulating chains in the cardiovascular (CV) system. However it is not possible to outline a complete model. That issue can be judged by examining a number of models, (5 - 9) textbooks, (10 - 13) or reviews (14 - 24). Principles or descriptive fragments are offered here which may contribute to a model.

1. While the operating state of any causal chains in the organism can be changed by various physical principles, a very central adaptive property is the strain sensitivity of blood vessels, providing capability for a number of regulatory transducing functions. In any region of mechanical stress tissue will likely grow to reduce the stress, suggesting a law of stress

boundedness. It can be used quasistatically to establish size, or cyclically to establish strain sensitive transducers. Nervous coupling with cyclic stretch sensitivity produces specialized pulse coded signals (myogenic and stretch receptors).

2. As a result of chemo-mechanical-electrical coupling, cellular complexes are competent to develop autonomous engines (25), e.g., myocardial tissue. The SA node in the heart of the successful animal provides a sustained beat through life. This is the law of the autonomy of the heart beat oscillator.

3. An embroyonic heart discharge into tissue; the new blood flow courses as in a porous medium; it returns to the heart (26). This 'porous' low pressure return becomes lined with a cellular layer to produce the capillary exchange system (two membranes, which divides the system into extravascular tissue (EVT) and the interior vascular bed), and further to form large storage volume return systems - the venous returns. The heart exits enlarge to develop high pressure small storage volumes - arterial systems - to receive the intermittent volume pulses of the heart. These developments illustrate fluid conservation by the law of the encapsulation of body fluids.

4. The encapsulation of body fluids in vascular tissue so as to permit exchange with EVT only through semi-permeable lipid-protein filter membranes sets up the law of the conservation of protein by virtue of an osmotic difference.

5. A beating heart, a vascular distribution system, a specialized osmotic exchange bed is sufficient to produce a hydraulic network, i.e., a pump characteristic, a demand characteristic (for exchange, and as a corollary, for blood flow), and some adaptive resistance characteristics. It does not fully determine the operative pressure level, although the osmotic difference does determine the minimum pressure level; thus a law of minimum 'arterial' pressure in animals of about 25 mm Hg. (There are animals that operate at that level.) On the other hand, if the system were sealed, the stress law would likely determine the maximum pressure; thus a law of the maximum design pressure of the heart as a muscle. Evidence seems to point to a peak of about 300 mm Hg. (11,27)

6. A 'mammalian' kidney has evolved. Its high pressure design may be viewed as an extra parallel filtration exchange system 'grounded' to EVT. Its design produces an approximate flat filtration characteristic over the pressure range 60-200 mm. All mammalia from the shrew (5 gm) to large whale (100,000 kg) operate with a mean pressure of about 80-160 mm Hg. (With some added hydrostatic problems for very tall animals.) The actual range in an individual or species is not absolutely fixed. Hypotensives can operate near 60 mm Hg, and hypertensives near 200, although neither extremes are assured normal life spans. As surmise, the operating mean pressure level is more determined by cross-vascular channel diffusive (or exchange) flow networks than by the convective vascular network. 'Pathologies'

- of kidney, pulmonary circuit, nervous system, endocrine system, etc. - may determine the actual operating pressure state.

It is not known how to account for the pressure characteristics by the diffusive membrane exchanges (see Guyton and Coleman (7) for an introduction; also Gauer (22)). The involved exchange systems are: Flow passage from the kidney's high pressure glomerular capillaries to an EVT space of water and excretory products. Pulmonary EVT interfaces with the partial pressure gas supply of oxygen, and the mechanical atmospheric gas pressure. A fluid return lymphatic pump provides low 'mechanical' pressure, and an osmotic pump furnishes 'chemical' pressure to return fluids and other constituents. In a dual heart, one side pumps high mechanical pressure, the other side 'pumps' high chemical partial pressure. These dual systems, involving the relative compliances of the various fluid storage spaces, including the EVT, and their diffusive resistances likely determine the renal filtration characteristic and thus the minimum CV systemic arterial pressure (e.g., 60 mm Hg), and the pulmonary capillary bed pressure (6 mm). The general problem that these systems solve in concert is to use a transport mechanism that passes and yet returns water, but also passes other products. The general design scheme uses 'ion' or 'osmotic gradient' pump control of diffusive flows at membranes.

That chemical regulation is involved in these exchange systems is suggested by daily and 3 1/2 day cycles in extracellular water (28) (Cortisol, aldosterone?). The daily (or the circadian autonomous cycle) is strongly an activity duty cycle. Thus we opt for an as yet undetermined fluid regulating chain that determines the venous fluid filling and the high pressure arterial operating point.

7. Homeokinetic organization is broadly hierarchical - mainly in the temporal domain (3,8,28). In each dominant temporal scale (each nested within longer scales), there is a linking of mechanisms by which functional characteristics associated with that time scale emerge. Even though the levels are statistically independent, there exists a congruence between action at different levels, which has been referred to as cooperative phenomena. This congruence represents an essential property of evolution. (Responding to environmental selection 'pressures', more complex regulatory chains can emerge that are compatible with existing ones. To succeed, the coding for the chain must capture a place within the genetic coding, by becoming a dominant 'mutation'.)

8. Components and functions likely develop by forming self-regulatory process chains. This captures the character of homeokinesis. However, it is only when primitive fully self-regulatory chains are developed (in the sense of buffers, pressure regulators, thermal compensators, or LaChatelier's principle) that any regulator or controller loop of higher frequency or complexity can be developed. The primitive chains achieve much of the systems' operation, minimizing the power burden. More responsive performance can then be obtained at relatively 'inexpensive' cost, or the avail-

able power can be mobilized for additional task complexity. The power limitation ultimately makes for modalities of organism behavior. For example, a mammal cannot put incompatible modal burdens on the CV system (e.g., heavy demand on gonads, GI tract, and muscle), but some humans can develop a coordinated controller program for running a four minute mile.

9. The concern here is with the quantitative character of the flow of blood through the mammalian system and the empowering oxidative process under steady states of rest and sustained exercise. "Blood circulates at a rate proportional to tissue metabolic requirements at a constant arterial pressure. Although this statement is an oversimplification, it is difficult to make one more elaborate that is more accurate." (21) Some rudimentary relations in the CV system under steady state conditions are:

$$M = h\Delta Q_{ox} \qquad [1]$$

Metabolism M is proportional to oxygen consumption ΔQ_{ox}; h is the heat of combustion of an averaged fuel. While there are high frequency fluctuations, (29,30) averaged over a few minutes time and in a post absorptive state, h is fairly constant. The period for thermodynamic equilibrium in metabolism appears to be about three hours (31).

The CO_2 to O_2 respiratory quotient (RQ) is a measure of the current fuel being oxidized, 1 for sugars, about 0.7 and 0.8 for fats and for many proteins; with a mixed diet it is about 0.85 as an average for various simultaneous metabolic processes or 0.82 in a post absorptive state. In strenuous steady state activity, it droops in about two hours from 0.85-0.9 to about 0.75-0.85 (32). Disregarding these detailed changes, a nominal constant h (4.8 kcal/ℓ O_2) may be assumed for steady state activity

$$\Delta Q_{ox} = Q_b \Delta C \qquad [2]$$

Blood flow Q_b injected into the arterial system and returned by the venous system, provides the oxygen ΔQ_{ox} consumed by tissue. Its measure is the arterial-venous (A-V) concentration difference ΔC across the microvascular bed in which O_2 is taken up and exchanged for CO_2. Hemoglobin is the chemical carrier.

While the oxygen uptake comes to near steady state in the whole body within a few minutes, (7,29,31,32,33) the blood flow continues to change its distribution through local beds with a settling time of the order of seven minutes (10,32,34).

$$Q_b = \frac{\Delta v}{\tau} \qquad [3]$$

Q_b is produced by the ejection of a stroke volume Δv during each heart beat interval τ. There are fluctuations in individual beats, regulation of the beat interval by sensors at the carotid sinus over 5-10-15 second periods (see Topham and Warner (7)), and 1-2 minute cycle of heart beat (7,33).

$$R = \frac{p_a - p_v}{Q_b} \qquad [4]$$

The arterial system side is maintained at a high pressure p_a, and returned at a low - near atmospheric - venous pressure p_v. The ratio of pressure difference to blood flow is used to define the systems resistance R. Actually with four chambers (two storage vestibules, two 'cylinders'), there are two 'high' pressure systems that are supplied by two pumps which are yoked together in the heart. One chamber (left ventricle) ejects to the higher pressure aorta, draining through the systematic veins to a vestibule (right atrium); the other (right ventricle) pumps to the lesser high pressure pulmonary system, draining through the pulmonary veins to the vestibule on the opposite side (left atrium). Both sides are regulated so that they stroke the same volume (see Rushmer (11), p.462) at the same rate. There are two resistance relations, one systemic R_s (seen by the left heart), and one pulmonary R_p (seen by the right heart).

$$\Delta p = \frac{\Delta v}{C_a} \qquad [5]$$

The stroke volume is related via the compliance C_a (= dv/dp_a) of the arterial system, to the systolic rise of pressure in the arterial system. There are a number of distortions of this relation, but it is fundamentally valid. There are two such relations, one for the systemic and one for the pulmonary system. For all species, the ramp is approximately the same,(27) 40-60 mm Hg when young, 50-70 at old age as the compliance diminishes.

$$\Delta p \approx \frac{p_a - p_v}{RC_a}\,\tau \qquad [6]$$

Similarly there is a diastolic fall of pressure in the two arterial systems, essentially an R-C decay from the end systolic pressure level.

$$P_{sa} \approx \text{constant} \qquad [7]$$

For most mammalia, the (mean) systemic arterial pressure is nominally 100 mm Hg (27).

$$p_v \approx 0 \qquad [8]$$

As an essential design relation, even though the CV system is 'closed', both venous returns and EVT fluid must be grounded somewhere near atmospheric pressure. In particular, the systemic venous return is very near zero.

10. The mechanical-electrical beat to beat CV events are described in textbooks (10-12). Of three parameters that emerge from the electrical events, the expulsion period, the beat period, and the stroke volume, the first is not independent, being principally determined by the beat period (24). (It is a fixed fraction of rest beat period in small mammals, and near constant for large (35).)

11. Neither the biosystem nor its dynamic processes can be described at one level of hierarchical organization. The persistance of the life process and the similarity of form and function - even more apparent as the focus is narrowed, here to mammalia - suggests its primitive nonlinear thermodynamic engine nature. (The alternate is a vitalistic principle.) The living organism is thus suitable for statistical mechanical study. The properties of open near equilibrium (i.e., they satisfy the Onsager relations) energetic systems, over steady state periods, can be decomposed into a near stationary spectrum of harmonic fluctuations. These fluctuations can then be explored theoretically in an attempt to identify system modes of operation, representing constellations of behavior that are made up of individual chains of action. The Gibbs formalism for such ergodic systems was developed to deal with their internal variables and degrees of freedom. Since such issues exist in the description of the biosystem or of any subsystem, (3,8) they will be dealt with, but in a primitive way. CV variables will be decomposed into three terms, e.g.,

$$X = X_{oo} + X_o + X_1$$

X = any variable

X_{oo} = a developmentally programmed 'basic' (i.e., with a genetic base) component (if any) of the variable.

X_o = an increment determined by the shorter term epigenetic status of the mammal; it depends on the prevailing chemical or nervous bias.

X_1 = the running variable 'moment' to 'moment' increment, in which the 'moment' will be undefined. It may represent any period over which a particular near steady state process can be assured. The operational assumption is made that the heart is not near failure. Thus mechanical and electrical performance over a 'typical' beat is itself 'near' a mechanical and electrical steady state, if the organism is in a steady state condition.

Consider also the following time averages (over specified near steady state periods).

$$(\bar{X})_{oo} = X_{oo} + (\overline{X_o})_{oo}$$

$$(\bar{X})_o = X_{oo} + (\overline{X_o})_o + (\overline{X_1})_o$$

$$(\bar{X})_1 = X_{oo} + (\overline{X_o})_o + (\overline{X_1})_1$$

$(\bar{X})_{oo}$ = time average at rest (i.e., it is the current status at rest). When lacking data, $(\bar{X})_{oo}$ may measure X_{oo}. (No activity measure)

$(\bar{X})_{o}$ = time average over a long period (e.g., months), representing the current status. (Average activity measure)

$(\bar{X})_{1}$ = time average over a period of sustained steady state at current activity. (Current activity measure)

This will be viewed as the principle of temperal decomposition. Illustratively:

$$\tau = \tau_{oo} + \tau_{po} - \tau_{so} - \tau_{1}$$

The existing heat period is made up of a developmental component τ_{oo}, a current status parasympathetic component τ_{po}, a current status sympathetic component τ_{so}, and the instantaneous component τ_{1} which depends predominantly on 'burden' put on the system.

12. Some of the variables which seem developmentally programmed for the emergent adult mammal are:

$$(\bar{\tau})_{oo} \propto W^{1/4} \quad [9]$$

The intrinsic period τ_{oo} of the isolated heart is a mammalian parameter that varies with animal weight W (The oo weight of the animal is also developmentally programmed); from shrew to whale, it only changes from 800 to 8 beats per minute (bpm).

$$(\bar{Q}_b)_{oo} \propto W^{0.85 \pm 0.05} \text{ or } (\bar{q}_b)_{oo} = \frac{(\bar{Q}_b)_{oo}}{W} \propto W^{-0.15 \pm 0.05} \quad [10]$$

This whole organism (or weight specific) relation for Q_b (or q_b), is the developmentally programmed demand flow of tissue (27,36). The specific variation in perfusion among organ tissues is not extraordinary (neglecting the high fairly constant perfusion of the kidney, with its special filtration relationship to the CV and EVT systems), high demand tissues range from 3 to 50 ml/min/100 gm, with a human body average of about 9 at rest. At peak activity, the muscular half of the body mass increases demand to a sustained level of 60 ml/min/100 gm and accounts for most of a 20 lpm human demand, other tissues changing little (i.e., 1 + 5 = 6 lpm rest, 18 + 5 = 23 peak). Also there is a near constant weight specific perfusion in like tissue for all mammals (20, 38).

A common belief is that the basal homeotherm state exhibits near constant heat production (and blood flow) per unit surface area M/A (12). Note that

$$A \propto W^{2/3} \quad [11]$$

i.e., surface area is nearly proportional to the 2/3 power of weight, (8,37) implying a certain general geometric mammalian similarity. One might expect blood flow to be proportional to $W^{2/3}$ (Klieber (39) found $W^{3/4}$), suggesting systems' design for overall heat loss. An alternate view is that these variables are basically related to average tissue design, i.e., proportional to W. A 'halfway' correlation with $W^{0.85}$ is found (27,36) suggesting the latter as a first approximation, to be accounted for in some average sense as a fundamental developmental relation in the microvasculature - in particular how arteriolar resistive and capillary exchange beds ramify throughout newly emergent tissue.

The development program for the heart muscle must include its growth to provide the cardiac output to supply this tissue demand.

$$P_{voo} \approx 0 \qquad [12]$$

This is the inlet 'grounding' of the heart, a developmentally programmed relation at the right atrium; the left atrium is also essentially limited in pressure. We surmise that the right atrial pressure change per stroke is programmed to be low (2 mm Hg, usually, if the body is not maneuvering (10, 40)) via low compliance. (Since the arterial pulse is about 50 mm Hg, the ratio of systemic arterial to venous compliance is about 25 to 1. The blood volume of the venous side is not 25 times the arterial side. Because of the nonlinear compliance, it is more like 6 times. The venous volumes are roughly proportional to mammalian weight (37), suggesting a developmentally programmed component. The essential constancy of the 2 mm Hg pulse near zero (which seems to be ubiquitous), may be due to developmental stretch transducer characteristics of the systemic veins themselves. Autonomic excitation may change its filling in exercise or postural change without changing its receiver compliance. Urquhart has proposed a concept of an "unstressed" filling volume. (8)) It is not clear what determines the left atrial pressure (usually 6-8 mm Hg).

Now a few details of a developmental program in some CV geometric factors: Genetics provides a blueprint for organs and nominal functions, and a nominal growth schedule. As a result of coding and youthful experience, the mammal completes growth phase with a body shape and weight W, and species specific functional organs and characteristics. Design rules are found in the arterial system (41). The resting aorta blood velocity $(\bar{V})_{oo}$ is a near-constant (about 15-20 cm/sec). It is a surmise that the aorta acts as a stretch 'transformer' to enlarge diameter to a point where the cyclic stresses do not produce a stimulus to further growth.

$$\frac{\pi}{4} D^2 (\bar{V})_{oo} = (\overline{Q_b})_{oo} \propto W \qquad [13]$$

fixes diameter D as a law of the aortic diameter.

A constant length L to D ratio (20-25) is found for the aorta and subsequent arterial levels, a law of geometric similarity in the arterial tree. Thus

$$\frac{\pi}{4}\left(\frac{D}{L}\right)^2 (\bar{V})_{oo} L^2 \propto W \qquad [14]$$

<u>a law for the aortic length</u>.

A ramification of tubes develops to extend the vascular bed throughout tissue. Roughly a tapering aorta fills out the trunk length, with significant branchings at about 3D spacings, so that there are approximately eight branches for the (here aorta) level, which ends at an equal bifurcation. These branches define the next level; geometry and topology is similar to the level it came from. Such rules are sufficient to fill the system with tubes down to arteriolar size (e.g., 10-15 micra). Developmental logic also provides the parallel return system, essentially of low resistance. (The vasculature develops as a high pressure low compliance system, a low pressure high compliance system, and an extensively ramified exchange system - the capillary bed.)

Such ramification establishes an internal arterial volume v_a. The walls have a tissue elasticity E. A remaining degree of geometric freedom in high pressure arteries is the wall thickness S to diameter D ratio which appears to be a constant (approximately 0.07). This seems to arise from the constancy of maximum stress σ_o and mean pressure

$$(\overline{p_{sa}})_{oo} = 2\sigma_o \frac{S}{D} \qquad [15]$$

13. The metabolic concomitants of the law of the tissue are quite similar to those for blood flow

$$(\overline{\Delta Q_{ox}})_{oo} \propto W^{0.80 \pm 0.05} \text{ or } (\Delta q_{ox})_{oo} = \frac{(\overline{\Delta Q_{ox}})_{oo}}{W} \propto W^{-0.20 \pm 0.05} \qquad [16]$$

expressing the parallel development, in the microvasculature, of the capillary bed for oxygen consumption. There may be a slight divergence between the results for oxygen uptake and blood flow, a possible slight weight dependent A-V difference of

$$(\overline{\Delta C})_{oo} \propto W^{-0.05 \pm 0.05}$$

Over the design range, shrew to whale, it appears that the A-V difference at rest for small animals is about twice as great as for large animals (8).

Thus there is <u>an oxygen consumption law of the tissue</u>; and also

$$(\bar{M})_{oo} = (h)_{oo}(\overline{\Delta Q_{ox}})_{oo} \qquad [17]$$

the metabolic law of the tissue, implying a developmentally cast machinery for the average heat of combustion of ingested fuel.

14. Perfusion demands are made under a rule that if the heart cannot provide the system does. The oo response of the heart is to grow in size ($\propto$ weight, (37)) so it can deliver a minimum $(\Delta v)_{oo}$ ($\propto W^{1.10}$). Δv must be at least as great.

$$\Delta v \geq (\overline{\Delta v})_{oo} = (\bar{Q}_b)_{oo}\tau_{oo}$$

One can also imagine a 'design' resistance R_{soo} that develops on the basis of a minimum renal filtration pressure P_{koo}.

$$(\bar{R}_s)_{oo} \geq R_{soo} = \frac{p_{koo} - p_{voo}}{(\bar{Q}_b)_{oo}} \qquad p_{sa} \geq p_{koo} \approx 60 \text{ mm Hg}$$

R_{soo} is a geometric-topological-hydrodynamic measure of perfusion vessels that fill emergent tissue from one aorta to 10^6 arterioles/kg. The first few branching levels are transmission lines that propagate the arterial pulse out to local regions (41). They have aorta rest velocity, $(\bar{V})_{oo}$. Next are local distributors. A third group (the last few mm) forms the resistance zone.

15. A fourth group, the capillary level, is a 'porous' distributing and exchange system, in which enough series-parallel channels are carved in local tissue to carry the blood with little pressure drop. (A detailed exchange law, Starling's model, though questionably perfect is still substantially valid in principle. Semi-permeable membranes filter material but preserve fluid by balancing protein derived osmotic pressure against hydrostatic pressure.) The density of these double membrane lined channels governs oxygen diffusion, and electrolyte and metabolite exchanges. The diffusive resistive layer poses a primitive biophysical problem. Yet complex emergent organs can operate from it, e.g., the capillary net regulates the muscle fiber's capability to do work. The net develops its ramification so as to achieve peak q_b and Δq_{ox} requirements. Not all channels are nutrient (42); we suggest only those that are smaller than red cell diameter, in which red cell passage is impeded and slowed. A major regulating mechanism may be the capillaries acting as an oxygen choke (3).

16. All steady state flows may be genetically cast. Fig. 1 - Q_b vs. ΔQ_{ox} (8,23,27,43) - seems to be independent of athletic status, and nearly weight specific (Athletes may operate at a lower rest point than non-athletes (24)); it must stem from self-regulatory characteristics of the capillary beds.

17. Moving to emergent regulation with changes in system status, they may have physical or chemical causes. Autonomic 'status' emerges with maturation, partly a developmental unfolding and partly an epigenetic development of behavioral patterns; it can change with pathologies, from operating distortions in its organs, and from physical and 'emotional' stresses of living. One well defined 'normal' stress is activity level. A mammal otherwise has a 'normal' complement of behavioral modes, (3), e.g., it eats, sleeps, etc. The day is an approximate division between status and running variables. A major degree of freedom open is the level of daily energy expense. A person may live quiescently on 1600 kcal/day; use 2800 for either an active or sedentary life; require 3500 if quite active; or sustain levels of 20,000 kcal/day for hours (32) if athletic. While the mammal goes through a performance cycle (sleep, wake, food search, work, etc.), one day does not change his CV status. This may occur adaptively in the order of four to ten weeks (43,44).

Steady state status is likely achieved if weight cycles of not more than a few percent of W are found (normally, there is a 1-2 percent of W change per 3 1/2 days in humans (28); but lesser net change over a near 60 day weight cycle); if the other mean CV parameters (Q_b, p_a, daily Q_{bmax}) have not varied too much; and if the daily (or weekly) activity and ingestion pattern has been reasonably constant over a few months. Key variables now are average daily metabolic parameters. Status variables are largely determined by adaptive changes in the (cellular) architecture of CV elements. However these cannot take place without coupling from the nervous system, particularly the autonomic system which is predominantly concerned with maintaining the state of 1 variables. The emergence of 0 variables takes place from the sustained signalling and ultimate 'biasing' by growth and change of the local architecture.

To illustrate some major changes - Fig. 2 shows a salient range over athletic to sedentary status, Fig. 3 the effect of activity, and Fig. 4 the normotensive versus hypo- or hypertensive. The heart rate for a given oxygen uptake diminishes with athletic status; conversely the stroke volume increases (The athlete's may be 100-180 as compared to 70-100 ml for a sedentary person), but shows little or no change with activity. With activity, the systemic pressure climbs some; there is less change in the diastolic (23,24). In activity the resistance changes as a running variable (apparently as a metabolic self-regulation of arteriole bore). On the other hand (Fig.4), the range in (rest) pressure is extensive. (As a status variable, the related change in resistance must arise from a change in the fluid exchange systems which shifts the self-regulation level of the arterioles.)

18. Space limitations only permit mentioning running variables. (Two notes: There is a difference in burden in a supine, sitting, or standing position. Unsupported standing is untenable in steady state. Venous pooling takes place at high hydrostatic pressure. "Rest' is somewhat ambiguous; there are considerable differences between a supine 'sleep', perhaps basal

state, and a little activity state. Also by using man and dog as central for mammals, we slur over moderate changes.) Time scales (human) that may affect CV running variables are:

'1'	second beat to beat period
'4'	second breathing event
'5-10'	second carotid baroreceptor period
'6'	second activity fragment (slight posture changes)
'50-100'	second cycles in heat, temperature, metabolic blood constituents, and periodic red cell stream
'400'	second changes in blood flow distribution
'20'	minute CO_2 balance cycle
'60'	minute water excretion cycle (may be a 90 minute cycle)
'90'	minute activity cycle (like REM in sleep)
'3½'	hour thermal balance and cortisol cycle, also the work epoch
'6-8'	hour sleep epoch
24	hour or circadian epoch (cortisol?, pineal?)

Metabolic characteristics emerge from status and operating settings in the microvasculature - in a minimal 1-2 minute cycle for ΔQ_{ox}, (29,31,45,46) and a 7 minute settling time for Q_b (32,34). The former is also concomitant with red cell fluctuation in the capillaries, (47) and in a cyclic O_2 tissue pressure (48).

There is some variation of heart rate, beat by beat, at a given activity (Scher (7), Olmstead (33)), if a beat interval is short (thus small pressure decay), the subsequent stroke volume is small (thus small pressure rise). This is regulatory for pressure and flow beat by beat. With small rise rate of pressure, the carotid sinus firing is small, cutting down the beat interval and increasing the peripheral resistance. The flow then diminishes. With little change in stroke volume, the beat interval must increase. Thus beat to beat variation tends to pull into the carotid sinus time scale for a given activity; it appears as 5-10 second fluctuations (Topham (7)).

The speed of response (11,49 or Topham (7)) upon exercise of cessation, within a few beats, suggests that the fluid systems and mechanical systems of the muscles are coupled in CV changes. The heart speeds up, Δv is essentially unchanged, the A-V O_2 difference increases, arterial pressure changes little. Upon start up (Rushmer,(11), pp 462,199), heart rate rises with about a two second delay. This is probably related to a ventilatory response (46). Involving as it likely does the autonomic setting, the increased Q_b is accompanied by a slower decrease in resistance (opening of arterioles) with a moderate arterial pressure rise. There is no essential change in right or left atrial pressures (the right atrial still shows its 2 mm Hg pulse (11), pp.49,199; the left atrial and diastolic remains at 6-8 mm Hg). In about five seconds, heart rate has climbed appreciably, and the arterial pressure a little. While the carotid baroreceptor has begun a response, it is likely the ventilatory system, the pulmonary exchange and the venous filling which dominates this time scale in start up.

The speed of response of breathing rate, Q_h, and ΔQ_{ox}, suggests a coupling to both the vascular and diffusive flow processes, e.g., a resistance drop of perhaps 40 percent doubles capillary flow (in muscle this corresponds to opening all capillaries), the rate governing O_2 flow is increased, a few blood passages (multiples, nominally, of 5-10 seconds average transit time) exposes a disequilibrium of the overall O_2-CO_2 exchange, the breathing response increases.

19. All these responses are sufficiently self-regulatory to suggest simple design rules; yet no one has succeeded in assembling a model. For example, with autonomic excitation of the heart blocked, flow continues with increased Δv rather than τ. Topham and Warner (7) blocked a dog's A-V node, externally paced its heart, and exercised the dog. As exercise and metabolism increased, Q_b increased. They inferred that cardiac output was under closed-loop control. We prefer to consider these results further indication of self-regulation. Tissue demand is primary. With exercise, an adaptive stretch receptor on the atrial side could provide autonomic signal to increase the blood flow, either by increasing the heart rate, or if prevented by increasing the stroke volume. It also appears that adrenal secretions are sufficient to maintain status. A dog with all peripheral sympathetics destroyed still has a 'normally' responsive cardiac output and blood pressure (personal communication, D. Jacobowitz).

To frame the self-regulation (predominantly chemical) we sense the following: Activity level puts a primary demand on ΔQ_{ox}. The brain assigns muscular tasks via nervous code. Muscle requirements are met by regulating their O_2 supply to not building up oxidative by-products. A number of chemical factors including the net local heat of combustion, set the opening of capillary beds and the constricted state of arterioles, regulating respectively the O_2 consumption and Q_b distribution. At the existing muscular status of the ventricles the catecholamines, wherever derived, are involved in a regulatory optimization, capable of energizing the heart to beat faster than its intrinsic rhythm or with larger than a minimum Δv, to supply the Q_b demand. The encapsulated diffusional fluid system (the vasculature) correlates the two sides of the heart. This continuing correlation leads to the development of the large capacitance systemic venous side, and an intermediate pressure pulmonary venous side whose status is possibly involved in regulating right ventricular performance. On the other hand, many have found it tempting to regard the systemic venous 'volume' as the determinant of changing flow on the right side (8) (Upon onset of exercise, "with the first contraction of the skeletal muscles, the muscle pump mechanism will immediately return an increased amount of blood to the right ventricle" (49)). As an independent issue, we consider high systemic pressure as governed independently from the fluid exchange systems.

Adding another non-contradictory facet, Sagawa (7), shows that the left ventricle output increases linearly with mean left atrial pressure. In the normal mean aortic pressure range 0-150, left atrial pressures 0-8 mm Hg and left ventricle output 0-2 lpm for a 10 kg dog, the relation is linear and independent of aortic pressures; at higher pressures nonlinear.

The hypothalamus then becomes a convenient center for optimizing processes already self-regulating. In shorter time (i.e., for various autonomic responses) it coordinates the action of various receptors which augment the process (e.g., beat to beat regulation; 5-10 second carotid sinus regulation).

20. While ($\overline{P_{sa}}$) seems well regulated, the pulmonary pressure does not. Its arterial pressure increases in exercise; a mean of 12 mm Hg at supine rest, 16 and 18 while exercising at ΔQ_{ox} of 1 and 2 lpm respectively (49). (Like increases while sitting.) The increases in systolic pressure are larger, from 19 mm Hg at supine rest to 36 at ΔQ_{ox} of 2 lpm. At low flow the right ventricular systolic pressure is the same as in the pulmonary artery, with Q_b of 20 lpm or greater an additional 10-20 mm Hg is commonly recorded across the pulmonary valve. Thus the right ventricular systolic pressure varies from 19 to 46 mm Hg as ΔQ_{ox} varies from 0.25 to 2 lpm. The pulmonary resistance approximately is of fixed moderately low magnitude with some threshold pressure drop (a check valve characteristic). Gregg (10) shows 40/10 mm Hg pulmonary artery and 2-12 mm Hg pulmonary vein pressures. Thus systolic-diastolic differences are less but like the aorta's (their compliances are comparable). There is rapid decay to diastolic pressure. (The drop across the pulmonary bed equalizes quickly because its resistance is low.) It is conceivable, if a right ventricular pressure reaches 46 mm Hg at mean blood flows of 20 lpm, that at stressed performance it could climb toward 100 mm Hg. It is tempting to suspect that the existing status of the pulmonary circuit governs the existing status of the right ventricle which may then possibly govern the existing heart status. If the peak work output of the right ventricle - in an existing status - is, say, 4 gm-m for a 10 kg dog (18), then an average pulse pressure of 50 mm Hg would represent a Δv of about 6 ml, a valid estimate. This might illustrate how an adaptive change of the right ventricular Δv took place. Exercise would increase the muscle mass of the right ventricle. The mechanism by which the two sides pump together and maintain a near zero p_{ra} would bring left Δv in concordance with the right. The left ventricular Δv thus need not be its total displacement nor any particular portion, but could be position dependent. An adaptive muscle stretch characteristic of the right ventricle could govern the current stroke status. This would bring the issue to the left heart. If the pulmonary pressure rises so that the left atrial pressure rises, either Δv rises (it cannot, it is tied to the pulmonary circulation) or the heart rate rises. This pulls the left atrial pressure down. The pulmonary pressure is thus reduced.

When the pulmonary pressure cannot be reduced adaptively, the system runs very near pulmonary edema. This is the tendency in high exercise, or in anoxia. For example, Grover (50), found an average mean pulmonary pressure of 25 mm Hg at rest for human students living at 10,000 feet. During vigorous supine exercise, mean pressures were 35-115 mm Hg. One athletic girl showed 165/95. Steers at 13,000 feet, who had mean pulmonary pressures of 25-35 mm Hg at 5,000 feet, showed 55-110 mm Hg after six weeks. At nine weeks, deaths that occurred were due to congestive heart failure. (Not with sheep.)

Thus at the existing status of the mammal, one might regard the pulmonary vascular pressure-flow characteristics as the regulator of longer term Δv and p_s and short term τ. In some vague sense, the pulmonary vasculature acts as a stretch sensitive regulator. Similarly, the systemic venous pressure-volume characteristics act as a short term regulator of flow. While self-regulation in the heart, via the pulmonary system, is such that it quickly increases the rate for activity (or if the rate cannot be increased by increasing Δv), the autonomic system augments the regulation by bringing the heart rate up to its final requirement; to maintain the pressure, it helps open arterioles; and changes a stretch bias in the systemic veins.

21. Summarizing the position reached: For well-practiced activities, ΔQ_{ox} and Q_b to satisfy tissue is known. We do not know what determines Δv, τ, or p_{sa} (within a 2 to 1 range - though all are bounded). We can offer some closing comments on a widely known network model for the low frequency (e.g., 60 day average) response, (5,6,7,8) to augment some views that Urquhart has advanced (8).

Represent the two heart circuits by R-C networks (Fig.5). First suppose a filling characteristic for the systemic venous side (Fig.6). There is another family for the pulmonary venous side. We surmise that each curve represents a different state of wall tension (the state may be achieved either by autonomic excitation of by the state of circulating catecholamines, etc.). Urquhart has identified a zero pressure intercept as the 'unstressed volume'.

At any operating state (Fig.5), blood volume is conserved.

$$v_b = C_{sa}p_{sa} + C_{sv}(p_{ra} - p_i) + C_{pa}(p_{pa} - p_i) + C_{pv}(p_{pv} - p_i), \; p_{ra} = p_{sv}$$

Relate all pressures via ohmic relations to venous values; solve for Q_b.

$$v_b = C_{sa}[p_{ra} + Q_bR_s] + C_{sv}[p_{ra} - p_i] + C_{pa}[p_{pv} - p_i + Q_bR_p] + C_{pv}[p_{pv} - p_i]$$

$$Q_b = \frac{v_b - p_{ra}[C_{sa} + C_{sv}] - p_{pv}[C_{pa} + C_{pv}] + p_i[C_{sv} + C_{pa} + C_{pv}]}{C_{sa}R_s + C_{pa}R_p}$$

Note that this is a steady state (D.C.) relation; it is the average over a number of strokes (e.g., 5-10 seconds). If we regard the inter-pleural pressure as constant (e.g., p_i = -4 mm Hg), then we may write

$$Q_b = \frac{v_1 - p_{ra}C_s - p_{pv}C_p}{C_{sa}R_s + C_{pa}R_p} = \frac{p_{sa} - p_{ra}}{R_s}$$

Differentiate to determine the sensitivity of change of p_{ra} and p_{pv} to change in Q

$$\frac{\Delta Q}{\Delta p_{pv}} = \frac{-C_p}{C_{sa}R_s + C_{pa}R_p} \qquad \frac{\Delta Q}{\Delta p_{ra}} = \frac{-C_s}{C_{sa}R_s + C_{pa}R_p}$$

$$C_s \approx \frac{100\ cc}{40\ mm} + \frac{100\ cc}{2\ mm} = 52.5\ \frac{cc}{mm} \qquad C_p \approx \frac{100\ cc}{30\ mm} + \frac{100\ cc}{5\ mm} = 23\ \frac{cc}{mm}$$

$$C_{sa} = \frac{100\ cc}{40\ mm} = 2.5\ \frac{cc}{mm} \qquad C_{pa} = \frac{100\ cc}{30\ mm} = 3\ \frac{cc}{mm}$$

$$R_s = \frac{100\ mm}{7\ lpm} \qquad R_p = \frac{8\ mm}{7\ lpm}$$

$$\frac{\Delta Q}{\Delta p_{ra}} = \frac{-52.5}{\frac{2.5 \times 100}{7} + \frac{3 \times 8}{7}} \qquad \frac{\Delta Q}{\Delta p_{pv}} = \frac{-23}{[\ "\ ]} = \frac{-7\ lpm}{12\ mm\ Hg}$$

Using human constants, these sensitivities indicate the change in venous pressures that would result from quasistatic changes in flow (here at 7 lpm).

With these results in mind, we can review the function curves used by Guyton (6) and others for analysis of the CV system; first for the right atrial return, Fig. 7 (i.e., imagine the left atrial pressure pinned). This is known as a "venous return" curve. Two states - of rest and exercise - are indicated. The shift is due to a change in autonomic setting with exercise. We view this as a 'pump characteristic' rather than a load curve as the name venous return suggests. Elementary electrical (or hydraulic) cases illustrate why (Fig. 8).

What is presented is a pump characteristic as viewed at the venous pool. An 'autonomic' setting determines Guyton's 'filling' pressure (or Urquhart's unstressed volume). We operate on one of the family of filling curves (Fig.6). Consider the status at no flow. Note that if Q_b = 0, then $p_{ra} = v_2/C_s$. p_{ra} is Guyton's choice of a filling pressure; v_2 is Urquhart's choice of an unstressed volume. However it appears that the compliance is a developmental variable, and likely the filling volume v_2 is also so cast (its oo component).

The circuit analysis, of what will occur if there are various flow demands put on the volume, shows

$$Q_b = \frac{v_3 - C_s p_{ra}}{R_s C_{sa} + R_s C_{pa}} = \frac{v_3}{[\,"\,]} - \frac{p_{ra}}{R_s C_{sa}/C_s + R_p C_{pa}/C_s} \approx \frac{v_3}{[\,"\,]} - \frac{p_{ra}}{R_s C_{sa}/C_s}$$

The relative compliances C_{sa}/C_s are likely developmental - of the order of 2 mm (change) to 50 mm rise. Thus

$$Q_b = \frac{v_3}{[\,"\,]} - \frac{25 p_{ra}}{R_s} = \frac{p_s - p_{ra}}{R_s}$$

In this form, one clearly sees that the relation carries no information other than that change in p_s and p_{ra} are just related by the compliance ratio. Thus the Q_b - p_{ra} slope also depends on the resistance R_s, which is a status variable not related to the capacitance ratio. Putting in the nominal rest resistance we get the experimental order of magnitude (Fig. 7).

$$Q = \frac{v_3}{[\,"\,]} - \frac{7\ \text{lpm}}{5\ \text{mm}} p_{ra}$$

This characteristic, depending on R_s and C_{sa}/C_s, is not a causal model, but an effect. Independent regulators for Q_b and p_s 'create' the resistance. The characteristic tells us little except that the system is designed to operate around zero pressure, and that - its venous compliances being developmentally cast - it must bias fluid contents in order to achieve this.

The other function curve, the "cardiac output", is a 'load' curve (Fig.9). It presents the fundamental grounding of the right atrium. In vivo, the heart will pump so as to maintain a near zero p_{ra}. The isolated heart will do the same (i.e., the Frank-Starling law). What happens when the pressure is not zero from pathology is not our present concern. Guyton (6) and Urquhart (8) essentially suggest that they can trace detailed compensations in the system (e.g., see Sarnoff (18)), that is the 'ground' is actually an active network.

Thus we seem left with the thought that flow must be a demand of tissue. Coupling with the ventilation response must be quite important in passing a signal to the heart. It would still appear that the pulmonary pressure is responsive to change in operating condition. The right atrial characteristic simply reconfirms the grounding characteristics, i.e., basically that the right atrium will operate near zero pressure for all activity levels. Its large compliance, further, will take up flow changes (such as postural changes - although these can, in extremes, be severe).

We come now to the left atrial characteristic.

$$Q \approx \frac{v_2}{[\ "\ ]} - \frac{C_p}{C_{sa}R_s} p_{pv} = \frac{v_2}{[\ "\ ]} - \frac{10}{R_s} p_{pv}$$

The droop, because of lesser pulmonary compliance, is less (Fig. 10). Even though the pulmonary resistance is low (e.g., 8 mm drop, say, and fairly flat with flow increases, as if it had a check valve characteristic) the droop is high because the two ventricular strokes are yoked together (except possibly in extreme maneuvers, where C_{sv} takes up the discrepancy).

It is clear (Sagawa (7)) that p_{pv} climbs moderately with increased exercise (say, from 4 to 8 mm Hg, for the mean pressure). One is highly tempted to infer from this that here lies the regulation of Q_b. It is plausible that pulmonary venous volume, or left atrial, or ventricle stretch status govern Q_b (in a self-regulatory way). The heart - in particular the right ventricle, either by self-regulation or with autonomic excitation - sorts out the stroke and beat time. If the autonomics are not available, it appears that the adrenals can also (in time) take up the regulatory function. Blood flow regulation emerges in a general way from a catecholamine regulation, and speculatively, always at specialized membranes.

Thus blood flow (i.e., at the right ventricle), systemic pressure (i.e., via the water exchange networks), and peripheral resistance (i.e., the arteriolar restriction) are all significantly status adaptive and self-regulated.

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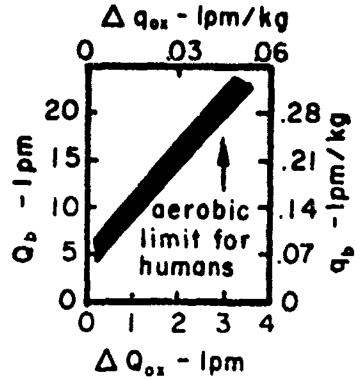

Fig. 1 - Generalized Human Blood Flow-Oxygen Uptake Curve (Independent of Status)

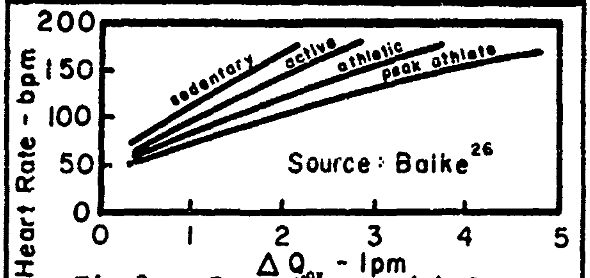

Fig.2 - Rate Change with Status

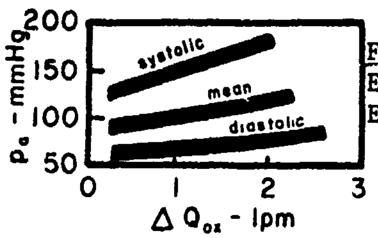

Fig.3 - Normal Effects of Exercise.[22]

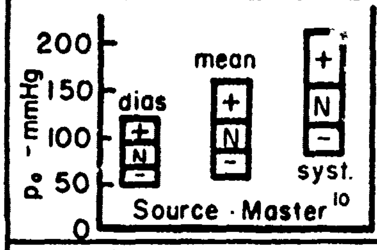

Fig.4 - Rest Pressure Hypo(-)-, Normo(N)-, Hyper(+)-, tensives

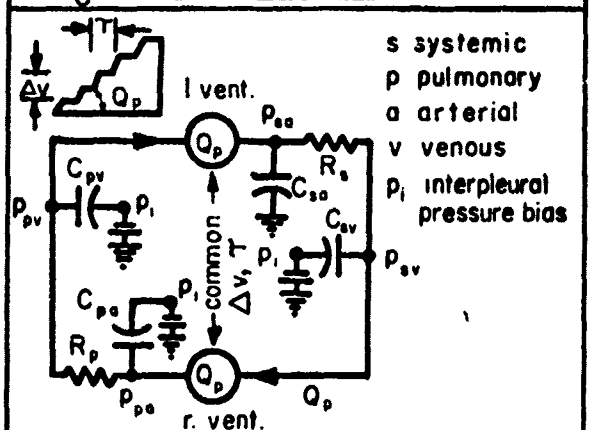

Fig.5 - Simplified Equivalent Linear Network for the CV System

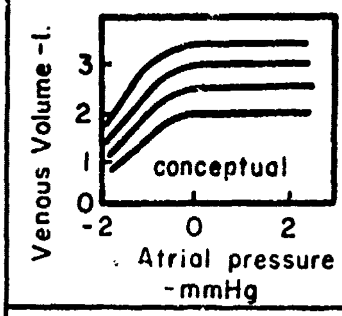

Fig.6 - Filling Curves of Systemic Veins (At Different Autonomic Excitations)

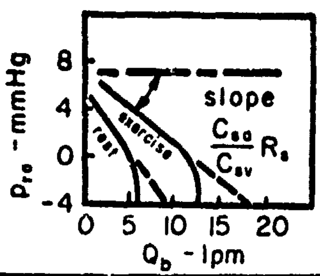

Fig.7 - Atrial "Venous Return" Curves

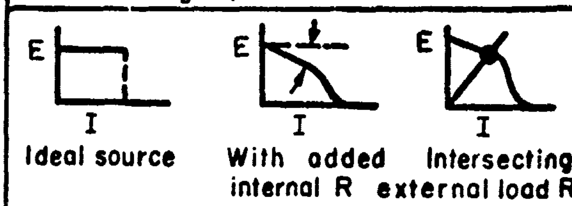

Fig.8 - Illustrating a 'Pump' Characteristic

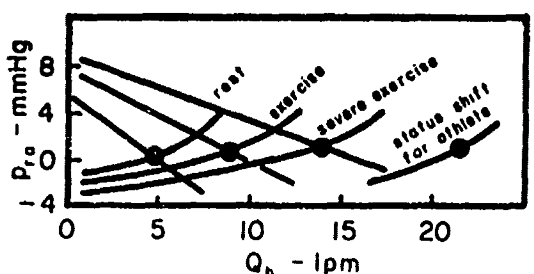

Fig.9 - "Cardiac Output" Curves

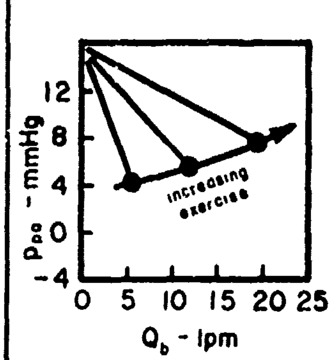

Fig.10 - Left Atrial "Venous Return" Curves

X. WATER DYNAMICS - SOME PRELIMINARY DISCUSSION

An important piece that had not been provided in NASA CR 1720, was a treatment of the water system and its regulation. We propose to remedy this. In this section is a brief outline of the essential elements that we are working up into a more extended model of that system.

A Phenomenological Introduction to Regulation of the Body Fluids

Starting with the notion that the organism is self-organizing, we add that an essential feature of its organization is the encapsulation of body fluids (e.g., retention of water). But since it is only function that can maintain form in the living system, the encapsulation of fluids reflects the operation of dynamic regulatory engines, and the persistence of form suggests that these engines function with sustained periodic behavior, as limit cycle oscillators. We therefore will begin our analysis with an inquiry into the nature of temporal organization in the regulation of body fluids. For a first round, this will be concerned with the phenomenology. We hope to develop the point of view in this description that causal chains exist which interact across several time scales so that the temporal hierarchy by which water content of the body is structured consists of having a given oscillator receiving its energy or material flux input from higher frequency oscillators, so that it can run at its own characteristic lower frequency. (As an example, by the use of squirt systems acting essentially as concentration 'escapements'.) But each oscillator may in turn be entrained in the operation of lower frequency mechanisms for which, periodically, a higher frequency oscillation provides the energy input. By the course of delineating such a temporal hierarchy, we will phenomenologically establish the known interactions that can provide a basis for the regulatory phenomena that interest us.

Thus, to orient the reader, Table 1 lists, in order of decreasing frequency, the various physiological systems which impinge on or are a part of renal regulation of fluid excretion (e.g., in man or dog), together with our best estimate of their relaxation times.

The heartbeat reflects the operation of the best known limit cycle oscillator. The operation of this engine insures adequacy of vascular perfusion. The determinants of instantaneous arterial blood pressure and heart rate are largely extra-renal but this instantaneous arterial pressure is integrated into a mean pressure which is a determinant of glomerular filtration rate. The formation of glomerular filtrate is the beginning of the fluid regulatory process. These pressures, and the flows generated by them, are the signals used to key the operation of the macula densa and renin-

Table 1

Temporal Organization of Fluid and Electrolyte Regulation in Man or Dog

heartbeat	1 second
respiration	4 seconds
renal pelvis	5 seconds
macula densa	15 seconds
peripheral vascular	100 seconds
renin-angiotensin	10 minutes
antidiuretic hormone	30 minutes
activity	90 minutes
insulin	2 hours
cortisol	3 hours
digestion	4 hours
albumin	12 hours
aldosterone	1 day
cortisol	1 day
thyroid	3 days
diet	3 days
menstrual	28 days
change in life status	60 days

angiotensin system in the kidney, and other causal chains activated in nonrenal tissues which finally have interactions at the renal level. The existence of lower frequency oscillations in arterial blood pressure is not well established in the conventional knowledge in physiology, but seems indicated from preliminary experiments now underway in our laboratories.

The respiratory pump is another well known limit cycle oscillator, beating in man with a period of 4 seconds approximately. The fundamental function of this engine is gas exchange.which insures adequate levels of oxygen and sufficiently low levels of carbon dioxide to permit operation of the renal engine. However, the pulmonary system interacts with the renal system in at least two important other ways. First, left atrial pressure, a function of cardiopulmonary mechanics, is itself a determinant of the rate of release of antidiuretic hormone. The output of these receptors is obviously oscillatory with several fundamental frequencies: the signal is transmitted neurally, so that it is pulsed to begin with; it varies with each heartbeat because of the pulsed nature of the circulation; it varies with the fundamental respiratory frequency; and it will clearly vary also with any lower frequency oscillations imposed on these higher frequency mechanisms. Low frequency oscillations in respiration are well known from the work of Lenfant, Goodman, and Priban, and from work in our laboratories. A second important interaction between the respiratory system and the renal system arises because the conversion of angiotensin I to angiotensin II occurs principally during passage of blood through the pulmonary circulation. How this conversion varies with variations in pulmonary perfusion is not known.

Ureteral peristalsis has a period of about 5 seconds. Peristalic rushes are initiated from a pacemaker located in the renal pelvis and very likely respond to tension or pressure or some variant of these. Because of the operation of this peristalic engine, the output of the kidney is fundamentally a pulsed one. Whether this pulsing has any influence on regulation is unknown. However, the hydrostatic pressure difference between distal tubule and renal pelvis is of the order of 5 cm H_2O. Oscillations of renal pelvic pressure of the order of a few cm H_2O will lead to oscillations in collecting duct fluid velocity. The major processes occurring in the collecting duct are aldosterone dependent sodium chloride reabsorption and antidiuretic hormone dependent water reabsorption. Oscillations in flow velocity will induce oscillations in the reabsorptive rates. In the absence of antidiuretic hormone particularly, urine flow rates increase and we presume the amplitude of the pressure oscillations will also increase, if not their frequencies as well. Thus in the absence of this hormone, variations in flow velocity may be expected to have a more profound effect on water excretion.

The macula densa is the point at which the thick ascending limb of Henle's loop becomes the distal tubule. This demarcation point is invariably also a point of contact between the tubule and the vascular pole of the glomerulus of that self same tubule. There are compelling reasons to believe that this contact is a signal flow pathway which is important in the autoregulation of glomerular filtration and renal blood flow rates. (See the work of Thurau.) Increases in flow through the tubular system are thought to lead to constriction of the afferent arteriole, decreases to dilation of this arteriole. This control mechanism is effective in maintaining relative constancy of flow over an arterial pressure range of 70-180 mm Hg. The complete details of the signal flow are not yet known. Some workers believe that the generation of renin from the granular cells of the juxtaglomerular apparatus is an important signal in this mechanism. However, activation of the renin-angiotensin system leads to vasoconstriction, while the stimuli to renin release are just those which cause dilation of the afferent arterial through the macula densa mechanism. We therefore conclude that the macula densa and renin-angiotensin systems are both responding to vascular signals, but that they then diverge. The major experimental evidence supporting the existence and operation of the macula densa mechanism suggests that this mechanism is capable of responses within a matter of 10-20 seconds. The major relaxations are therefore likely to involve mechanical compliances and diffusion over short distances. Therefore, the fundamental frequency driving this engine is that of the heartbeat; it will have its own fundamental frequency of about 15 seconds (certainly a minute or less), and it will follow slower frequencies generated by other systems in the list.

Several groups have now established the presence of oscillations in capillary blood flow in a variety of peripheral tissues with a period of 100-300 seconds. We believe these reflect the operation of water shifts in and out of the vascular space. If these water shifts are synchronized, they have profound implications for renal regulation because they suggest that plasma colloid osmotic pressure will oscillate at this frequency. This protein system interacts with arterial pressure in the following way: arterial blood drops through a resistor, the afferent arteriole, into the glomerular capillary bed. Glomerular filtrate is formed in this bed, its main rate determinants being the usual Starling formulation. That is, the glomerular filtration rate is proportional to the surface area of the glomerular capillary bed, the difference in hydrostatic pressure between capillary lumen and Bowman's space, and the colloid osmotic pressure difference betwen the two compartments. Under normal circumstances, 20% of the plasma flowing from the glomerulus is filtered through the glomerular endothelium, in the course of which the plasma protein concentration rises. The hydrostatic pressure drop through the glomerular capillaries is negligible, probably because there are bypass channels which clamp the pressure at both ends of the capillary net. Glomerular capillary blood is then collected into an efferent arteriole and then distributed through a second capillary network, the peritubular capillaries, which perfuse the space occupied by the proximal and distal convoluted tubules. The glomerular filtrate flows down the proximal tubule and fluid is reabsorbed (about 75% in the proximal tubule) by the operation of a sodium chloride pumping mechanism. Reabsorption is in all cases isotonic so the sodium chloride concentration remains that of arterial plasma through the length of the proximal tubule.

The mechanism thought by most workers to account for this isotonic reabsorption is the so-called standing gradient osmotic flow system (J. Diamond). In this hypothesis, NaCl is pumped by an active energy-consuming mechanism into the intercellular spaces, making these regions hypertonic. Water flows by osmosis from the cells into the spaces and because the channel is closed at one end, the fluid then flows out of the basal end of the intercellular space. Because the absorbed fluid is confined to the intercellular space for some time, water flow occurs by osmosis from the cell into the space until osmotic equilibration has occurred and therefore the emergent fluid is always isotonic. This fluid then enters the general interstitial space and there it is absorbed into the peritubular capillary. Determinants of this reabsorption into the capillaries are the difference in hydrostatic pressures between capillary lumen and interstitial space, and the difference of colloid osmotic pressure between capillary lumen and interstitial space.

A recent finding of considerable interest is that the overall reabsorptive rate from the tubules is determined by the forces which operate across the capillary endothelium. Thus, any device which raises capillary lumen hydrostatic pressure will inhibit tubular fluid reabsorption and vice versa, and any device which raises colloid osmotic pressure in the capillary lumen will enhance tubular reabsorption. Recent evidence suggests that there may be a shunt pathway for salt and water to flow through the tight junction separating adjacent epithelial cells. Flow through this junction provides a leak back into the tubular lumen. This backflow is controlled by hydrostatic pressure difference between the intracellular space and the lumen and the osmotic pressure difference between the two points. The membrane separating the interstitial space from the intercellular space is a low resistance hydraulic pathway so that any change in interstitial pressure will affect the hydrostatic pressure in the intercellular space and its geometry. An increase in interstitial pressure from whatever reason will increase backflow through the tight junction and dilate the intercellular channel, reducing the maximal osmotic pressure at the closed end, which will reduce an osmotic force tending to draw water from tubule lumen into the intercellular channel. Thus, in a real sense the peripheral tissues can signal to the kidney through the albumin concentration of the plasma. Interstitial pressure variations in peripheral tissues will cause appropriate water shifts into or out of the vascular space and the accompanying changes of plasma protein concentration will generate appropriate modifications of salt and water excretion from the kidney so that the volume of the body fluids is adjusted to maintain appropriate interstitial hydrostatic pressure everywhere. The fundamental frequency driving this mechanism is generated in nonrenal tissues; the renal response is probably that of a follower although relaxations involving the distribution of renal interstitial fluid and lymph may be rate limiting. Oscillations in sodium chloride reabsorption by the proximal tubule with a period of 200 seconds will induce variations of tubular flow rate with that frequency, and these are frequencies to which the macula densa may respond as a follower. The amount of control power tied up in this mechanism is substantial since it represents 30-40% of the filtered load of sodium chloride and water, and its successful and continuous operation appears required for the maintenance of fluid volumes and the successful operation of lower frequency mechanisms.

Renin is a protein released from granules in the afferent arterial smooth muscle cells. Renin acts as an enzyme to hydrolyze a decapeptide, angiotensin I, from a circulating protein, renin substrate, which is made in the liver. Angiotensin I is generally inactive except as a substrate for the converting enzyme which hydrolyzes two amino acid residues and leaves the octapeptide, angiotensin II. The two known actions of angiotensin II are as a potent vasoconstrictor, and a stimulus for aldosterone secretion at the adrenal zona glomerulosa. When renin is injected into the general circulation, it brings about a substantial rise in arterial blood pressure with a relaxation time of about 7 minutes. The major stimuli to renin release from the juxtaglomerular apparatus are fall in arterial blood pressure, stimulation of the sympathetic nerves to the kidney, and chronic dietary salt restriction. There has been some speculation that the macula densa mechanism might also involve the renin-angiotensin system as a signal, but the evidence on this point is conflicting and unconvincing. Until recently, the most commonly accepted view was that renin-angiotensin had no role in physiological regulation of arterial blood pressure, but Guyton has presented compelling evidence to suggest that the renin-angiotensin system is in fact involved under normal circumstances in this regulation. The high frequency input to this system is therefore the arterial pulse whose adequacy is maintained by the operation of renal excretory control mechanisms. The postulated 7-10 minute period for renin would then have interactions on the aldosterone system, on the arterial blood pressure and also weak interactions on the control of thirst in the central nervous system and of ACTH release, also from the central nervous system. We believe the evidence very suggestive that the renin-angiotensin system is in fact crucially involved in the interaction across several levels of the temporal hierarchy.

Antidiuretic hormone is released from the posterior pituitary in response to dehydration of the arterial plasma and to reduction of left atrial pressure. Major high frequencies impinging on this system are therefore those generated in the left atrium which are principally determined by cardiopulmonary relaxations. The fundamental frequency of response to the antidiuretic hormone is probably determined by the response of the distal tubule and collecting duct system with their changes in water permeability. The hormone induces an increase in water permeability in these two structures, permitting increased reabsorption of water from the tubular space back into the vascular compartment. Injections of the hormone to overhydrated animals whose endogenous hormone supply is inhibited by the hydration result in reductions of urine flow in about 15-30 minutes. The renin-angiotensin system may also interact with the ADH system because of the conversion of angiotensin I to angiotensin II in the pulmonary vascular bed. This point is largely unexplored. Another point of contact between these two systems is in the central nervous system where it is now known that injection of angiotensin II into the third ventricle of the brain causes thirst through dopaminergic pathways. Thirst induced by angiotensin will lead to drinking which will hydrate the plasma and reduce an osmotic stimulus to ADH release.

Posturally related activity is known to have a period of about 90 minutes. When a subject arises from a seated or supine position, renin is released from the kidney and the various controls that operate because of its action are invoked. In this frequency range, the renin-angiotensin system is acting as a simple follower. The activity is obviously generated within the central nervous system, but whether its determinants have anything to do with a need for variation of renin-angiotensin levels is at this point unknown.

Insulin is known to oscillate with a period of 140 minutes when the glucose system is forced. Insulin is also known to stimulate isotonic reabsorption of sodium chloride from the proximal tubule so that any oscillations in insulin will produce similar oscillations in salt and water excretion. The operation of this mechanism is probably responsible for the disproportionate weight increase seen when a subject changes from a low carbohydrate diet to a high carbohydrate diet. The resultant increase in insulin activity probably signals increased reabsorption of salt and water and excessive fluid retention. Although the 140 minute oscillation of insulin will not occur in the normal subject, an oscillation of insulin concentration certainly will, with the same frequency as the eating frequency, a period of 4-8 hours. (We will not discuss the complex of water events that accompany digestion separately). Similar oscillations in salt and water excretion due to the variation of insulin levels are to be expected.

Cortisol has two important frequencies, a three-hour burst mode which is seen at the height of its 24 hour secretory phase. Cortisol is known to have an important controlling effect on glomerular filtration rate and distal tubule and collecting duct water permeability. High levels of cortisol are accompanied by increases in glomerular filtration rate and decreases in water permeability, so that high cortisol means in general increased salt and water excretion. The action on glomerular filtration rate is a vascular one, probably similar to the generally well known vascular action of cortisol which is to potentiate the action of catacholamines by inhibiting catechol-o-methyl transferase activity. The action on water permeability appears to involve an effect on protein synthesis. Three hour frequencies may be too fast for protein synthetic effects to appear, but 24 hour frequencies clearly can be followed by mechanisms involving protein synthesis effects.

Albumin has a half life of about 12 hours. Alterations in its rates of synthesis or degradation which occur periodically can be expected to induce oscillations in its concentration. Postural effects, as for example, prolonged bedrest during sleep, will also cause changes in albumin concentration because of water shifts in or out of dependent tissues. Oscillations in albumin concentration will affect salt and water excretion by mechanisms already discussed for higher frequencies. In this case the albumin kidney system is acting strictly as a follower for oscillations determined by other relaxations.

Aldosterone is a steroid hormone whose principle action is to promote sodium chloride reabsorption from epithelial tissues generally, including the kidney. Its major effect is to stimulate protein synthesis, and the protein synthesized in response to the presence of the hormone carries out the controlling function on electrolyte reabsorption. The principal stimuli to aldosterone secretion are angiotensin II, high plasma potassium, ACTH, and chronic dietary salt restriction. We have already adduced evidence to suggest that angiotensin II concentrations will oscillate at relatively high frequencies, and also at somewhat lower frequencies. These angiotensin oscillations clearly control the aldosterone system which acts as a follower at 24 hours. The 24 hour cycle appears to be related to the sleep-wakefulness activity cycle. Higher frequency oscillations, though conceivable, are not described for aldosterone.

A potent stimulus to thyroid hormone release is cold exposure. The relaxations are of the order of 2-3 days. Cold exposure is known to induce a 3 day oscillation in glomerular filtration rate and salt excretion. This oscillation undoubtedly involves the thyroid system, and we are now in a position to provide an explanation for how the thyroid system activates the fluid system. The work of Edelman makes it clear that a principal action of thyroid hormone is to stimulate the synthesis of sodium potassium dependent ATPase in cell membranes. These ATPases are intimately involved in the operation of sodium potassium exchange pumps. These pumps are ubiquitous and are responsible for regulation of cell volume in tissues generally. Any mechanism which stimulates their operation will lead to extrusion of sodium chloride and water from cells, a rise in extracellular fluid volume, and a stimulus to salt and water excretion by any one of a number of the mechanisms previously listed.

Changes in diet generally involve changes in salt and carbohydrate load. By mechanisms discussed earlier these will effect salt and water excretion. The controlling relaxations are unknown. However, we note that when an animal is loaded with aldosterone in supermaximal doses, retention of salt and water continues for about ? days until a phenomenon known as escape occurs. Escape refers to increased excretion of salt and water despite the high levels of the mineral retaining steroid. The escape phenomenon appears to involve dilution of plasma proteins so that the albumin concentration may oscillate with a 3 day period in certain dietary states.

A very well known oscillation in humans is the menstrual cycle. Retention of salt and water before the onset of the menses is well known in women. We suggest that the salt and water cycle of men may also become behaviorally entrained in the menstrual cycle of their women companions.

Changes in life status appear to have settling times of the order of 60 days, and effect many facets of physiological activity. Unquestionably these involve operations of the central nervous system with potentially many points of contact with the fluid and electrolyte system.

The thermoregulatory system makes adjustments normally every 3 months because of seasonal variations and ambient temperature. We have already seen that the thyroid system will oscillate when activated and has an oscillatory effect on salt and water excretion. Therefore, behavioral concomittants of the thermoregulatory system may be the long term one year engine for the water system.

As a final comment, this description may leave the impression that the high frequency 'escapement' phenomena leads or governs the low frequency follower behavior of the active water processing, which would tend toward the more conventional outlook of biology toward such systems. But the fact is more likely that the low frequency self regulation system, in each case 'determines' or calls upon the high frequency system, truly as an escapement (e.g., as a squirt) to provide its sustenance. But it does not have to do so in a very sharply regular way; a very sloppy high frequency character is sufficient. Truly the low frequency systems run the show. In the future we will tend to complete the model implications of this thought.

XI. METABOLIC DYNAMICS - SOME FURTHER DISCUSSION

The biological paradigm of the past century has developed a rather consistent, but static view, of the metabolic process. Thus we might say that for a first round of physical review (1942 to present), our objectives were to add enough information about dynamic processes to provide consistency with the overall near static equilibria described by the biologist. Our first work revolved around respiratory equipment design for high altitudes and for full pressure suits. We began to come to grips with the physiological problem in the late 1950's around clothing issues.

In an earlier study (1), data were obtained on human metabolism that indicated metabolic cycles of 2 minutes, 7 minutes, 20 minutes, and 3 1/2 hour periods. Attempts were made to align these with hormonally regulated cycles (2). In particular, efforts were made to reduce the number of degrees of freedom in the description of the regulation of components of the metabolic reactions; that is of

$$\text{fuel} + \text{oxygen} \longrightarrow \text{carbon dioxide} + \text{water}$$

Thus studies were made of blood sugar, oxygen, carbon dioxide, lactate and free fatty acids in blood (3). It was somewhat surprising when high frequency blood glucose cycles were first found and then reported on in additional studies (4), because it was more expected that glucose and insulin would be implicated at a slower time scale.

Nevertheless, these 'homeokinetic' studies have served as a jumping off point to a more extended study of the metabolic process as found in blood, and in particular, in unanesthetized dogs. We may regard these new studies as being the second round reaction of responsible and responsive biologists to the perhaps overly loose first round of physical attack.

Recent Progress in Regulation of Metabolism

As discussed earlier in the report, the solutions of nonlinear differential equations with dissipative terms may show orbital stability in the phase plane. We liken the periodic behavior typical of such limit cycle oscillations to the persistence of biological systems themselves and have sought evidence that physiological regulation might be brought about by limit cycle oscillators. Since a sine qua non of limit cycle oscillation is the presence of energy dissipation in some form, physiological systems concerned with regulation of energy flow in the organism provide a crucial testing ground for these ideas. Clearly a hypothesis which arises from considerations of energy consumption cannot be generally valid if it is not true in systems concerned principally with this function.

The elements of the glucose regulatory system are well known. Glucose is absorbed from the food through the epithelium of the small intestine whose perfusing blood passes first through the hepatic portal circulation to the liver. The liver may take up glucose from the circulation and metabolize it, or store it as glycogen. The primary stimuli to the uptake mode are a high blood glucose concentration, and insulin circulating in the blood. Typically, the liver extracts glucose from the blood immediately following a meal during which hepatic portal concentrations of glucose are high. In the fasting state the liver releases glucose to the circulation, taking it either from glycogen stores or making it de novo from precursors such as amino acids. Net glucose output from the liver is governed principally by the hormone glucagon.

To the extent that the dynamical behavior of liver glucose production or consumption is known, this organ appears to be a simple follower depending for its dynamics on the temporal pattern of circulating blood hormones and glucose concentrations. The brain and kidney medulla are two tissues that depend exclusively on glucose for their energy supply. Fasting hepatic glucose output is concerned mainly with maintaining an adequate glucose flow to these organs (to the brain, especially).

Other tissues, notably skeletal muscle, can use glucose provided that insulin is present to stimulate the uptake. In the absence of insulin, free fatty acids provide the major energy supply for most other tissues. The insulin effect on glucose uptake is, to a first approximation, a stimulation of the rate of glucose transport into cells. The transport behavior of skeletal muscle and most other tissues follows Michaelis-Menten kinetics. The transport reaction is in the first order range over the physiological range of glucose concentrations; insulin stimulates the transport rate while leaving this transport system still in the first order range, so that uptake is essentially that of a linear follower mechanism.

The two important hormones, insulin and glucagon, are made in the islets of Langerhans of the pancreas. The principal action of glucagon is on the liver to stimulate glucose release. The chief stimulus for glucogon release from the pancreas is a low blood sugar concentration; the secretory dynamics of glucagon appear to have some striking nonlinearities, including an overshoot in response to step forcing with low glucose blood. The major stimulus for insulin secretion is high blood sugar, an effect which is potentiated by high plasma amino acid concentrations. Glucagon is another potent stimulus for insulin secretion, and catecholamines inhibit release of insulin. Insulin secretory dynamics in response to step forcing by high glucose concentration shows a number of striking nonlinearities, including an overshoot followed by a continuously rising secretory rate, which, after two hours has already exceeded the height of the initial spike.

The conventional view of glucose metabolic dynamics is based on the application of feedback theory. There are at least ten models of this system in the literature. The simplest, by Bolie, is a pair of linear ordinary differential equations describing the temporal pattern of glucose and insulin in blood following impulsive forcing. More sophisticated models have been introduced and the most complex are those of Foster and Srinivasan. These last two include some of the dynamics of glucagon and concern the metabolism of fatty acids as well. All the models share in common a viewpoint derived from classic feedback theory and also a preoccupation with the analysis of data from standard glucose tolerance tests. The dynamic pattern imposed on the system in this test is one of simple impulsive forcing with glucose. The system is observed sequentially in time until the glucose concentration has settled back to control values, usually in about two hours. The usual intent of such models is to fit parameters from the relaxation curve. None of the models predict spontaneous oscillation or oscillations in response to simple forcings of the system.

Recent experimental evidence concerns attempts to find oscillations in arterial glucose and insulin concentrations. High frequency oscillations of the order of 30 seconds to two minutes have been reported previously, but using an integral sampling technique in conscious dogs, we were unable to find fluctuations of arterial glucose concentration which could be differentiated from the noise of the analytic method. We continued the search for oscillations at somewhat lower frequencies, and found that in about half of the 15 dogs examined at 5 and 10 minute sampling intervals, a models oscillation of 10 - 15 mg% amplitude and 1 - 2 hour duration could be found. In the other half of the dogs no oscillations were seen and there were no obvious differences in the protocol to suggest a basis for the inconstancy of the finding.

It should be recalled that little glucose consumption occurs when animals are fasted, and these initial studies were all done on fasted dogs. Therefore, we concluded that the system had to be switched to a glucose consuming state in order properly to test for oscillations in the regulation of carbohydrate metabolism. We decided to infuse glucose intravenously at a constant rate which was 50 - 100% that of the endogenous liver supply of glucose. After an initial rise followed by a fall, the system settled into a period of sustained oscillation for about 3 hours and maintained this oscillatory mode for the duration of the infusion, up to 12 hours. The majority of dogs showed a single dominant frequency in this oscillation, approximately 140 minutes in duration. Other animals showed some variation, but the shortest period was of the order of 80 minutes. All animals tested showed this oscillatory behavior.

Measurements of arterial insulin concentration in the same samples revealed similar oscillations. In about half the dogs, the oscillations could easily be seen to be correlated with the glucose concentrations, and power spectra showed significant peaks in the insulin data at the same frequencies as those found for the glucose data. In others, the oscillations of the glucose and insulin were clearly dissociated both in the temporal pattern and in the power spectra. In this group of experiments, the insulin oscillations were invariably of shorter period than the glucose oscillations; in one experiment, an insulin period of 30 minutes was found but 80 minutes was more typical of the experiments where the dissociation between insulin and glucose occurred.

At this stage in our work, we conclude that the glucose metabolic system is indeed run as if it were an ensemble of loosely coupled limit cycle oscillators whose oscillation is most clearly revealed when the machinery is made to do significant work by supporting energy flow through glucose consumption in the organism. We also extended these observations to include free fatty acids. In fasting animals, free fatty acids provide the major fuel supply for the organism, and under these circumstances we found an oscillation with a period of about one hour. Glucose infusions caused the free fatty acid concentration to drop precipitously into the noise level of our method, and we are unable to decide whether the oscillation is sustained in the glucose consuming mode.

The next step is to attempt to define the significant elements and operations of the glucose regulatory system. Of all the models currently available in the literature, none will predict an oscillation for either arterial glucose concentration or insulin concentration, when the system is supplied with a constant glucose source. The failure to find such an oscillation is not terribly surprising, since all these models were fitted to single relaxation data, not a dynamically rich source. None of the published models contain the real nonlinear dynamics of pancreatic insulin secretion. We therefore imbedded these dynamics in a system model containing linear sources and sinks, but again could educe no oscillation. The temporal dissociation of glucose and insulin oscillations in our experiments suggest the presence of other important system components that serve to decouple various elements in the system. The two most likely candidates for these interfering components are glucagon and the sympathetic nervous system. At the present time we are attempting to build a model incorporating these two components to see whether the experimentally induced oscillation can be predicted.

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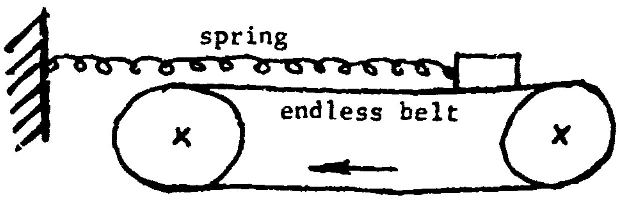
XII. A NOTE ON 'PRACTICAL' LIMIT CYCLES

A recurring theme that has faced us in our confrontations as physical scientists versus biological scientists has been the question of inferring determinateness in periodic or causal spectra. This problem was quite vexing since it was made quite clear in Goodman's work (1) following our work in ventilation and metabolic dynamics (2) that the ventilation periods warbled. In effect, the biologist asked, how does one know when he has a thermodynamic engine limit cycle?

The theoretical structure we offered was the following:

1. If one had a near constant homeostatic maintenance of concentrations, sizes, pools, etc., in the biological organism over an extended 'lifetime' period, instead of cessation to a halt, that mean state would have to be maintained as the rms state of a variety of fluctuating thermodynamic engine cycles. This would require that any finite segment of time series data should reveal a comparable spectrum of harmonic effects. And in fact this provides what appears to be the only reasonable test for such causal systems, namely that every segment of measured data should show a comparable spectrum. If the spectrum was a system of limit cycles, the only theoretical frame we can provide from mechanics, then the phase performance in any segment could be either deterministic or stochastic (e.g., if noise crept in from the open environment), but the amplitudes and frequencies would have to be more nearly deterministic. Both from our data and Goodman's data and from Goodman's analysis, it was clear that the warble or wobble could be considerable.

The biologist could not quite accept this with such great ease. Thus two simple mechanical examples were suggested for study. The first is a well-known elementary illustration of a crude limit cycle.



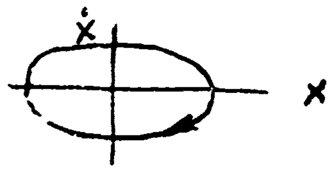
A horizontal mass attached to a spring rests on a rough endless belt. The belt pulls the weight along until the spring restori force makes up for the binding friction force. The weight 'stutters' b until the friction force binds it to the belt, whereupon it is pulled along, etc.

The parameters can be easily chosen to where the arrangement is 'unstable', namely it will invariably be pulled and fall back, forming a repeated cycle. But the cycle is sloppy. Nevertheless it is fully determinate. With some variation in its chatter frequency, the cycle will take place. It is nonlinearly stabilized.

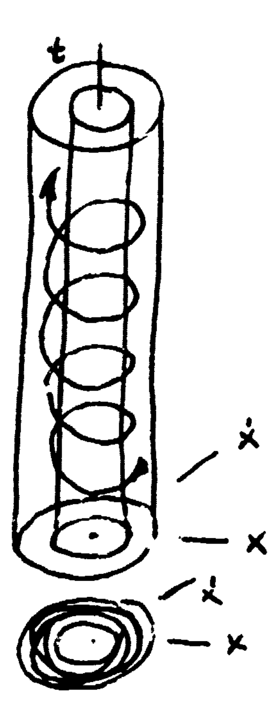
Now we wish to report on a simple second experimental situation which will provide some insight into 'sloppy' or 'fuzzy' limit cycles.

Strictly speaking a limit cycle is a closed singly connected contour in a phase space of x, $\dot{x}$ for a one degree of freedom system x, which is defined by

$$f(x,\dot{x},\ddot{x},\dddot{x},\ldots,\overset{(n)}{x}) = 0$$



However in practise, some modest generalization of the concept is needed. For example, in coupled m degree of freedom systems, it is not essential that any one degree of freedom be completely decoupled in the autonomous sense indicated above. If the effect of other not completely autonomous degrees of freedom is quite restricted, or if the effect of other time varying noise is also highly limited, then it would seem that the concept of a limit cycle could still be applied to the particular degrees of freedom which were nearly autonomous. To restrict the illustration for purposes of simplicity and clarity, this can be illustrated for the case of noise. Thus in the following figure, the 'extended' limit cycle idea is illustrated in a cylindrical space.



What is depicted is a space between two cylinders, which is filled by a monotonically unfolding spiral that remains bounded between the two cylindrical walls. As G. U. Yule illustrated with regard to what he regarded as a resonator type of cycle, it is as if a group of boys with pea shooters constantly provided small 'noisy' input impulses to a massive mass-spring system. This would constantly spoil the phase but not particularly affect the near isonchronism. Here the concern is not with isonchronism, but with a bounded limit cycle. 'Noise' can be expected to arise from parametric variation in the system or its environment. The mathematical details by which other coupled degrees of freedom permit similar near autonomous isolation is better left to the mathematician.

We have attempted to illustrate the 'real' nature of fuzzy limit cycle generators by recommending two experimental situations to colleagues. The first, which we have mentioned already, a classic one, is the sliding mass attached to a horizontal spring (e.g., rubber bands) dragged by an endless belt surface which possesses friction. Although the motion is erratic, it is intrinsically unstable, and a crude limit cycle will invariably emerge if the motion is bounded.

The second experimental situation is a cylinder holding fluid, with a bottom heater, and a quantity of insoluble wax of comparable density. The device is used for display purposes as a dynamic ongoing eye-attracting process. Wax spheres settle, fall into a blob, reheat to reduce their surface tension, tear off into near spherical shape, rise, cool off, change density, and settle back. The process is neither random nor fully determinate. Namely it is not clear what slug of wax will tear off, but it is clear that some piece will invariably tear loose. Thus it is a nonlinear lossy system which must provide some resolution of the instability it is presented with over and over again. The issue with regard to its limit cycle behavior is how good a 'clock' does it form.

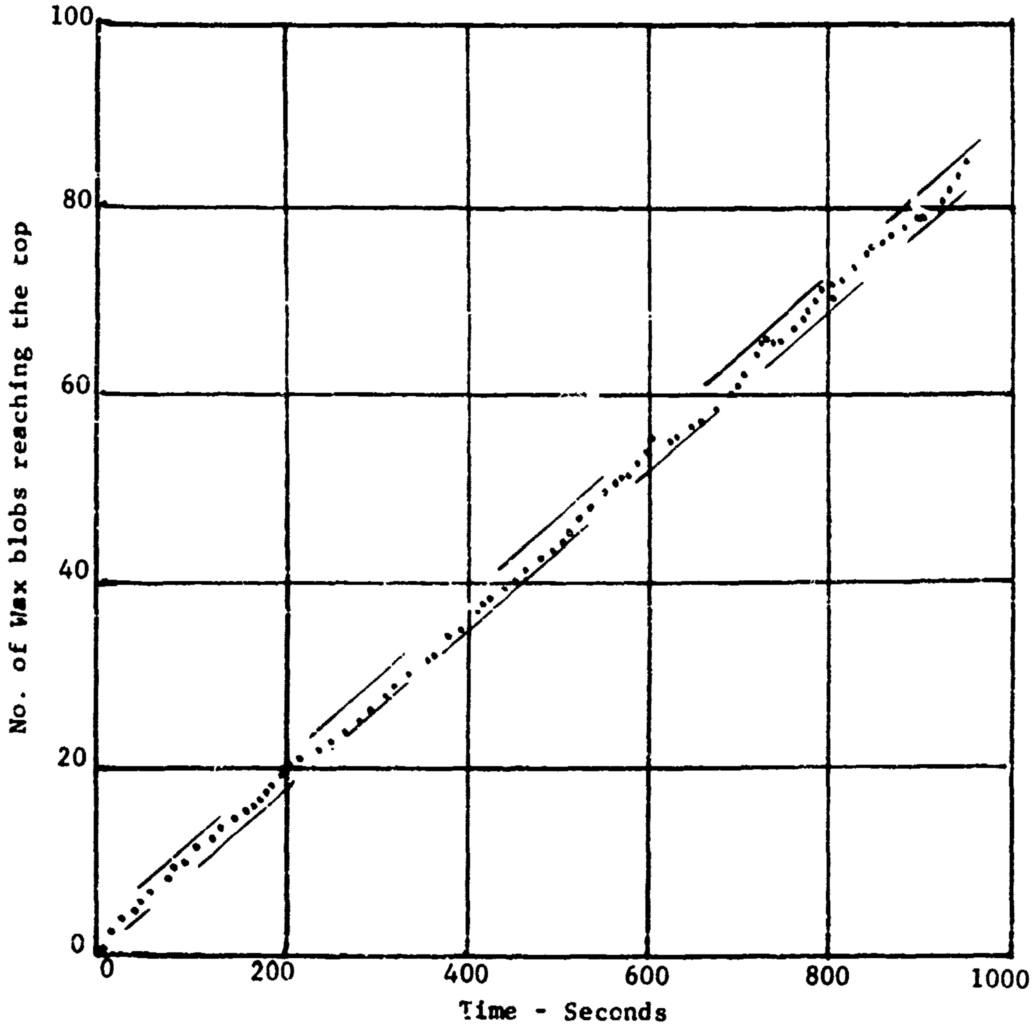
Superposition of a delayed flight, a restless mind, an airport, such a device, a piece of paper, and a clock suggested that the 'Gedanken' experiment could be turned to reality.

Experiment - Airport - Paris (Orly); date - June 16, 1972; time (local) - 5 P.M.; cylinder diameter - approximately 4 inches; cylinder height - approximately 8 inches; rising wax sphere diameters - approximately 1 inch. An imaginary line was noted approximately ½ inch from the top surface, and those wax spheres that passed that line were timed and counted. This excluded very small droplets that were occasionally noted, and some few small spheres that didn't make it to the top (i.e., they cooled off prematurely).

The data thus gathered over a 20-minute period are plotted below as the cumulative number versus the time of cumulation.

The average slope indicates a mean interval of about 1 sphere per 11 seconds. The mean interval (taken from the difference statistics) is about 10 ± 5 seconds (mean and average deviation). The clocking is not high quality, but on the other hand it is not an indifferent timekeeper. One notes a considerable sequential correlation in the data, namely individual epochs of perhaps 50-100 seconds seem smoothly coherent. But the derivatives are only piece-wise continuous. The maximum and minimum timekeeping rate differ by about a factor of two from the mean. But over a segment of say 300 seconds, a reliability in the keeping of the order of 10% is achieved.

Limit cycle or not? By timekeeping standards, one would say yes. One would say that this is a sloppy timekeeper, but whose statistical properties - except for the accuracy range - is essentially similar to that of much higher precision clocks. Namely, one detects the segments of piece-wise continuity that suggests local coherence; yet in the long run there is no extended drift from a mean performance.



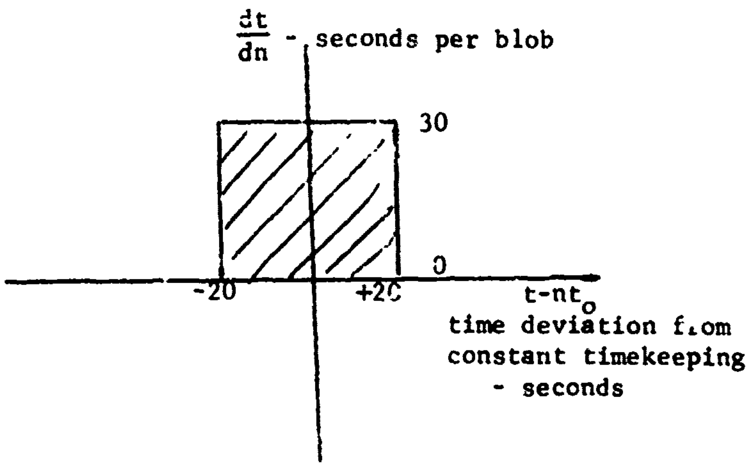
Repetitive blobs found rising from a heated wax pool

Presented as a limit cycle, one may plot the deviation in time from the mean time line, i.e.,

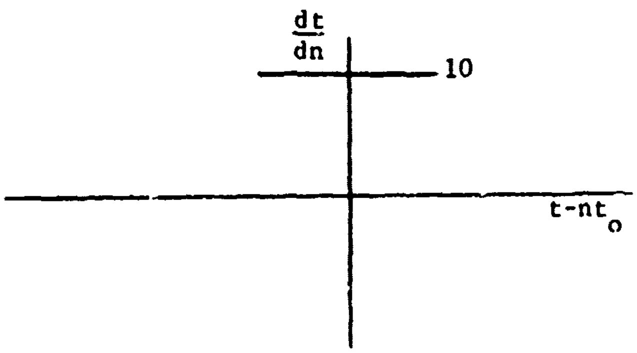
$$t - nt_o$$

versus $$\frac{dt}{dn}$$

the changing slope. The essential fact is that both are well bounded.

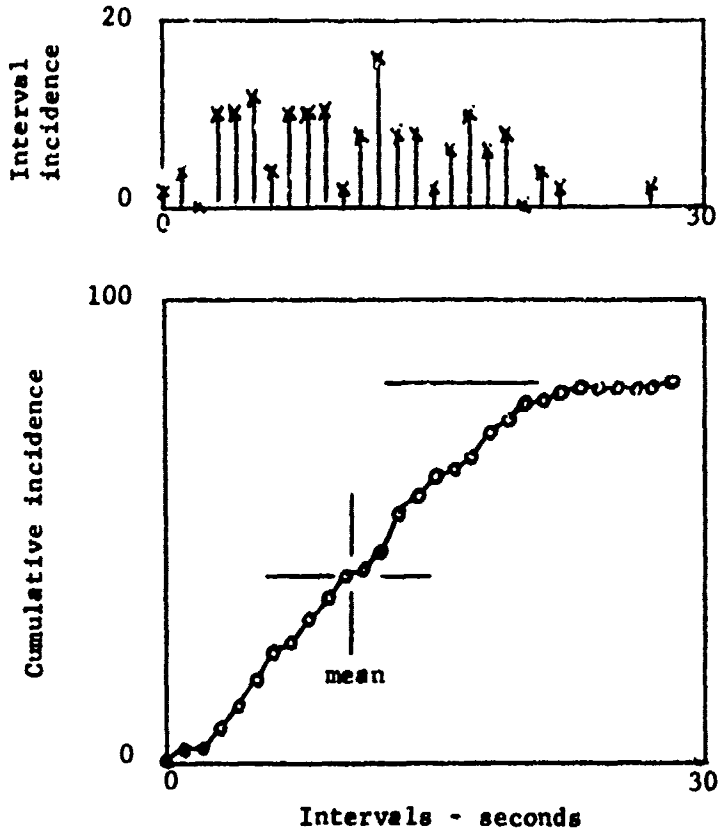


Thus we are dealing with a solid cylindrical domain, whereas an 'ideal' limit cycle would consist of the following



an extremely narrow cylindrical sheet.

The distribution of intervals is shown below.



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XIII. INVITED TALKS DELIVERED THIS REPORTING PERIOD

A. Commentator's Remarks at the Fifth World Congress of IFAC, June 1972 for the Biocontrol Sessions

A prepared text that deals with the content of the papers presented is included in the published Proceedings of the Congress. The following was the text used for a verbal presentation.

Comments on Biocontrol

Various circumstances prevented me from presenting my views on control themes - particularly biocontrol themes - to previous IFAC Congresses. Perhaps this was fortunate, because it is only in the past few years that one might say that the possibility for some generalizations that are of importance to regulation and control of complex systems - such as the biological, and the social - is coming into existence. I would like to create a frame of reference for my distinguished international audience. A broader background to the point of view may be found in a recent article by Dr. Benjamin Gal-Or in the April 7th issue of Science; or in my recent book, TOWARD A GENERAL SCIENCE OF VIABLE SYSTEMS (published by McGraw-Hill this year).

Dr. Gal-Or begins his article with the statement, "An old crisis in science is receiving renewed attention in response to recent discussions of the thermodynamic foundations of the natural sciences. The crisis manifests itself most clearly when attempts are made to provide answers to such fundamental questions as: Is the origin of irreversibility in nature local or cosmological? Is it in the laws or in the boundary conditions? What might be the physical interrelationships underlying the expansion of the universe, information theory, and the thermodynamics, electromagnetic, biological, and statistical arrows of time?"

Today we are concerned with the nature of the regulation and control of the life processes themselves, on the surface perhaps not in these global terms, but on the other hand the control of the water system - life's basic 'blood', or the regulation of heart functions by substitutes, or the elaboration of life's processes in a bacterial colony, or the regulation of the physiological parameters of a living man are not trivial subjects. They contain in their sustained nature, life's arrow of time.

Now my concern is with systems' modelling, and the basic question I have intended to raise by my written commentary, in an attempt to stimulate both the authors and the audience to thinking about it, is how basically shall we model complex viable systems?

First, what is a complex viable system, and how - if at all - does it differ from the engineering systems we have heretofore been concerned with?

A complex viable system is first and foremost an autonomous system. Namely, given constant potential sources and sinks, it can abstract energy from the source in some cycle of performance and reject energy to the sink, and for the expense of that transformation, do some work. It can continue to do this indefinitely, given these constant or near constant energetic boundary conditions.

But a viable system has an additional characteristic. It can adaptively seek out in the environment necessary source and sink potentials and modify its operating cycles accordingly. The difference is profound.

The first kind of system is a simple thermodynamic engine. There is a charge on the universe, a loss in the ordered energy of the universe, or technically stated a gain in entropy. As a result of natural processes - and living is natural - disorder in the universe increases. The second is more than a simple thermodynamic engine operating between source and sink. The viable system includes its local environment as part of its 'being'. Thus it manipulates both itself and its local environment to maintain i 'life' in some larger scale near constant potential source and sink. N ly, biological life lives from the sun and rejects to space. In between it manipulates its surrounds to survive.

As a third aspect, it cannot do this forever. Thus we find a more common 'engineering' system problem. We require maintenance, repair, and ultimately replacement of the system. These issues are on the agenda of history. In the past two decades, they have become concerns of biomedical engineering, and today's child, genetic engineering.

But what issues of modelling can and should we be concerned with as engineers? I submit that you consider the following list:

1. Our concern is with mechanism - the stock in trade of every engineer, whether mechanical, electrical, chemical, or civil.

2. Our concern is with system - an ordering of mechanisms.

3. Our concern is with thermodynamic engines - systems devised to obey the second law of thermodynamics ('all systems must run down'), but which can do useful work for their 'lifetime'.

4. Our newest concern is with viable thermodynamic systems. In these systems, we do not put the human in the loop to maintain the larger range operation of the thermodynamic system. The system itself is capable of its own life maintenance, and repair, and replacement.

I submit that the modelling for these four levels of problems are different. In our early technical training, we are all taught the mechanisms of our trade, clearly. The mechanical engineer has his gears and machines and machine tools, his prime movers; even his mixed electromechanical devices are highly mechanical. How much does he know or learn of the unit processes of the chemical engineer. or all of the latest modular electronic devices. And so forth - the same story unfolds around the ring, La Ronde.

Of course, the control engineer claims a familiarity with everyone's mechanisms, but I would claim that the familiarity is superficial. This is clear if you give him a detailed design problem, e.g., design an inexpensive pressure regulator that has certain very specific pressure flow characteristics.

The most rudimentary idea of a system is taught to the engineer by the time of his graduation. A system is some complex of interrelations among components and moving parts over which man lords. Without man, the system usually does little except performs routines. But suddenly with man on the scene, its 'purpose' is discovered.

When most of we practicing engineers leave school, we are thrown into such a system - for example, a factory or plant - or we are concerned with design or maintenance of such systems - for example, aircraft, weapons systems, servo systems, network receivers, transmitters, amplifiers; or with chemical plants, and so forth.

The control engineer has been taught his trade for such systems. Modelling for such systems, carried to their ultimate, are represented by such efforts as Forrester's INDUSTRIAL, URBAN, or WORLD DYNAMICS, Meadows' THE LIMITS OF GROWTH; or in the biological world, Guyton's global model of the cardiovascular system (which has just come out in the 1972 issue of the Annual Review of Physiology). Incidentally, it is my belief that Guyton's model will be as seminal for physiological thinking as the contributions of Darwin, Marx, Freud and Einstein to their fields.

Nevertheless, I do not find myself in sympathy with such models. In particular I do not regard them as isomorphic with the real systems they purport to model. In spite of the fact that this is such a major challenge I can do little more than to enunciate the challenge and objection rather than to document it. Suffice it to say that those interested may have to examine the start of the argument in my book.

But I join with a number of allies in enunciating a different point of view, basically a thermodynamic point of view. This can be noted in such references as: Dyson's article on energy flow in the universe in the September 1971 issue of Scientific American, or Eigen's article on "Self-organization of Matter and the Evolution of Biological Macromolecules", in the October 1971 issue of Naturwissenschaften. Most appropriate in this locale is to refer to Monod's recently translated CHANCE AND NECESSITY. Monod points out that purpose in the biological organism is coded for at the genetic level. (Monod's specific theses are that reliable and invariant reproduction precedes purpose in all living systems; this invariance arises from the genetic code; and that protein is the essential molecular agent of purpose. Purpose, he believes, emerges from the sterospecific nature of protein molecules to furnish a machine code.)

What we are saying is that purposive organization is already coded for genetically, so that complex autonomous behavior emerges epigenetically from the interaction of the self-organizing organism with the environment it finds itself in. It is as if the blueprints for the system, not only self-organize materials and mechanisms for the system, but are sufficiently rich that a self-sustaining autonomous life will emerge whether the system is or is not provided with a very specific local surround. Our system modelling to date has not reached that point.

We expect the answers to lie in the domain of irreversible or nonequilibrium thermodynamics. To date we only have the rudimentary examples of the equations of simple hydrodynamics to guide us. In my 1950 transmission line paper, I showed all of the content of those equations in the small. The equations lead to degradative thermodynamic processes - due to viscosity, diffusivity, and thermal conductivity. We know that they also lead to the 'organized' (sometimes 'chaotic') state of turbulence. I am well aware of the difficulties in that problem, having attempted much serious modelling in that field.

Now we must push the frontiers to the biochemical processes of life itself. Here the names, to mention a few, are Britton Chance, Zhabotinsky, Brian Goodwin, Prigogine, and Katchalsky, truly an international galaxy. We mourn Katchalsky's senseless murder in Tel Aviv.

It is toward such descriptions that I would like to draw your ultimate attention. But now we must turn to the immediate papers at hand.

25.1 The water system in the human. Life, as Claude Bernard indicated, remains imprinted with the mark of the oceans from which it originated. To a considerable extent, especially clear in simple organisms, life is little but the maintenance in size of an active pool of water. A bacterium can be looked at as a simple system, a relaxation oscillator, that grows in size and divides. In the complex human, regulation of the watery pool of life is involved in many more regulatory chains. Grossly, humans drink each day and excrete. The 'purpose' of the system is to rid the organism of waste products of complex metabolism. It is the task of Drs. Merletti and Weed to give us some more detailed insight into some of the regulatory chains in which water is caught.

25.2 Control of vital functions. Academician Petrovsky, Professor Shumakov, and their colleagues have undertaken to provide us with a simulation of the physiological regulatory basis for the vital functions of the organism. Their purpose is to provide us with a base for normal regulation of the system under conditions of substituting artificial organs or augmenting operating deficiencies. Their intent is not to tell you how to design an artificial organ, but to indicate more or less what are the normal operating conditions that will have to be fulfilled. They have done my former colleague, Warren McCulloch and I the honor of offering our dynamic time scale of homeokinesis as the temporal background for the necessary vital processes. The problem we shall face in comprehending their paper is whether they provide us with enough descriptive insight and a sufficient experimental data base that we can see that the regulation is sufficiently complete. To cite as illustration, it is still not clear whether complete heart transplants are based on a sufficient understanding of the vital functions of the cardiovascular system, beyond the issue of tissue rejection.

We commend their study of being on the way toward a thermodynamic description, but it is the details of the processes we must now note.

25.3 On a heart pump. The authors will report on some mechanistic details of a heart assist device, in particular how some useful control functions have been realized.

25.4 Estimating cardiac output. An excellent introduction to the problem of measuring cardiac output by both direct and indirect ways is Guyton's 1963 book on CIRCULATORY PHYSIOLOGY; subtitled CARDIAC OUTPUT AND ITS REGULATION. This can be used in addition to the Handbook of Physiology reference that Drs. Bekey and Maloney offer. We will be presented by an indirect Fick method for measuring cardiac output, one of the main responsive parameters of the living organism, by which the organism supplies its needs. To an essential extent, the law of cardiac output is the law of the organism's tissue by which it makes its needs both periodic and immediate felt at the heart. The authors' particular contribution will be to show an identification of parameters scheme to draw out the cardiac output from a host of relatable respiratory data.

25.5 Control of movement. In our paper on the organizing principle of the living system, Warren McCulloch and I put down as a major algorithm for the animal kingdom, that the animal eats to move so that it can continue to eat to move. The mechanisms of movement thus are a primary subsystem in viable systems. The authors take up the problem of pointing or aiming and maintaining a postural attitude as an input-output study.

It would be helpful to the audience if the authors make the geometry of their system more explicit. Where is the flexing-extending and abducting-adducting taking place with regard to the body and the binocular vision system? (Gesture). Is the hand permitted extra degrees of freedom in pointing?

They propose, for your consideration, some basic inferences as to how attitude with motion are maintained at a complex joint.

25.6 Microbial growth. Finally in a last paper, the authors offer you their insight into regulation and control of a bacterial colony. Their problem is how to control the nutrient to a colony to optimize its steady state harvest.

[x = bacteria concentration; s = nutrient, 'substrate' concentration, u = flow rate of incoming nutrient = outgoing total flow.] The control problem involves a particular nonlinear optimization.

Thus in overall perspective, we shall discuss the implications and consequences of such relationships as

$$\frac{dx}{dt} = K\ x$$

If K is negative, we have decaying processes; if positive we have aggregative processes. But there is a more difficult specter in the works, or thermodynamic ghost in the machine. Perhaps both detailed and general issues will emerge in the discussion that will follow the authors' remarks.

In closing, if the authors of this session regard my written commentary as somewhat strong, I wish they would not consider it as a personal matter, but one to be seen in the following light. Our modelling efforts cannot be taken seriously by both physiologist, medical practitioner, control engineer and physical scientist unless we can assure them of the following.

First, that we are willing to untangle all the detailed facts that may be known to physiologists, so that issues can be seen by arguments pro and con for different points of view. This will impress the physiologist and physician.

Second, that our choice of modelling relations has the valid mathematical properties to span the dynamic field of concern to the operation of the system. This will impress the control engineer.

Third, that our systems' modelling is cast within the domain of physical science - in particular by relations compatible with irreversible thermodynamics, statistical mechanics, kinetics - then our systems identification will be impressible to the physical scientist.

I invite you all to participate - to prepare, to learn, to teach, to argue, to correct - at our IFAC meeting next August 1973 in Rochester, N.Y. We will attempt to find out, by bringing physiologists and engineers together, whether we have any modelling maturity to offer. Thank you.

B. Invited Talk to the Biomedical Engineering Group of Case Western Reserve - April 22, 1972.

Modelling - An Iconoclast's View

The two previous occasions at which I was invited to lecture at Case-Western Reserve are quite spread out in time. The last time was by the Chemical Engineering Department of Case, about ten years ago. Seymour Calvert invited me to describe how "A physicist looks at the frontiers of chemical engineering". The previous time, I think, was almost a decade earlier. Dr. Wallace extended me an invitation, on behalf of the Pediatrics and Internal Medicine Departments of the Medical School at Western Reserve, to present a physical view of thermoregulation. It is comforting to be welcomed once every decade.

Today, I have been invited by Dr. Plonsey, on behalf of the Biomedical Engineering Group at Case-Western Reserve to talk on systems modelling. What I intend to talk about, in some faithfulness to what Bob Plonsey asked me to discuss, fits in with the problems and issues that I myself am presently concerned with. I will try to provide a commentary on the art of modelling. I was asked by John Milsum, about five years ago, to consider a book on the subject, but I declined, feeling that my ideas had not reached sufficient maturity. In my opinion, the subject is still an art. Thus, Plonsey and I agreed that the best way for me to attack the problem is from an iconoclastic view. I can only do that if you will accept the following character for my effort: In attempting to examine an art form seriously, one's outlook will be greeted with admiration and antagonism, many will polarize into friends and enemies. Of which is which, one can't be certain. So I would like to feel free to make comments and not have to identify for you whether I am picking on friend or enemy. Everyone - including myself - is fair game.

I've brought with me about 50 pounds of modelling documents. It could have been 100 pounds, but actually that's all I could fit in my bag. The papers and books represent a great variety of modelling efforts of all different kinds. If any of you in my audience are interested, later on you can take a look at some of them.

For the problem I propose to deal with, how to model reality, there are a great number of dichotomies that have to be faced. I am a non-academic, in fact you might say anti-academic, so it is not my intent to 'can' the problem for you. My problem, if anything, is to produce as much polarization, as much recognition of what are alternate views on various questions, so that you can face modelling problems with the richest possible concept of reality. This requires facing a great variety of polarizations, of A and not-A. I'll name some of them as they occur to me.

One of them is the issue of

physics versus engineering

Any attempts at modelling have to be conscious of the fact that one can take these two different views. First, you have to start with a basic view that the modelling of systems is not an exercise in theoretical physics. There are just a handful of people in theoretical physics who concern themselves with the nature of reality in important senses, and they attempt to originate whenever and wherever they can. That's their business. On the other hand, if you want to model a system or process, you must learn a lot, experimentally and conceptually, about the field you propose to model, as well as about the nature of reality. That is both an exercise in engineering and philosophy. The philosophy is to help you see that what you are proposing to do is to put some kind of structure under the field that is well founded.

I have inserted the cards in a variety of places in the books I brought along. They mark statements made by a number of people on their views on the nature of modelling, and I shall take exception to some of their statements. Thus, for example, to illustrate another polarization, there are a considerable number of statements that, regardless of how sophisticated it is put, regard modelling as an exercise in curve fitting. I do not regard it so. As an ultimate objective, as my view of modelling, I regard it as a process that attempts to represent the reality of portions of the physical universe by some notably condensed descriptive summary that is essentially isomorphic with that reality. In other words, I touch here on another dichotomy.

There are representations that are formal, and there are representations that are isomorphic. My principal concern is with descriptions which are essentially isomorphic. I consider my use of the term isomorphic as peculiar, idiosyncratic. If you can suggest a better one, I will be glad to use it. I use the root morphic not in the sense of geometric form or shape solely, but of the form or shape in a dynamic phase space of positions and velocities. That is, I am concerned, in systems, with dynamic structure. That is, in my view, dynamic form and function has to be cast in the modelling, whereas formal modelling, in a sense, only represents a scaffold which outlines a problem. This is not to my taste. I don't particularly accept that kind of modelling. I regard it as a view that can be accepted for engineering description, but not scientific description. In that case, my concern is with foundations which are isomorphic and physically representative by what is considered to be hard scientific fiat. These requirements turn out to be very serious limitations of what one can do with regard to systems.

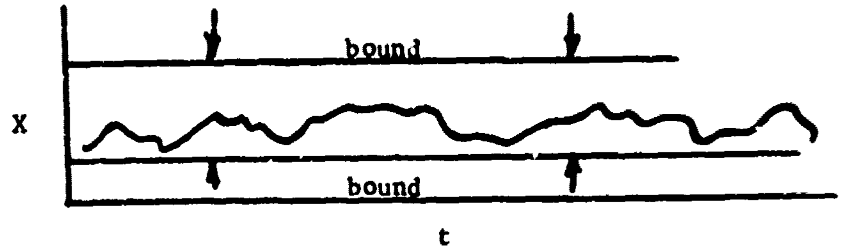
To start things off, I would like to create another distinction, as it were, between two kinds of systems one can model. In one kind of system, we deal with sub systems or elements. We deal with mechanisms. We deal with, and are accustomed to deal with, functional entities of a great variety.

These entities are not, in principle, complete systems. The alternate entities I would like you to consider are autonomous systems.

If you want to consider the first category of simple mechanisms - which I don't intend to talk about - I would view it as a useful art form on which to cut your eye teeth in modelling. It comprises a set of details which you have to learn for all businesses. It teaches you how to deal with mechanisms and mechanics, how you apply laws of electromagnetic theory, and whatever else may have been classified as a real scientific relation. If you manage to learn this art in a great variety of ways or for a great variety of fields, you might begin to regard the descriptions as being somewhat catch-as-catch-can. This strikes me as a peculiar kind of summary to make about this broad class of phenomena at this time. Yet one spends one's technical youth - at least I felt that I spent my technical youth - in dealing with a great variety of problems of this sort. You can put a sort of a keynote or catch phrase on this first systems category. One might consider that these processes or subsystems act so as to require that you deal with them as aperiodic phenomena in a variety of ways. If you're interested in things which enter onto the scene, you're going to see a certain amount of dynamic action. Then the action may disappear or merge into some kind of behavior, which is no longer interesting. The process or motion may become steady or something that you are willing to dispose of in that way.

Of course in its own right, such behavior is interesting, but one could have a feeling, at least after many years of playing the engineering or scientific game, that one has had enough of such problems. Clearly most technical people stay with such specific bounded problems forever, but finally I think it begins to have its limitations. It is a useful beginning. I am thus implying another dichotomy, between the general or integrated and the detailed view of system versus subsystem. Now, we come to the second, the integrated side. Therefore, we may basically regard that we are dealing with things that are persistent and in principle, for first round, with conceptualization of systems by mathematical theorems. Essentially therefore, we must qualify the problem of describing processes which are not aperiodic, but which basically are periodic.

I don't know why the following statement doesn't seem to have much general acceptance when it is asserted, but I always seem to have trouble in having it immediately accepted. Let's consider the flow of time and the occupancy of an n-dimensional displacement space, which I can illustrate with a one-dimensional space presentation. X is some parameter which characterizes the system. To talk about systems which persist, in my opinion means that they stay around. If they stay around, this seems to mean basically that in the space that I have portrayed, you have a behaviour that is bounded. This is the only way the system could stick around. If the entity takes a walk and goes from here to infinity, perhaps it may come back occasionally, in some aperiodic sense, but this is not the idea of a system, at least in the sense that I'm talking about.



If the entity stays around in a bounded sense, then there is a mathematical theorem that states that a bounded function is decomposable into a harmonic sequence either as a series or an integral (there are some ancillary conditions, for example, that the function can't be too wiggly). It seems to me, that the underlying concept of periodicity arises fundamentally from this property, which makes periodicity intrinsic to the description of systems which are going "to stick around". Thus the concept of lying around, persisting, seems to involve processes which are going to be repetitive in some important senses.

Another characteristic I am concerned with, within the concept of its persistence is that the systems behavior is autonomous, and that seems to involve that through their own motive power, they are capable of their persistent action.

If you accept this idea, what I can do is I can begin to represent systems of this sort whose performance is persistent and bounded by an utterly boring model. This performance is first equivalent to a DC network. There is a potential source (note that physics requires that there be a potential source) and then there is some kind of a network, in general. One would say, if one were not interested in the theory of the particular potential source, that this is a very uninteresting kind of problem. Everyone knows the equivalent of any such network in a DC sense is simply a potential source feeding a resistance. Well, that would be true only if you're dealing solely with linear networks. But the general problem that we have with systems is how to deal with nonlinear networks. The general question is given the existence of potentials, which are capable of sustaining a system - where the system in some sense will create fluxes - our problem then is how to describe the correlations of bounded fluxes and potentials within the environment in which the system is embedded.

I can take the description one step further. This will split autonomous systems into two kinds of systems. In this added distinction, my thoughts are not so complete as my remarks might tend to indicate, but anyway I'd like to make the effort. Distinguish between systems of a first kind and systems of a second kind - under the general construct of persistent autonomous behaviour. Systems of the first kind will be represented by systems in which the environment is basically a boundary condition. In this case we look at our 'black box' as being a nonlinear system, immersed in a variety of environments which can present inputs which press on this box. The action which ensues (in order to make the picture a little more definite, in the sense that I am discussing, the environment presses on the system with a variety of potentials) depends on the environment. One should note that the typical potentials we likely must face are things like temperature, fuel, etc. Then this class of systems unfolds its action with the potentials around it presented as boundary conditions. Under this kind of constraint, I can have autonomous systems. I can make an engine which will run as long as the fuel is supplied at the boundary. The system will run indefinitely or until it wears out. But wearing out, at this point, is not part of the prescription of the system. It is an aperiodic process. This class of systems, in which the potentials are boundary conditions, permit us to play a more limited modelling game.

I would like to remind you in principle that the two categories that I have described so far - mechanisms that may be used aperiodically at will, or thermodynamic engines entities - describe essentially all the content attended to in engineering teaching. I did not use the term 'physical' teaching, more inclusively, because the principles of physics are supposed to be subsumed for engineering education. Another category, applied physics, is regarded by many physicists as engineering, or something quite close to engineering. We accept that the principles of physics, chemistry, etc., are applied to the categories we have identified.

So in ordinary engineering teaching these two categories are lumped, and it might have been a little surprising to you to hear me make this kind of distinction. I'm certain it will appear quite surprising if I lump the aperiodic entities and the simple repetitive engine entities together into one category. You will probably be disturbed at putting a generator which can run a system into the same category with aperiodic mechanisms. The generator will run some kinds of aperiodic systems indefinitely. I say that you have cheated in your prescription because in order to get the generator to work, what you haven't done to complete the problem is to connect the generator itself to a prime mover which was supplied with potentials. Thus this prime mover only keeps working while somebody puts fuel into the system to run the generator. So basically, if you so broaden your system outlook, then you may begin to see that the generator-run system is really aperiodic.

If you accept that point of view, then you'll understand that I've connected my description of systems to engineering tasks, because it turns out that the total engineering task that we deal with is not so fragmented. The engineering task not only has to deal with the 'operation of the system', but it turns out appropriately that engineering also deals with the construction and the maintenance of systems. Thus you really have a three-fold function in engineering. The only time you know you have a good engineer is when you have a person who is perfectly willing to attempt any of these three tasks as fundamentally part of the overall engineering problem. In that case therefore if you see these three tasks, which have been the ultimate thrust of engineering, then you'll understand that you are really back to the problem I have identified as aperiodic tasks and descriptions. An engineer does not design and build things that last forever. His problem is with the limited concern of a system or part which is going to come into the universe, it is going to perform its function, and finally it is going to leave the universe. All of these problems I lump within one category, rudiments of systems that require engineering description.

Now I am up to a second category of systems, truly autonomous systems, which are embedded in a larger universe. In this universe, which our non-linear autonomous system inhabits, there may be a set of superior potentials, by which all the systems immersed in that universe are bounded. But now we are dealing with the problem in which the system that concerns us is bounded by, the term I like best, its proximal milieu. The earliest person I have been able to trace the thought to was Sechenov, who pointed out that the organism is not a system which just exists within its own surround, but that basically the organism consists of its internal systems plus its surrounding. What I'm trying to propose here is not a trivial concept. It represents the basic form of an autonomous system. It is the interaction between environment and the system that creates the autonomous system. Both are now embedded in the larger universe. That is, we have now changed the problem in which the potential sources are herein coupled to two interacting systems which we have to deal with. And that then becomes a system of the second kind. The potentials now are not boundaries; they interact with the system.

Now, if you are willing to face this more complex systems' problem, and this is just a primitive philosophic structure that I have offered behind reality, then the problem that you will face is how do we characterize or model such systems. That is the ultimate thrust and drive of what we're going to deal with. A part of the answer to the question of course from the physicist's point of view, is that all these issues become and remain exercise in energetics. Basically you are still dealing with physical systems, and that means that you are dealing with the disposition and flow of energy. That's why it was no accident that I constantly discussed the issue in terms of potential sources. Then of course the problem is to answer how energies are stored and flows disposed in a system.

You may wonder how this very abstract thread of description began. It began because my colleagues, Gene Yates and Don Marsh were asked to write an integrated outline of the biological organism, along the lines of what course would biology take for the next twenty-five years. Gene Yates asked me to join in the effort. So, we managed to yoke our effort together. How? The answer to the hidden coupling is airplanes and telephones. One writes on airplanes, and thinks by phone. In our joint effort Yates put forth at least four kinds of modelling issues. Part of what I'm giving you here is in response to issues that he forced us to dredge up. The first one was the merit of 'abstract mathematical modelling'. We turned away from that.

Then the second one was 'control theory'. We threw some dubious lights on that. Then the third one we put forth was 'computer modelling'. We put 'tongue-out-of-cheek' on that. Then we drew a line under those three and asked 'What remains'? What remains, we finally decided was basically, statistical mechanics and statistical thermodynamics, that is, the generalized theory of irreversibie thermodynamics.

Now, I don't want to speak against these other paradigms too much except for a few brief remarks. For example, the objection we have to pure mathematical modelling is that it is free of content, whereas the problem that we're dealing with in real systems is to fill our model with real content. Not that we object to mathematical modelling. It represents a metastructure from which we draw on when we feel we can see a suitable fit. Then we use the games of mathematics, as a whole to draw upon, as we can. The thought of whether abstract mathematical modelling itself is capable of leading any field of science, or of applied science, is one that we question. We put our 'tongue in cheek' on all answers to that question. There are those on one side, and those on the other. I have no absolute opinion.

The problem with 'control theory' - and remember that my technical origins are in that area, so I don't speak from ignorance - is not that it hasn't been tried. I regard that the difficulty with the usual description on this level of modelling is that it assumes that all phenomena it describes are 'equipollent'. That is the best term I have been able to find to use. This means that all the entities lie at one level, and that you can continue to yoke these things together. I think an extreme version of such a description is contained in a most recent modelling of the cardiovascular system. The issue that you have to ask as a serious question is whether a network diagram that you represent on a page represents the cardiovascular system isomorphically. The issue that I consider presented by that question is contained in the following: Do you believe that a point A on the diagram is connected to another point B by the pathways which, in principle, you can trace in such a diagram? My feeling is "No". That is, all loops and nodes presented are not equipollent. What that will mean is that, in both time and space, the phenomenon that is pressing at one point, does not press with the same measure at another point. What I'm trying to say, using another analogue, is that once upon a time - at the age of 17 - I had a great love and there was a tight coupling between us and so we were equipollently bound. But in the universe in which we now dwell the connections are broken; the past relations really don't exist any more. If you insist, you can trace remnants in a decayed process, but these remnants are no longer coupled to active mechanisms which are of any concern to where the system is now, and it is illusory to insist upon that kind of continuing relation. That will be clear, I hope, in a few more sentences.

The basic objection is that simply because it is possible to put down certain kinds of formal connections, to insist that all such discerned connections remain, in the same dynamic sense, coupled I think is a serious error. Really such computer modelling is not that much different from control theory because really computer modelling in a sense not only contains the idea of networks, but also of feedback, compounded further to use all feasible relations catch-as-catch-can. Such modelling uses what I refer to as equations of convenience. We will fill in the mathematical space with anything we can, so as to see if we can "complete the model". I don't want to leave the implication that people who do these don't understand mathematics. They do. The problem that they generally have to deal with is to get enough variables and enough equations that can fill up the space. As I see it, the question at issue is, are they filling up a space that is useful - which is complete.

Now we're up to the question of why I basically elect to think in the alternate terms of a general theory of irreversible thermodynamics. Well, again, remember I'm talking about autonomous systems, really both types of systems that can operate from constant boundary potentials and that can roam in an environment and seek out its potentials. What I'm trying to say is you're welcome to do 'catch-as-catch-can' anything that you think is appropriate for description on the engineering side. How far you go is up to you. But for the systems which persist, which are a part of us, which will run indefinitely, we must conceive of a scientific description. I think that the ultimate drive for such a description always has to remain ultimately basically thermodynamic, because what a system says is, "I, an autonomous system, must continuously deal with the issue of energy. I cannot hide energy. There are really two things I must worry about. I can't hide mass, and I can't hide energy." There is a fancier physical construct that says, "Yes, indeed mass and energy are really tightly coupled completelv", but we don't have to worry about that l--el unless we deal with cosmological issues. At a level just removed from fundamental particles or the universe, these two variables of mass and energy are not disposable in any sense by any magical incantation. So if you're going to deal with these measures, you must basically face the issue of thermodynamics all the time, because in principal, this is what thermodynamics is all about.

As another basic dichotomy, the problem that you are led to very quickly, in a generalized thermodynamics, is the difference between degradative processes and sustained processes. It turns out that the underlying issue arose in thermodynamics a long time ago, Fortunately it was clarified. Basically thermodynamics, first of all, states that as energy changes, it is conserved. The second thought is that because of the ordering of processes, as a result of such energy changes, basically there is a loss in the ordering of energy, whatever that means. And what that means is that there is a hierarchical ordering, or a preferential ordering, in which energy flows from ordered forms to less ordered forms, always winding up in a sink of heat. From this underlying premise, we surmise, from the second law of thermodynamics, that in the end all natural processes must be degradative. That we must take as primary.

Over a hundred years ago, the question arose, when we were dealing with thermodynamic processes, whether it was possible to get any kind of sustained action in a system. Carnot furnished a basic positive answer. It is possible, working with the construct of a constant potential source and sink and a 'black box', to get processes which are sustained, and that basically this could be done through a thermodynamic cycle. The question was, is that contradictory to the idea of degradation? The answer is "No". In the long run, you must pay for degradative losses, but what you can do either temporarily or in sustained fashion, is to charge your potential source a certain amount of energy per unit time, a certain amount of ordered energy, in order to run the process and make up for the losses. Then while overall the process has to be degradative, a certain additional amount of energy can be put into a periodic and persistent form. Engines are of that sort. The underlying mathematical and mechanical answer is very simple. In order to obtain an engine process, it must be a nonlinear process, or as it is usually categorized in mechanical engineering, "Who put the valve action there in the cycle?" The paradoxical problem of constructing a persistent clock mechanism is illustrated by the fact that you have to use a linear process to give you a high quality timing phase; but you have to couple a nonlinear escapement which will somehow be able to take potential energy from a source to keep the process ongoing. Take the steam engine. When someone said, "Put a valve here", showing that he knew enough to release expanding steam after it had done work and before admitting new steam, the engine process was 'solved'. So this dual of ideas have been reduced to practice by the use of nonlinear processes.

Thus, the general answer to resolve the paradox that a system must admit both to being a degradative process and a sustained process depends in principle on the thesis that there is only one way by which you get sustained processes. The system must basically include a thermodynamic engine. Whether an electrical engineer wants to call the prime source an oscillator, or a clock, or a D.C. to A.C. converter, it is still basically a thermodynamic engine. So one must ultimately confromt the thermodynamic issues. That is fundamental. Whether you want to look at autonomous communicational systems or power systems, fundamentally, the ongoing characteristic must come from a thermodynamic engine source. That also means that whether dealing with the source or the receiver characteristics of a communicational system - regardless of whether it is going to communicate or not - one still has to deal with issues in a thermodynamic sense. That is a fundamental thing. Now if you permit the argument so far, and permit me to talk about models in a generalized thermodynamic sense, then we are up to a very subtle point. A valid systems model must be able to give you either process (either degradative or sustained). Overall it must be degradative; yet, you must be able to change boundary conditions so that the same equation set, the same modelling description, on the one hand, can be degradative overall (meaning that overall there must be an irreversible production of entropy) and yet on the other hand, under other boundary conditions, can represent an ongoing systems' process. Instead of the dead nothing problem that it can come to, all of a sudden you can have a lot of interesting things going on in the box, things that you are going to consider lively or at least colorful autonomous behavior. That is a very fundamental point. You will find that most modellings do not possess this dual capability. That is they're not isomorphic enough to provide a complete set. But I don't want to put that as a criticism, I want to put the issue forth in a positive way. In that case, if you're going to deal with a description that is capable of handling the energetics of all systems - but as you realize of a certain class of phenomena, because you are going to embed this particular class of nonlinear phenomena in its surrounding environment - you're proposing simply to describe autonomous systems by an irreversible thermodynamics. Then the question is, what kind of processes provide statements of adequate purpose to represent models for autonomous systems. Now this question already formulates the problem - the whole problem as it were - within the domain of physics. It turns out for such formulations there are not very many equations. In essence, I have really been thinking of trying to get to this question for the past 20 years, and to squeeze out one or two additional equations beyond that for simple physical systems is about as much as I can do. I don't know whether it is my lack of insight or what have you. It is just that for me it has been a difficult problem. Now the question is, what can generalized statistical mechanics tell us about what makes an equation set? It turns out by the way that this issue was not clarified until the 1930's; this is not an ancient 100 year old problem. The essential questions were not clarified until after the beginning of irreversible thermodynamics; the clarifications are in the work of Onsager, Chapman and Cowling, Herzfeld, and others. It turns out that the only statements which you can make are statements which have to do with what are called the summational invariants. That is if you have process changes going on in a system - interactions - then you can only write valid assertions that will work indefinitely for a limited number of variables which have certain cyclic properties. In order to make that clear, let us put the problem aside for awhile, because what I have to do first is to give you a big systems picture, and hopefully all of a sudden you may suddenly see what I'm talking about in here.

If we are going to talk about these kind of self-sustained systems, autonomous systems, what we must assume is that there is some level at which autonomous systems exist. In other words, one can start out and say, atoms exist, or nuclear particles exist, or cells exist, or ghosts exist, or humans exist, or stars exist, or galaxies exist, or universes exist. You are free, for entry, to suit yourself at any level that you want to. So now you have posited that there exists in fact an autonomous entity. The assumption is that there is a quantized entity in the system which somehow can do the thing that I said before. It can run around in the system's environment and persist. You must assume that this exists, on at least one level. That is the story starts, "There be beasties", and we will see what the consequences are of that. Assuming that we have one such level of active atomistic elements, of course there is another characteristic that was implied in the energetic construct, it is that these entities have the capability of exchanging energy. Now remember the fact that these are atomistic has already built in some implications which you should realize already boggle the mind. These entities are atomistic for a very simple reason, because if they weren't atomistic, they would join each other and dissolve. They would break their boundaries, 'melt' and join together in a blob. But they don't, so the two characteristics that you have is the fact that the atomistic entities are characterized by a barrier, a wall, that is impenetrable in some sense. Not necessarily for all boundary conditions and for all times, for all systems can be broken in a sense, but at least in some operational sense they are impenetrable. That is what makes them exist, each at their confined level. But on the other hand they can exchange energy. This is a basic premise.

Now given such a level with its exchange characteristics, then it turns out, within the framework of statistical mechanical concepts, that you can easily see that the interactions give rise to a mean free path and a relaxation time within any ensemble, which, in some sense, you can imagine to be contained. By the way, I've already told you something about systems. Systems have two properties, that I've already shown you. They have a small limiting size. That is they are boxed spatially with a minimum size which has to do with their atomism; and as a maximum, they are likely bounded by whatever container size the universe that you're going to talk about permits them to exist in. The same things that I have just said in the spatial domain of minimum and maximum size, is also true in the temporal domain, because there is going to be a minimum relaxation time between interactions, and there is ultimately a time in which the system really does dissolve itself and you can no longer pay the same kind of interest to it. So you have this double boxing from above and below. Remember that is one of the characteristics of systems. The system is not autonomous forever, even if its interactions are universal. So you have a finite space-time construct.

Now if I put these entities into a box, which will represent the playground in which I am going to watch processes take place, then as the vantage point gets further and further away, the ensemble of entities begin to look like a continuum. There are specific conditions under which this collection approaches a continuum. Usual statements are the dimensions should be larger than a mean free path of motion, and times should be larger than relaxation times. For autonomous systems, our systems' description is going to be of how they act as a continuum of processes. In a certain sense there are two categories of such modelling which I can perform, one being a description which can hold for continua and the other one which will be descriptions which which hold for aperiodic or isolated phenomena. In principle I've already implied without going into it, that the energetic games that you play for the aperiodic systems are likely to be those of concern to subsystems mechanisms, functional entities and things of that sort. At present I am trying to bring in a little more of what is representative in descriptions for continua. I regard the biological organisms, for example, as being a continuum problem (unless I'm looking at them as social atoms, and say look there is 200 million of them). But at the sustained systems' level what you see is a continuum. That will be the description we seek.

If you will remember what I said about degradative and sustained processes, then the first thing you ought to see is that whatever set of descriptions is valid, the modelling for this system should in principal be able to exhibit degradative phenomena. That is, it must be consistent with a continuum thermodynamics, and you have to find in fact that all of its processes can in fact relax. That should be a major kind of behavior of that system. If I gave you a description for such a system, you would find by applying the theory of small vibrations, as a first test, that as you approach near equilibrium, or near rest equilibrium, the equation set would begin to show, in fact, the degradative phenomena. Thus one of the equations obviously has to deal with the irreversible production of entropy, and it would show you that there is a dependence of the irreversible production of entropy on certain parameters which are positive definite and that's what makes the system relax.

But then, on the other hand we expect another kind of phenomena by which, as the scale of the phenomenological field gets larger, the field becomes unstable. We know this to be true in a couple of fields, and the object of my surmise is that the generalization holds true. Now that generalization applied in our proposed equation sets, because the behavior becomes unstable results in the fact that this field, which was a continuum, now itself breaks up and quantizes into superatoms, where the superatoms themselves are continua field made up of the active subatoms. And so this field therefore, at sufficient scale, will produce superatoms. Thereupon a description of these superatoms becomes a part of the systems modelling on an aperiodic scale But if you have an extended enough field, what will then happen is these superatoms themselves, at the next hierarchical level, form a continuum, a super continuum which then in sufficient scale becomes unstable and produces super superatoms, etc.

And so, therefore, the basic thing that you have, in looking at systems, starting at any level that you want to, is this alternation of character. By the way, I do not mean to imply that this alternation goes on forever. It goes on as far as we are capable of tracing, and then if you want to, you are permitted to take a dive below or a flight above and see if you can find a sub or super field. The two limits are that we don't know what is the stuff out of which nuclear particles are made of. (The field is currently in speculative turmoil.) We wind up on them with the usual statement that in interactions, nuclear particles produce nuclear particles! On the other hand, we don't know how to get out of cosmology, although now with black holes, and so forth, there is the question of whether there is a connection between the two upper and lower levels (e.g., extracosmological space and nuclear particles).

But in principal, therefore, for the list of systems that we're dealing with, we have this alternation between atomism and continuum - A1-C1-A2-C2-etc. - all the way up. If you understand and accept that, then you will understand that the problem you are dealing with, in characterizing a system all the time is that you have to make up your mind which level it is you propose to describe. It is forced upon you, it is encumbent upon you, that you recognize the atomistic level from whence you came. But outside of saying, there be atoms, or there be molecules, there be cells, etc., you are not obligated to think and deal only with them for systems descriptions. As my friend, Gene Yates, put it so well, "If you decide to go swim on a sunny morning in the Pacific Ocean, it is not your molecules that made that decision." You can't discover the systems' problem in those terms; you've got to examine it in terms of a description of the people who really want to swim, and that's a different level than the decision making that influences the lower level. For example, there's a recent book which Gene Yates and I have written a review on, Monod's CHANCE AND NECESSITY. It's an important book - that's not why we wrote the review, but it is an important book for our systems' descriptions. I think you should read that book (that is, after that, you can read my book). There is a reason for reading it. Because Monod proposes that he can deal with the subject of purpose and organization all the way through all systems' levels to man by simply saying that "I postulate that there be atoms with a particular kind of connection at this level" - namely at the level of the genetic code and he then says QED, therefore purpose emerges at all levels. We have no objection. The problem at issue that we see is that you cannot go in a smooth continuous fashion from the atomic level of the gene up to human. And the reason that I introduced a comment on Monod's book is that our construct for systems would not be clear without this introduction. And in this introduction, as you can see, what we have done is say, Yes, this description guarantees the next description, etc. by connectivity. But these descriptions are only piecewise continuous. You cannot divine the purpose of man, simply because he's molecular. If you want to try, be my guest, I'll be glad to furnish you free pens.

So, under those conditions, therefore, as you see if I postulate that there exists atoms, then my problem is to obtain a continuum description of the next level. It turns out that the continuum description then would have to be in accordance with thermodynamics, and it would turn out that we would have to provide descriptions for two kinds of phenomena. First of all we would have to come up with an estimate of why you have a statistical distribution in which an equipartition of energy takes place; in which because the atomistic entities can share energy, there must be coalition formations in which they decide how to divide up the available material among themselves. That is one kind of systems problem that you have to deal with. It becomes the equilibrium problem, but, remember, it's a dynamic equilibrium. I find in talking with biologists that they find it's a strange concept to talk about equilibrium as a dynamic thing. We talk about this as a steady state - as a dynamic steady state, described by the statement that as many go from State A to State B as go from State B to State A. Your problem in the dynamic steady state is to manage to describe this kind of equilibrium, how many are going between states, etc. That then represents the thermodynamic noise, or thermodynamic equilibrium statement. On top of that, having achieved that description, what you are concerned about is the equations of change, because you know that according to thermodynamics, what these equations have to do is to provide a path of relaxation from any disturbed state to that equilibrium. Otherwise a statement of equations of change would have no meaning. Thus such systems modelling which represent equations of state and change, and that's what the subject of irreversible thermodynamics is about, then has to be able to deal with the thermodynamic issues in some way.

Now I'm back to where I want to be. At this level, then the only variables which I can relate the matters of change to are the so-called summational invariants. What this boils down to, is this: if I am an atom and you are an atom and we collide and do our thing, the problem that I am concerned with is what are those things which, after we have done them, that the next person watching can't tell the difference between where we came in from and where we left. And that means that before the collision I'm going this way and you're going this way and we collide and now you're going that way and I'm going that way but the other person who wasn't paying attention, in detail, can no longer distinguish A from I. Those processes exchanges which he cannot really distinguish represent the summational invariants. If I come onto the scene, childless and unmarried, and I get married and produce my progeny and then I relax, and you blink and look again and say, "My Lord, there's another Iberall on the scene!", that represents summational invariance. These are the things,which after the process changes have taken place at the atomistic level, remain unchanged, then it is for those and only those that you are prepared to write equations of change; and that means therefore that basic systems modelling can only deal properly with a very limited number of sets of variables.

If you are faced with modelling at any level, there is nothing wrong with seeking to find equipollent modellings at that level. But the structure that you have to deal with is the summational invariance of mass, energy, or momentum and perhaps of number at that level, and it must be out of these that you must get a complete modelling. You may be shocked to find that the number of systems models which let's say deal with these issues and only these issues, are almost infinitesimal. There is, of course, the prototype on which you can cut your eyeteeth. This is the hydrodynamic field. This is about the only field in which you can assert a complete equation set for a certain space-time domain and you find that you are faced on one hand with the problem of showing all the degradative processes, and on the other hand at showing the aggregative processes, such as how turbulence and other formal processes begin to emerge. In the general issue, how does form, as it were, emerge from these functional characteristics? That becomes part of this kind of systems' structure, but that issue is not immediately amenable. (Read my book. The book was not designed for that design purpose, but actually it takes quite a few hundred pages of introduction to prepare for that kind of structure.)

You may now realize, in other words just to put it formally, and to end on some note of triumph if I were providing a systems' model of the hydrodynamic level - which is a continuum molecular level, then I would write something like the momentum equation - an equation of motion; I would write an energy equation, which has to do with the irreversible production of entropy; I would write a conservation of mass, which is continuity, and then there are about two thermodynamic relations which relate the two additional variables; and that is all I would write. And that is complete enough.

Additional processes that I could add for chemical systems are more than one molecular species; I would then have additional equations for diffusion. If I wanted to I would couple electricity to these systems. Then I have the equations of electrohydrodynamics and magnetohydrodynamics, etc. And, if now you ask the question, "Yes, but how far does this get us into biology?", then the answer is, "Now, you're up to the frontiers!". Thank you.

Questions and Answers

Q. Assuming you were on a biomedical engineering factulcy, what would you teach your students? What modelling?

A. I would answer briefly by giving you a reading list. My purpose is to show you that material exists; that there is a passage that is academically acceptable.

1. Grobstein - THE STRATEGY OF LIFE. An excellent 'kindergarten' start.

2. Morowitz - ENERGY FLOW IN BIOLOGY. There may be a gap between these two; you're academics, you can figure out a bridge.

3. Lehninger - BIOCHEMISTRY. I haven't seen it, but I'm assuming in advance that it's the right book.

4. Iberall - TOWARD A GENERAL SCIENCE OF VIABLE SYSTEMS. I suggest it, not out of personal pride, but because it deals with the problem of organization at all levels. The students will sweat, but basically it's good for their souls.

Now, we get to more detail.

5. Iberall, Cardon - "Regulation and Control in the Biological System - A Physical Review", N.Y. Acad. of Sci. Many academics have used it; it's a good first overview.

Now, you can put them on

6. Grodins

7. Milhorn

8. Milsum, etc.; the sources that are considered standard biomedical engineering texts. I don't mean to be misleading; I think that they should look at such technique books, but I don't want them to take that kind of modelling as complete.

Then as not a bad beginning

9. Bloch et al - "Introduction to a Biological Systems Science", NASA CR-1720. This is not an advertisement. We put it together as our first effort toward such a text, and it has the advantage that it can be obtained as an inexpensive thing.

Then, at this point, there is at least one book from your school

10. Mesarovic - SYSTEMS THEORY AND BIOLOGY.

A most elegant beginning was

11. Stear, Kadish - HORMONAL CONTROL SYSTEMS.

You can see why I brought 50 pounds of paper. The texts I've mentioned are getting there; they are not all the way there.

At that point, I could likely go into the paper literature, but I think that's enough of an introduction.

Q. You talked about modelling in terms of equations of motion, mass balances, etc., yet you didn't mention one book that really deals with these issues. You are on a metaphysical level.

A. I can give you papers to read -

Q. You don't need papers to read, there are books.

A. Will you name them for me?

Q. I can name one, a standard book in engineering, by Bird, Stewart, Lightfoot called TRANSPORT PHENOMENA.

A. I'm sorry, I admire that book and books like that, but those I put down on the other column of subsystems and processes, books on unit processes, etc. If you want me to name those books, the subsystems books, I have not included them in my reading list for systems books, I would be glad to give you a list. I would certainly say, without the slightest doubt that the Bird book is an excellent book but I would start the list out with Whittaker's ANALYTIC MECHANICS. There are a number of such books which gradually put tools and pieces into the users' hands, but they are not systems. If you want to do systems, you have to face these subsystems issues. For example, if you want to do transport, I brought an article called "Theory of Transport Coefficients for Moderately Dense Gases", and this says, April 1969, Review of Modern Physics. Quote - if you want to know about the theory of transport coefficients, it's in poor state - unquote. Or if you don't like that, I'll be glad to give you Hirschfelder's INTERMOLECULAR FORCES, of a few years ago, and if you attempt to put that literature in front of engineers, or for that matter physicists, or chemical physicists, etc., you will find it surprisingly lacking in detailed content. Outside of naming the unit processes - and I could name a number of good books for that subject - but to provide good models, that is not in such good shape. As you will see in the same issue of the Review of Modern Physics, there is an article, "Review of Some Experimental and Analytic Equation of State Data" and it turns out that even the equation of state description is not in good state either. So we are stuck with there being many unresolved issues even at modelling at the subsystems level. But there are good books, I agree.

C. Invited Talk to the Biomedical Engineering Department of the Univ. of Southern California - August 10, 1972

Thermodynamic Modelling of Viable Systems

Drs. Yates, Marsh and I wrote a piece on an integrated view of the bio-organism, which will shortly appear in a new book edited by John Behnke for the AIBS. I would like to provide a foundational construct for the modelling of viable systems, such as the complex living organism.

As engineers, you learn about simple machines, and physical and chemical principles, and about running engines. Then out of geometry, statics, kinematics, kinetics, dynamics, electro- and magneto-statics and then dynamics, and some systematic analysis from chemistry, you approach various descriptional or identificational problems by various isolational techniques - free body, loop, degree of freedom, compartment analysis, reaction chain, unit process.

The scientist has a similar range of what perhaps may be best described as process outlooks, each appropriate to his field. The physicist, for example, uses such concepts as the quantum process, or renormalization; the anthropologist, synchronic functionalism; the economist, value function; the biologist, releasing factor, the chemist, catalyst, or aromatic chain, and so forth, with countless more examples and in countless more fields.

But now we wish to approach a more widely embracing question. How do we model complex autonomous systems? It is not the case that all the pieces that we have dredged up are wrong or inappropriate; but just that they do not embrace the system. If you want an introduction to such questions, you may find one in my recent book, TOWARD A GENERAL SCIENCE OF VIABLE SYSTEMS.

A viable system, in my view, is one born in the womb or other fashioning workshop, and then released into a generally appropriate environment, wherein it can autonomously roam its environment to obtain those materials and fluxes necessary for its continued existence. A living species, in addition, is coded for, internally, so that it can self-reproduce by some procreative cycle.

The distinction between a simple engine and a viable system is that an engine system uses fixed potential sources and sinks, for materials and fluxes, as boundary conditions for its sustenance, whereas a viable system roams a noisy environment beset by vicissitudinous impulses to seek out its necessary sources and sinks, as part of its dynamic chain of existence, rather than to find them as boundary conditions. In the case of the viable system, the environment itself may be run as a simple engine, e.g. it may run from a solar source.

I want to stress that the environment for a viable system may itself develop into a large number of engine processes; and to the viable system, these processes will not appear as constant sources, but as active changing processes that may be tapped for their content. It is their changing appearance that is referred to as vicissitudinous. Rain water does not fall at a constant rate, it appears impulsively, and so forth.

So with this introduction to a system, I want to cast a framework for scientific description of systems.

The trouble is, when you try this limited range of techniques, that somehow the systems continue to escape you. As Yates and I put it, borrowing the term, somehow there is a ghost in the machine. And, of course, the descriptive problem of systems has perplexed the greatest minds of the western world for 2500 years with its difficulty. We cannot make the mistake of thinking that we are the first ones to see the problem and to be able to easily formulate or solve the problem. To cast the issue in a peculiar way, I would like to introduce the problem as the artist has it.

I am quite pleased that for the first time in my scientific-engineering career I can finally see my way clear to indicate the role of the arts. So consider, first, the pole of art, as a taking-off point for the content of description.

Suppose you are a poet, describing a loved one, or a moving experience. It is conceivable that you might take a million words for the description. Is this a false picture? No, I submit that the poet's vision is authentic. The trouble is, from a scientist's view, the description offered is a unique vision. The poet is not concerned with what is common between his loved one and the rest of the world. Thus his word picture is overredundant, artistic. He is using words (or symbols, whether visual, or aural, or oral, or kinesthetic) for other purposes than to achieve a generality of description.

Now for a second pole, view the concentration of effort on what may be considered scientific-technical description. I submit, contrary to the artist's objective, such description tends to seek generalization, to seek by an economy of description to cover the content of many experiences.

But in that domain of description, scientific description, we recognize an axis of processes. To provide it with a one-dimensional measure, we can characterize the axis by the signal to noise ratio. Thus along that axis, we recognize two polar processes. There is a stochastic pole to science which deals with problems with large noise and small signal components. The scientist at this end is least comfortable with those processes in his systems that he views as 'biases', i.e., systematic components or processes, which he considers 'errors'. At the other extreme, there is the deterministic pole. The scientist at this end is happy with small noise or random error, as he views it, and is quite content to dismiss those issues by routine applications of canned statistical processes - the Gaussian error curve and the like.

In between, at signal to noise ratios of the order of unity, of course, is the very difficult field developed during World War II as operational research. The theory of games was developed notably by Von Neumann and Morgenstern, as one technique for this domain.

But I would like to propose one added split at the deterministic pole, a split between engineering and scientific description.

The engineering description can be epitomized as a description 'halfway' between the artistic and the scientific. The engineer is also interested in the unique. It is well known that the engineer does not care to stay put at the level of what he considers 'abstract generalities'. He wishes to come to grips with the content of his specific problem as quickly as possible. He is not concerned with an economy of description, but with a sufficiency of description. He is willing to use any pieces of science at hand, but he does not feel totally constrained by gaps. He will fill up, or cover over (sometimes paper over), any gaps in his knowledge catch-as-catch-can. A prototype for such description has been developed in network analysis, or in its more extended current form of computer network analysis.

The engineer feels free to identify as many variables, by whatever means he considers suitable, that he thinks can account for a problem description or solution. He then has to find sufficient relationships, for those variables, that a deterministic noncontradictory mathematical game can be played out. This makes up the 'loops' in his network. He is not concerned with the isomorphic quality of his model, solely that he can stretch enough relations that will cover the field.

As a starting version for many fields of description, there is nothing wrong with the technique, and much of science has unfolded from the application of this strategy of description. It is artistic, it is creative. And in time, it may be modified or replaced, as better insight is acquired into the system or field.

Nevertheless the 'artistic' technique of engineering is still not scientific description. Scientific description is concerned with the highest degree of reductionism to the very fewest number of assumptions, the most sparse form of assertions that can account for a system or field.

Now at last our problem emerges. What is the most economical form of valid description for viable and, in fact, living systems? I submit that the greatest economy is achieved by irreversible thermodynamics. What does that mean, and why is that? There are further reductions possible in mathematical and logical identifications of systems, but in my opinion, the irreversible thermodynamic is the irreducible physical description for real viable autonomous systems.

What in principle is implied in a thermodynamic description, and why is it essential in an irreducible sense to viable systems?

Remember that irreversible thermodynamics is also applicable to simple engines. This is what thermodynamics was developed for in engineering. Really it was developed by an engineer, Carnot, for a specific reason. After a certain point in the 19th century, it was then clear that engines were possible. Let me sketch out the logical problem. According to the first law of thermodynamics energy as a whole is conserved, but according to the second law of thermodynamics, you lose ordered energy as a result of natural processes. Energy leaks out in the form of heat. To sustain a system would require making up for the losses in ordering of energy. Thus there appeared to be two poles in ongoing processes. At one end, there were lossy processes, wherein the losses appeared through so-called transport phenomena involving viscosity and thermal conductivity and diffusivity. At the other pole, what seemed to be contradictory, was that you could have processes that were ongoing. It was not contradictory if you had a source and sink of potential energy, and you could arrange a cyclic process between source and sink which would transfer the necessary energy to make up for the loss. It has turned out that you don't need isolated sources and sinks, you can do it with a gradient of potentials, an inhomogeneous source of potential. Thus by metering the flow of energy by the cyclic process between the two sources, it becomes possible to put power into flux. As thermodynamics requires, you have managed to take a working substance through a cycle, accepting energy at one potential and rejecting it at another without any contradiction. (It is useful to remind electrical engineering students, not so much mechanical engineering students, that you must always satisfy the prescriptions for prime movers if you want systems that can run.)

But we were concerned with the further problem of simple engines and viable systems, and the problem that the viable system has to face is even more severe. It must not only transform energy between sources, but it must also chase up the source where that process is itself an engine process.

Schrodinger raised the question in the mid-30's as to whether the living system was compatible with thermodynamics. In the end, it seems to me, that the living system and every other viable autonomous system achieves a solution by the same fundamental process of convection. That is, the system arranges patterns or channels of convection including, as I demonstrate, stuffing myself with a cookie. One should watch a hungry man eat to literally 'see' the convection. But the point is that convective process in general is really involved regardless of the mechanistic process arranged to achieve it.

But then you must have a real structure for thermodynamics that includes such processes, and these you cannot do conveniently by engineering networks. (One might view Kron's efforts to encompass a network theory for rotating machine as a partial effort to extend network theory.)

So that brings us back to the issue of an irreducible number of statements that we can make about a system. The luxury of highly redundant description doesn't get at the problem of what we minimally need that a system can work. And that brings us back to irreversible thermodynamics.

Now many of you will consider that this introduction was very elementary. But to understand the status of systems description better, you would have had to have gone to quite a few places during the past five years and follow the frontier efforts of workers working at the frontier question of the origin of life. To name a few workers - Morowitz, Prigogine, Pattee, Goodwin, Katchalsky. Their concern has been with dynamic constructs that could account for the organization, in particular the self-organization of life. Because if you cannot come up with processes for this to take place, then you require some other act of creation.

The meetings at which these issues have been discussed and debated have been recent Biophysical Congresses and meetings, at the recent AAAS meeting, at the Munich IUPS meeting (for example, Katchalsky's address). And the concensus of opinion is moving toward the belief that it is the physics of rapid flow processes which is the empowering source for getting life organized. And that subject is the extended irreversible thermodynamics of the hydrodynamic field! I will try to introduce you to its ideas in a general way. It is the simplest field that will exhibit the process of convection.

As a construct, irreversible thermodynamics puts forth two sets of ideas. First, it puts forth the idea of thermodynamic equilibrium - the idea of classical irreversible thermodynamics, which perhaps can be best described as thermostatics. Second, it puts forth the idea of equations of change, a description of states near to thermostatic equilibrium, toward which the equations could relax if they weren't kept is a sustained deviational state. Then, even more fundamentally, it puts forth the idea that these equations can only be cast around those processes which are conserved at cycles of collision or interaction. Those processes are identified as summational invariants.

As a minimal structure for a mobile system capable of convection - and mobility of sorts seems to be required for viable systems - we require the equivalent of such parameters as pressure and temperature and velocity. We then may have to add other parameters, to represent chemical reactivity, but we know we at least have some essential ingredients for systems. What we will find ourselves concerned with in describing systems are certain parameters and processes that will present a concept of invariance.

Let us take the hydrodynamic example, not in great detail but to illustrate the structure of a thermodynamic description. We start with the thermostatic description. That refers to the fact that gross external movement seems to have ceased, we have a system staying put, but there may be a great deal of internal milling about. On the average, as many are going in any direction as compared to the opposite direction, so that on the average, the system stands still. In a simple thermodynamic equilibrium state of mobile molecules, with one phase of matter, its macroscopic state will be characterized by two variables. Why? Well first, the molecules will come to some kind of energetic equilibrium with the walls of their container. The equipartition of energy among all the mechanical degrees of freedom at the mobile molecules is measured by the intensive parameter temperature T. The walls and the molecules will exhibit, upon time averaging measurement, the same temperature T. It is the total energy contained in the molecular motion which is available for transport that will represent a summational invariant. (Namely, summed over process exchanges, energy is conserved.)

However, these mobile molecules collide with the walls of the container, and thus communicate a momentum to the walls. (If they didn't change their momentum on collisions, they would fly apart and 'diffuse' out of the container.) That momentum is the same in all directions. By time averaged measure, the momentum will be represented by the intensive parameter pressure p. The molecular momentum available for transport will represent a summational invariant.

The theory of statistical mechanics, as exhibited in thermodynamics, states that all other equilibrium parameters of the ensemble are functions of two independent state variables in a single phase chemically unchanging substance. Thus, for example, the equation of state reads for density ρ

$$\rho = f(p, T)$$

or

$$d\rho = Adp + BdT$$

with suitable identifications for the parameters A and B in terms of p and T. A second parameter, the entropy S which measures the measure of ordered energy in the molecular state, can be similarly written as

$$dS = Cdp + EdT.$$

Now we can turn to the summational invariants. From the thermostatic state, we surmise that these invariants represent conservation as momentum, energy, and mass. Thus we would view these statements as being equivalent to (reckoning on a specific volume basis, e.g. momentum per unit volume, mass per unit volume, entropy per unit volume)

$$\rho \frac{D\bar{V}}{Dt} = 0$$

$$\rho T \frac{DS}{Dt} = 0$$

$$\frac{D\rho}{Dt} = 0$$

$\bar{V}$ = vector velocity ($\rho\bar{V}$ representing momentum per unit volume).

These are the statements that may be made at equilibrium about summational invariants. But near equilibrium, there are 'slow' 'small' rates of change that are permitted. These equations of change indicate how summational invariants may change a little to permit diffusive transport. Thus for example we can write

$$\rho \frac{D\bar{V}}{Dt} = - \nabla p + \mu\nabla^2\bar{V} + \frac{1}{3}\mu\nabla(\nabla\cdot\bar{V})$$

$$\rho T \frac{DS}{Dt} = k\nabla^2 T + \mu\Phi(\bar{V})$$

$$\frac{D\rho}{Dt} = - \rho\nabla\cdot\bar{V}$$

to represent the equations of change. The parameters μ and k, the coefficients of viscosity and thermal conductivity, represent transport coefficients. (Φ is the dissipation function, a quadratic form of the velocity.)

With no gradients in the container, the equations relax to exhibit their summational invariant form. With small gradie-ts, so that quadratic terms are negligible, one finds that the equation wi relax if the transport coefficients are positive definite. That satisfies thermodynamics. But the equations have a second set of solutions.

With large gradients, somehow this equation set can represent the formal process of turbulence. Somehow these are related to various nonlinear processes such as convection. (Or, with a little extension, other formal processes such as Bénard cells, fixed vortex structures such as G. I. Taylor demonstrated for rotating cylinders.)

But what has such hydrodynamic modelling to do with biological systems? It turns out as I have mentioned that workers at the 'origins of life' frontier of biology have become convinced that similar rapid flow structures represent the foundations for the origins of life and processes. And that brings us to problems of current research. You can note this in the Proceedings of the Biophysics Congress of a few years ago (at MIT), or of the proceedings of the AAAS meeting last year (in Philadelphia), or in a most thoughtful article by Eigen last fall in Naturwissenschaften.

With these issues, we move away from the geometric issues of the double helix, the genetic code, etc., into the field of dynamics - hydrodynamics - where actions take place. To offer a metaphor, it is one thing to describe your loved one statically, but wait until you try on the dynamic interaction of marriage!

In Eigen you will find the beginning dynamics of catalytic enzymes, a most difficult current problem. For this you will find that the extension of equations you require is to the conservation of molecular types by catalytic action, and to the kinetics of molecular interactions. And that brings us up to the frontiers of biological systems' description in a dynamic economical sense. I think I will close on that note.

Questions and Answers

Q. It was not too clear in the introduction distinguishing simple machines and viable systems why you considered boundaries important for the first but not the second? Is it just that there are more boundaries in the latter?

A. It is quite clear, as engineers, that we know how to build systems, electrical or mechanical say, and to make them work. The physiologist cannot do this yet. We can take potentials and apply them as boundary conditions and run our system. But not in the most trivial way do we know yet how to make a living system, that is a system which is truly adaptive. It is one thing to supply an electrical outlet and say to a Mickey Mouse, "Mickey, run around and make out." But if I remove the one type of source, the system is through. It can deal with one disturbance. Thus my model system solution, the Mickey Mouse, is still an illusory solution for a viable system.

In two recent National Geographic issues, a group of young people were taken to an island and asked to make out. As long as some potentials were available and could be found, they succeeded in making out as a life process. The point to recognize is that the environment is part of the prescription of the living system. It is not simply a boundary condition.

Q. I don't see how that differs except in order of complexity.

A. Fine, then as an engineer you should be willing to build a living system. My point is I don't know how with the existing algorithm.

Q. Except for marriage (reproduction) is there any difference? (Between living-self-reproductive, and viable-autonomous?)

A. In the future we may have to revise our view. Non-reproductive animals would be considered living, yet they don't have progeny; many couples don't either. Thus reproductive capability is essential for the species, to characterize it as living, but not for the individual.

Q. Your answer on the difference is a cop-out. I still don't see a difference between simple machines and viable systems.

A. Without cynicism, I can teach you how to make simple engines, but I can't do the other yet. So if you can see no difference, you must teach me how to apply the ideas of one to the other. I cannot. The issue is can you design a system which will run, which is self-adaptive in a great variety of unknown (to it) environments, and which can make out with its life processes? None of us in automatic control know how to do it. It is that challenge I must leave to you. That is your advantage in being young. I can leave you problems.

XIV. MATERIAL - PREPARED OR IN REVIEW - RESULTING FROM THIS CONTRACT DURING THIS REPORTING PERIOD

1. "Physiological Control - A Physical View: Life and the Biochemical Oscillator", Chem. Eng. Symp. Series 67 (114), 190, 1971.

2. "Illustrating Key Problems That Can Lead Toward a Quantitative Physical Biology", Amer. J. Physics, 40 (6), 902, 1972.

3. "Comments on the Biological Problems Session", Proc. 5th World Congress, IFAC, Paris, June 1972.

4. "Blood Flow and Oxygen Uptake in Mammals", Ann. Biomed. Eng. (in press).

5. "Introducing Some Operational Characteristics of Mind - The Human Outlook and the Dynamics of Society", Trans. ASME, J. Dyn. Syst., Meas. Control (in press).

6. "On an Additional Third Dimensional Manifold of Mind - A Speculation on its Embodiment", Intern. J. Psychobiol. (in press).

7. "Integration of the Whole Organism - A Foundation for a Theoretical Biology", in AIBS Anniversary Vol., John Behnke (Ed.), (in press).

8. "On the Physical Basis of Human Thermoregulation" (under review).

9. ON THE PHYSICS OF MEMBRANE TRANSPORT (in preparation)

10. ON PULSATILE AND STEADY ARTERIAL FLOW - THE GTS CONTRIBUTION (in preparation).

11. "Flow and Pressure Regulation in the Cardiovascular System", (under review).

12. "On a Naive Biophysical Model for Human Behavior", (under review).

13. "On Global Stability: A Strategy for its Achievement in Viable Systems (under review).

Talks

1. On Biosystems Modelling - invited talk to Biomedical Engineering Department, Case-Western Reserve University.

2. On a Global Thermodynamic Model of Systems - invited talk to Army Research Office.

3. On Systems Modelling for the Ecology - invited talk to Bioscience Group, NASA - Ames Center.

4. Comments on Biocontrol - invited Commentator's talk to 5th IFAC World Congress.

5. On Scientific Modelling of Viable Systems - invited talk to Biomedical Engineering Department, U. Southern California.

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