New Thoughts on Bio Control[1]

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My colleagues, notably Dr Cardon, and I have been pursuing a closely coordinated novel view of the complex biological system. This is contained in nine basic reports written for NASA and a number of derived papers that we have given or reported on at various meetings [1]. I will attempt to give you some sketchy outline of our central ideas up to date. (It is only fair to the reader and ourselves to state that Dr Cardon and I are physical scientists only recently concerned with biology.)

Starting in our first report—available as a N.Y. Academy of Science review of September 1964—we sought to define the regulating and control functions of the system as a whole.

First we sought the central theme of the biological system and found it well enunciated in the biological literature in the form of Bernard's and, later, Sechenov's and Cannon's [2–4] insistence on the primacy of the interior milieu and of its regulation—homeostasis—as the significant theme of operation of the complex system. We then found and accepted H. Smith's view of the kidney [5] as the master regulator of the system, for in its function, more than anywhere else, does the preservation of the character of the watery internal milieu lie. As physical scientists—basically in the tradition of the modern chemical engineer with a view of flow charts, unit processes, and regulating and control functions—we thus had a core model of chemicals in a watery environment with a master flush valve at the exit to preserve the watery environment and regulate concentration contents.

It was clear, next, that ever since Wiener [6] the internal electric system had to be related to possible regulating and control functions. However, within the spirit of discovery that we were seeking, it appeared not so much that Wiener had developed key knowledge about the electrical system—Adrian and Sherrington [7, 8] were much more influential and important from a biological point of view—but that he called attention to a control (cybernetic) point of view for the system.

At this point it was necessary to put some mechanisms, systems, and processes into the bath. Here we had to start with what would be specialized and peculiar to physical theory and its dynamic analysis. If one were to look for regulating and control chains, it would be first necessary to dispose of any self-sustained

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[1] This report was substantially presented, by invitation, for the local Biomedical engineering section—IEEE—Phila., Sept. 1966; Dept. Physiology—U. of Pittsburgh, Dec. 1966; Serbelloni conference on Theoretical Biology, Lake Como, Aug. 1967.

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oscillatory or so-called limit cycle phenomena. These are indicative of unstable linear chains that have unknown causality and 'purpose' to begin with in the analysis of a new unknown system. We proposed to tease these out and lay them aside and then to continue to look for regulators and controllers.

To those who might consider this idea vague, it really consists of the following: what is unique in the description of the dynamics of a system—whether by equations, physical chains, or verbal chains—is the set of singular states of motion of a system and the kinds of operating stability that one finds around these singularities. It is thus that the actual 'stable' dynamic motion of a system is cast. This is the topological overview of non-linear mechanics in considering the dynamics of systems. As Minorsky [9] puts it so well, the non-linear limit cycles of Poincaré are the stable non-linear steady states of operation of a system, just as the damped oscillation is the stable linear steady state of operation of a system. Whether a system be linearly stable (at rest) or non-linearly stable (in limit cycle oscillation) depends upon the specific character of its singularities. In an *a priori* unknown system, they can only be discovered experimentally.

We therefore went searching, and began to tease out a broad spectrum of oscillators, which may also be called engine cycles, rhythms, DC to AC converters, or non-linear limit cycles. In fact, after a while, it dawned on us that we had become keepers of biological macrospectroscopy, the dynamic spectrum of biological effects, in which the chains are biochemical, bioelectric, and biomechanical. (When we were introduced to Brian Goodwin's work [10], we regarded him as a keeper of microspectroscopy.) We found so many such chains that we were led then to believe a key idea: that what the biological system consisted of was a great collection of limit cycle oscillators; basic regulating and control functions were to be found in the mediation of the stability of these oscillators, mainly by inhibition; that the slowly varying DC parameters of the milieu mediate the operating point—in amplitude, or frequency, or in actual stability margin—of these oscillators so as to achieve desired regulation.

I can name some of these 'major' physiological oscillators for clarity and suggest their nominal time scale.

bioelectric nervous waves (spikes, etc.)	0·1 sec. per cycle
heart beat complex	1 sec.
ventilation	4 sec.
blood circuit flow	10 sec.
blood flow oscillations	30 sec.
metabolic oscillations	100 sec.

vasomotor oscillations	400 sec.
many fast endocrine oscillations	300–1000 sec.
gas exchange oscillations	2000 sec.
metabolic fuel oscillations	5000 sec.
heat balance oscillations	3 hours
circadian rhythms	24 hours
water cycles	$3\frac{1}{2}$ days
many longer range endocrine rhythms	20–40 days

Since Cannon's concept of homeostasis, on careful reading, was a concept of a regulating process or chain, but with the implication (in his examples) of quasi-static regulation [4], it seemed appropriate to propose a change in name to indicate a more dynamic nature of the regulation. For this, the term homeokinesis was offered, for it is by manipulation of the kinematic variables—of space and time alone—that this dynamic regulation takes place.

By our fourth report [1] we were then prepared to propose a new operational definition of life.

'Thus life is tentatively defined 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 of seeking out in the environment and transferring and receiving those fluxes of mass and energy that can be internally adapted to its own satisfactory preservative operation; that is capable of performing these preservative functions for a reasonably long period of time commensurate with the "life" of its mechanical-physical-chemical elements (i.e. clocks made of parts that should wear for hundreds of years that run for two seconds are not crickets); and—likely as a luxury part of the definition—that are capable of recreating their own system out of materials and equipment at hand (one will have to note in the future how much of the biological system can be rebuilt, or one can recall the story of the amorous young bridegroom who has watched his bride remove most of her apparent charms before his eyes—teeth, eyes, hair, wooden leg, etc.).

'The purpose of this definition is to guide the physical search for "explanations" of the operation of the biological system; and to leave the physical scientist closer to some physical base by which he can model, "build", or assess systems that resemble naturally "living" systems by suitable operational definitions; and a clue that "life" does not have to be explained by only one mechanistic scheme per system, but may involve many possible types of successful operation.'

We view the function of such a definition, in an operational Bridgman sense, that it should give us a hunting licence in the form of a basic concept of what we are hunting for. In this definition it is declared to be dynamic regulating chains. These may be fully unstable and oscillatory, or may be marginally unstable and aperiodic. We would hope that by this means we can have forced the intrusion of thinking about dynamic processes into biology. The significance of dynamic AC analysis of systems does not have to be stressed to any group who has been influenced by modern electrical engineers.

Further, to give the system its primary functional keynote, its 'purpose,' we have proposed the following catch-phrase:

The biological system is an intermittently self-actuated motor system operating in both short and long term, that seeks to sustain the metabolic reaction: fuel + oxygen → carbon dioxide + water, plus sufficient power so that it can continue its self-actuated motor activity to seek to sustain its metabolic activity.

Shorter still: *the system eats and moves about, so that it can continue to eat and move about.*

Thus, for example, in our second summary paper at the 1965 IFAC Symposium in Tokyo, we could represent our overview of the biological system two years after our N.Y. Academy paper. As an excerpt:

'The experimental survey of a complex biological system like the human discloses a large number of autonomous oscillators continuously operating in the system. A partial frequency spectrum in man would consist of primary neural frequencies in the range of 5 to 50 cps, a muscle motor unit frequency at about 10 cps, a heart beat about 1 cps, breathing rate about 1 cycle per 4 seconds, several eating cycles per day, circadian rhythms of 1 cycle per day, sex urge approximately 1 cycle per few days and menstruation about 1 cycle per 30 days. To these may be added cycles, demonstrated within the past few years, in ventilation rate, local skin temperature, and metabolism of approximately 100 seconds, 400 seconds, 30 minutes, and 3 hours. The first appears to be an engine cycle, primarily in skeletal muscles, in which the major heat production takes place. The 400 second cycle appears to represent a vasomotor action which partitions blood flow among the major organ circulations. The 30 minute cycle may be a gas exchange cycle, likely representing a total body carbon dioxide equilibrium, and the 3 hour cycle is probably an overall thermal balance. A 3-day cycle has been found in body weight. It has been tentatively identified as a water balance cycle.

'It has become increasingly apparent that the many oscillators in the biological system are not incidental characteristics of the system, but represent the working components of the system. In summation, they are the biological system. In accordance with this view, it is proposed that homeostasis, Cannon's organizing biological concept of a complex regulation characteristic of the system, is obtained as a result of shifting the stability of these intrinsic non-linear oscillators. The oscillators are likely modulated or shifted in operating point by electrical and chemical signals. In our view such action is an illustration of dynamic regulation. It is possible that the biological system is not able to operate in any other way. In fact, it is likely that the same type of instability mediation is the foundation for all automatic control theory. However, the more general thesis is beyond the scope of discussion in this paper.

'To illustrate the mechanisms of homeostasis, a number of biological systems will be discussed. A first case in point is that of heat production in mammals, which is of interest as part of the system of human thermoregulation. Local skin temperatures, ventilation rate, and oxygen consumption rate all show sustained limit cycle oscillations with a prominent component near 100 seconds. We have postulated that this is a heat engine cycle; that the engine consists essentially of skeletal muscles; that the level of operation of local muscle engines is regulated by an oxygen choke which limits the oxygen supply and thus the rate of local oxidation; that regulation of oxygen rate is achieved in a 100 second cycle of capillary red blood cell flow, mediated by the vasodilatory effect of adrenaline. That adrenaline is the hormone mediator of the cycle is suggested by its calorigenic action, its vasodilatory effect primarily in skeletal muscles, its effect of increasing muscle activity and a time of action for transient effects in a range between one and two minutes.

'The mechanism of the adrenaline action is not known.'

The essence of the matter, as this last thought intends to imply, is that having now proposed all of these grandiose systems views of the complex mammal, the human, the burden of proof is now upon us to make the description stick. This, to us, has meant that we must identify and run down these dynamic regulating chains. This is what we are now beginning to try to do. However, there are so many of them that we have to choose carefully and for the most hard-hitting value. Our resources are really quite limited. However, to add some more flavour to the presentation, I think I can add what we had in addition grasped more recently and expressed in our sixth report, August 1966 [1].

In the metabolic reaction:

A matrix

Time elements	Fuel +	Oxygen →	CO_2 +	H_2O
1				
2				
3				
4				
5				

we basically consider that there seems to be a matrix of regulation levels and effects, a hierarchy of regulation functions that seem to pile up under each item; the regulation of fuel, oxygen, CO_2 and H_2O. Many of these are quite independent and tend to appear redundant. What we expressed in the past, coming more nearly into focus in this sixth report, is that when the ecology provides cueing sensitivities of a temporal type which may have survival value, and there is a suitable cyclic time fracturing (or phase locking) commensurate with this period provided by possible physical-chemical chains, these chains will become a dominant dynamic regulating element in the system. Thus, the spectrum of effects we have identified seem to fit this scheme. However, beyond this, we have finally vaguely seen that the spectrum tends to be even more limited. We have further said in our sixth report:

'The apparent competition between autonomous physiological oscillators and the environmental cues (day, month, year) is to be resolved by recognizing that cycles must fit and thus be entrainable as small numbers with all such cues. We eat, defecate, urinate, sleep a few times per day. These are useful adaptations. An animal (call him a dinosaur) that must chase food for too long to make one meal can't make it. He will not satisfactorily entrain. Time is against him. When time is ample, then the system instabilities will lead to an orbital entrainment in such cycles that can fit the time comfortably. This is one added thought of how the patterning richness is regularly reinforced. The second thought emerges even more strongly from endocrine considerations.

'Each endocrine gland seems to put forth a spectrum of hormones, and it has been a little discouraging to attempt to exhaust, by long lists, their apparent multiplicity of functions. Yet major functions emerge, and the spectrum covers functions that are usefully adaptive. However, it also emerges that more than one gland may put out hormone components that collaborate at common functions. In reviewing time constants, it appeared fascinating that, while the spectrum is rich, it tends to appear finite in number. Thus the concept of time fracturing of physical-chemical chains seems to roost on a more specific perch. Any particular ductless gland may contribute hormonal elements. However, most of them will be involved in chains with a small number of time constant ranges. (For example, we might propose some typical numbers, 0·05–0·1 second, 0·5–1 second, 5–10 seconds, 20–40 seconds, 60–120 seconds, 300–500 seconds, 20–40 minutes, 3–4 hours, 20–8 hours, 3–4 days, 20–40 days.) It is not the case that they must be involved in such time ranges. However, those that can be entrained in chains that have considerable adaptive value have greater survival value for their species. Thus the hormone patterns are interlocked–from gland to gland– to form a matrix of chain function (sugar metabolism, for example) and time. It is this highly locked-in matrix that exists in the endocrine system, the nervous system, etc., that provides the underlying functional structure of the system. The patterns then form and wrap themselves around these more permanent poles. The final ingredient, of course, is that these salient polar times fit, by small numbers, and interact with the AC cueing of the environment. The night–day cycle is a most powerful polarizer. The breakdown of time ultimately to the 1–2 minute or the 0·05–0·1 second cycle time is of course more subtle. The 28-day menstrual cycle drive is quite real, and the breakdown into 4 weeks is reasonable. It is disconcerting to consider cues for a 3½ day water cycle. Which is causal for which ?' (That is, the week for the water, or the water for the week ?)

'The existence of such time cycles does not mean that all animals must share them. Development in each species can have occurred independently. It is likely that similar chemical cycles may be arrived at, but this arises because the biochemical chains, in general, are not so specific, although particular ones may be sharply deterministic.'

Thus far, we have sketched out our scheme for the system via its more 'involuntary' physiological oscillator chains. Now I will discuss a little our proposal that this is extendible to the less 'involuntary' psychological or behavioural system.

We have postulated that what is most characteristic of behaviour is an orbital synchronization with various elements in the milieu. This model has been subconsciously influenced by a quantum mechanical model of free electron conduction in metals. In Frenkel's *Wave Mechanics* [11] there is a delightful modelling of the electron motions as follows: The electrical field causes an accelerated motion of free electrons with a relaxational phase on collisions. The free electron path is thus defined as a sequence of mean free path relaxations and mean relaxation time between collisions with what are basically not crystal lattice points but lattice dislocations. However, at any point the electron is not locked up for one oscillation but it makes a number of pinwheel rotations. The human–it is proposed–acts similarly. A signal DC or AC in the milieu–for example, the flick of the skirt of a passing comely female, or the pulsations in the stomach, or a painful nerve signal, etc., each mediate the oscillator complex, and lock the system 'posture' for that 'moment' into an orbital synchronous path. The command algorithm (an extremely large code book) was not all determined at birth, or did not emerge at various maturational points. It was partially 'learned' and developed out of the matrix of experience. Such development, I was taught a long time ago, represents an epigenetic process.

To give behaviour some picturable substance, consider the bank of physiological oscillators as not being rigidly closed but with partially open inputs, and quite a few in number. Let the oscillators resemble the various resonators of a piano or organ, each of which can have its pitch, amplitude, and timbre mediated. Now let the input winds of the milieu–both internal and external–play over the bank of open inputs. They will make melodic patterns in the organ. Thus far, we only have an instrument like a passive Aeolian harp–even if the individual resonators are active elements.

However, let these oscillations also drive the motor system into space-time orbits. Then the system will be urged to drift down the path of life, however not continuously. It will lock up, circle quite a few times, pass on, etc. There are open portions in this path motion.

Continuity of behaviour is provided by the learned part of the algorithm. Mother, in the mother-child relation, teaches the child various patterns that are fairly adequate to provide the range of needs that will saturate the physiological oscillators over time.

To make this more comprehensible, there is likely a two-state oscillator complex–this is Freudian derived–representing a satisfying or 'euphoric' state, and an 'anxious' or 'dysphoric' state. In this view we find Henry Stack Sullivan's formulations [12] most nearly fitting what we were looking for. Any first infant experience may be satisfactory or not. However, all that can emerge in time is an alternation of such states. In the infant brain, the major signalling complex is the oral one. We consider that this signalling complex, pounding into the plastic brain, develops correlates for satisfying and unsatisfying states. Later, as the nervous system develops and the more detailed outlining of the system, descending toward the anal and genital regions, gradually helps set up a conflict of signalling into the brain, there is a tendency to separate out and segregate these signalling interfaces into the brain, becoming represented as analogue imprints of these system interfaces in the brain. The summation of these signalling complexes, as represented by their imprints in the more primitive structures in the brain, we think of as representing the structure of Freud's id (or *es,* the *it* of the system, as he named it in his own language). It is this measure which somehow is to lead us to anxiety-provoking or euphoric states. We then visualize that the coordinated summation of this oscillator complex, projected into higher centres, represents the ego sum of the system. A more nearly unitary measure of the buzz of information to ego centres is provided by a part sexual flux of libido. Its state presents a measure of the existing, satisfying, operating state of the system. Guided by this measure, system operators fall into an anxious or euphoric state, represented as a two-state operative complex.

As another integrative measure taken by the brain, unification of discreet signal information into an integrated analogue of the information represents the gestalt of the analogue. The brain is thus compacted with a large number of unified analogues to various signalling complexes and motor responses. It is such analogue packages that the mother helps develop in the maturing child together with a program routine of a tolerably satisfying nature that threads through the system hungers.

The missing ingredient is Freud's super-ego, the ego ideal, which represents the image of a satisfying ego state. This, added to the developmental algorithmic content on how to achieve a satisfying ego state, provides the motion for the behavioural patterning that emerges. The conflicts from all the signalling interfaces are not to be satisfyingly resolved by moving in some direct path. The super-ego is developed as a rule book on what motor actions will preponderately move in the direction of a more satisfying state. The speed of motion will also depend on the oscillatory two-state operator system—whether overall anxious or euphoric.

Thus modulated by the two-state oscillator, under the driving guidance of the super-ego algorithm, the system will hurl itself into motor activity that will synchronize in orbital paths with specific oscillator patterns.

In the larger developmental picture there are a number of large-scale flaring instabilities of a maturational nature. Two of these we can be certain of physiologically, and the others, if not yet clear physiologically, are certainly clear observationally, even under comparative anthropological study.

The first is the oral interface of infancy. The primacy of food seeking and of establishing routines for food acquisition may be fairly detailed.

The second is the great flaring instability of adolescence. The physical characteristic changes are, of course, noticeable. However, equally noticeable is the interest in the opposite sex and the preparedness of the system behaviourally and physiologically for mating—the maintenance of the metabolic reaction through reproduction of the species. The adaptive value of this aperiodic flaring of an entire sexual cycle is obvious.

The third newly-emergent flare is Sullivan's chum or peer stage in which the child is integrated sufficiently for it to suddenly break its tie to the mother's orbit and discover its own kind, its peers and chums.

Each of these periods is marked by the continuing development of the guiding algorithm, within the framework of interpersonal relations and the surrounding milieu. A useful thought is that man is an instrument to be used by and for man. It carries with it the idea that the system gain at zero frequency is indeterminate. (This means that the system is unstable at rest.)

The basic command algorithm for behaviour can be considered to be a continued adaptation to make the ego image agree with the ego ideal by means of the sequence of practised analogues that are stored within the brain.

The marginal stability of the system is such that environmental signalling is always blowing over the inputs and putting the analogue systems into continued melodic lines of response. The system is always practising its repertoire. It is this continued response that makes a follower-type characteristic melodic line appear for each and every questing and questioning environment.

In a successful biological species there is a satisfactory patterning of behaviour which threads all of the system hungers. In an unsuccessful individual it may lock up or become too wild. I have presented these ideas less sketchingly in our eighth report as a joint effort with Warren McCulloch. The report became available just at the time of this conference. An additional ingredient that emerged in that report is the foundation for interpersonal forces, the keynote of behaviour stressed by Sullivan. If, in the interior, there is this well-coordinated body image of both inside and outside the system, with its many vector dimensions, then upon meeting a member of a like (or similar) species in a reacting situation, there is an exchange of body image. The individual imagines the nature of his body image projected into the other individual as the other person's apparent actions emerge. If the image and actions are concordant, then an 'empathy', a binding 'force', emerges. The basic two elements of concordance, likely, are complementarity and congruence.

By these means, roughly, we have attempted to bring a dynamic concordance through the biological system by its spectrum of dynamic oscillator chains. Our problem now is to demonstrate the reality of these chains.

We can provide a more rudimentary illustration. We have taken a large motor system—the hind limb of the complex mammalian animal—as a suitable laboratory to test some of these ideas. For example, we are attempting to follow the detailed metabolic reaction in that system.

So far, in the gross animal we have demonstrated appreciable dynamic cycles in :

respiration rate
heat production rate
temperature.

From their temperature concordance, we have postulated that their operative dynamics are to be associated with pulsing dynamics in the cardiovascular system at the level of the microcirculation. We have demonstrated corollary dynamics in the femoral system (for the first 3) and in capillaries (for the 4th) :

blood sugar oscillation
blood oxygen oscillations
blood CO_2 oscillation
red blood cell oscillations.

We have traced a line of evidence from Krogh, Sir Thomas Lewis, among modern microcirculationists, and others.

To illustrate briefly, we postulated that there should be a chemical engine cycle faster than a thermal relaxation time of three hours. We found it in thermal, metabolic, and ventilatory cycles at 100 seconds, 400 seconds, and greater. We have chosen to highlight the 100 second cycle as the engine cycle because of its large magnitude of variation. For example, we have found a running variation of near two to one in metabolism and ventilation at the 100 seconds level, ranging as much as peaks that are 5–10 times larger than minima in a 5 hour observation period [13].

We have decided that the large cycles must stem from major mesodermic organ systems such as muscle, liver, heart, brain, etc. We have sought and found allusion to such time scales in the microcirculation and expected to find it in capillary opening and closing. Instead we found the cycle in the red blood cells flow. We postulated that the engine cycle could either be run by metering of fuel, oxygen, or a combustion by-product. The high level of regulation posed for fuel and the rapid follower regulation and storage capacity for CO_2 ruled these two out, whereas the more limited storage of oxygen suggested that the engine cycle must be run by an oxygen choke. In this view, the muscles were considered to be an unstable system capable of metabolic conversion at any level to which they were supplied with oxygen. The fluctuation of red blood cells was an additional step in the evidence for this concept. Early in 1966 another step was found in the experiments of another investigator (Whelan), who showed that oxygen tension in the tissue was low and oscillatory—in the range of 0–5 mm Hg, with a period of the order of 100 seconds.

We are continuing in our effort to show an adrenaline involvement in setting this local system into its oscillatory chain. We carry with us the provocative thought that the brain sets a motional pattern, but not the resisting load. Then it must implement its choice by providing the needed oxygen carburettor to run the muscle engine.

In any case, the story and proof of such chains is exciting business. Yet it is beset by the following situation.

We have measured and found ventilation to be oscillatory time and time again. It has been verified by a few other investigators, for example, Goodman [14], now at NIH; more recently, Lenfent [15]. Yet we can find no other ventilation physiologists who report these results.

We have found normal heart rate to be oscillatory. This has essentially not been reported by other observers.

We have found that Anderson [16] and others (for example Hansen [17]) have found blood sugar to be considerably oscillatory and we have verified these findings; yet many physiologists deny these findings.

Thus, many of the observations of fundamental dynamic findings are themselves in doubt. We have sufficient confidence in our experimental findings to make even the consideration of the validity of our theses to hang on the validity of our dynamic observation. If the others are right and we are wrong in measurements, then it is dubious that our dynamic concepts should receive much attention. However, if measurements in normal unanaesthetised animals held normally quiescent or normally active demonstrate such dynamic oscillations, then we feel that our ideas may warrant the attention that we believe they deserve.

References

1. A. Iberall and S. Cardon. (1) *Ann. N. Y. Acad. Sci., 117* (1964) 445.

A. Iberall and S. Cardon. (2) NASA CR-141, Jan. 1965.

A. Iberall and S. Cardon. (3) NASA CR-219, May 1965.

A. Iberall and S. Cardon. (4) NASA CR 129, Oct. 1964.

A. Iberall, S. Cardon and T. Jayne. (5) Dec. 1965, Interim Report.

A. Iberall, M. Ehrenberg and S. Cardon. (6) Sixth Report to NASA, Aug. 1966.

A. Iberall. (7) *Math. Biosciences, 1* (1967), 375.

A. Iberall and W. McCulloch. (8) *Currents Mod. Bio., 1* (1968), 337.

E. Young. (9) NASA CR-990, Dec. 1967.

A. Iberall and S. Cardon. In *Proc. IFAC Symp. on Syst. Eng. for Control Syst. Design* (Sci. Council Japan, Toyko, 1965).

E. Young, A. Iberall, M. Ehrenberg and S. Cardon. *Proc. Ann. Conf. Eng. in Med., Bio.*, Vol. 8, 1966.

M. Ehrenberg, C. Oestermeyer, E. Bloch and S. Cardon. *Microvasc. Res.* (forthcoming).

A. Iberall, M. Ehrenberg, S. Cardon and M. Simenhoff. *Metab.* (forthcoming).

2. C. Bernard. *An Introduction to the Study of Experimental Medicine,* Schuman (N.Y., 1949).

3. I. Sechenov. *Selected Physiological and Psychological Works* (For. Lang. Pub. House, Moscow, 1952).

4. W. Cannon. *The Wisdom of the Body* (Norton, N.Y., 1939).

5. H. Smith. *From Fish to Philosopher* (Ciba, N.J., 1959).

6. N. Wiener. *Cybernetics* (Wiley, N.Y., 1961).

7. E. Adrian. *The Mechanism of Nervous Action* (U. Penn. Press, Pa., 1932).

8. C. Sherrington. *The Integrative Action of the Nervous System* (Yale U., Conn., 1961).

9. N. Minorsky. *Nonlinear Oscillations* (Van Nostrand, N.Y., 1962).

10. B. Goodwin. *Temporal Organization in Cells* (Academic, London, 1963).

11. J. Frenkel. *Wave Mechanics* (Dover Repr., N.Y., 1950).

12. H. Sullivan. *Collected Books* (Norton, N.Y., 1953).

13. A. Iberall. Trans. ASME Series D, J. Basic Eng., *82* (1960) 92, 103, 513.

14. L. Goodman. Trans. IEEE, Biomed. Eng., *13* (1966) 67.

15. C. Lenfent. *J. App. Physiol., 22* (1967) · 675.

16. G. Anderson, Y. Kologlu, C. Papadopoulos. Metabolism *16* (1967), 586.

17. K. Hansen. *Acta. Med. Scand. Suppl., 4* (1923), 27.