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GENERAL TECHNICAL SERVICES, Inc.

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451 PENN STREET — YEADON, PENNA., 19051
Phone: Area Code 215 MA 2-4420 MA 2-4421

August 27, 1965

Dr. George Jacobs
Code SB
NASA Headquarters
Washington, D. C. 20546

Dear Dr. Jacobs:

Reference: NASW-1066 - General Dynamics of Physical-Chemical Systems in Mammals." Fourth Quarterly Progress Report, August 27, 1965

In accordance with the requirements of the referenced contract, we are submitting this progress report covering the period May 21, 1965 to August 20, 1965.

I. Summary of Work Performed.

1. Work is continuing on the mathematical modelling of the hydrodynamics of the arterial system. Discussion with Dr. McDonald has raised some questions relative to the geometric model of the arterial system. This area is considered important to provide a suitable base for consideration of the actual events taking place in the arteries. Attempts are being made to develop a model which will describe the geometry in terms of diameters against length, changes in cross-sectional area with division, and number of levels of arteries according to diameter. This work will be described in some detail in a technical report which is being prepared and will be submitted during the next quarter.

The detailed transmission line treatment of the arterial system has been delayed pending completion of the geometrical modelling.

2. Work on the microcirculation is continuing with attempts to expose active normal tissue so that the microcirculation can be observed. Plastic windows have been placed in guinea pigs over muscle areas. The problems of suitably illuminating the tissue appear to be severe but far from hopeless. The use of fiber optics is being considered and some observations have been made. However, it appears extremely difficult to contain the tissue in a living animal in such a controlled condition to permit viewing with the high powered microscope. The objective is to be able to determine rate of flow of blood cells in the microcirculation of the unanesthesized animal. In addition to the window technique we are also considering the observation of open areas of tissue with the overlying skin removed. It may be possible to coat such areas with silicones to permit observation under relatively normal conditions.

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3. To begin experiments on blood constituent dynamics a bypass has been placed around the femoral vein. It is proposed to use this bypass to obtain blood samples for analysis of oxygen, pH, and some other blood constituents like carbon dioxide, lactic acid, and hormones. It may also be possible to study temperature dynamics in the venous flow.

4. Thermocouples have been placed adjacent to the femoral artery and vein. It is proposed to examine dynamic temperature differences between arterial and venous flow in and out of the large muscle masses supplied by this circulation. It would be interesting to have correlation of blood constituents and temperature in and out of such an area. Such information can further the exposition of the heat production mechanisms in mammals.

5. A paper has been prepared for delivery at the London meeting of the International Federation of Automatic Control. It is concerned with dynamics of control in the microcirculation. A copy of the talk is attached.

6. It is planned to purchase an accurate scale and extend the weight experiments described in CR-219 with dynamic measurements on more subjects.

7. A proposal to study biological oscillators for medical and physiological purposes has been submitted to the Aerospace Medical Laboratory of the U.S. Air Force, attention Dr. Hyde. An expansion of these studies should result in greater yield from this program as well.

8. Preliminary discussions have been started with Dr. Hastings of the National Heart Institute. It is felt that the results of the present studies on the hydrodynamics of the cardiovascular system can be useful in the NHI program on the development of an artificial heart.

II. Principal Investigator

The principal investigator, A. S. Iberall, has devoted 262 hours to this program in this report period.

Very truly yours,

GENERAL TECHNICAL SERVICES, INC.

Samuel Z. Cardon

Samuel Z. Cardon
Vice President

SZC/am
Encl.

METABOLIC CONTROL IN THE MAMMALIAN MICROCIRCULATION

A. S. Iberall & S. Z. Cardon

The microcirculation in mammals is responsible for providing a flux of oxygen under adequate partial pressure to its perfused tissue. In some tissue one could suppose that this might be supplied by passive diffusion through fixed resistances. However, in actively consuming tissues, an active control mode is required to supply oxygen to meet demand. Since essentially the same control modes of actions are used for a very wide range of ambient excitations independent of the excitation type or mode and coupling, it may be considered to be an adaptive control system. The skeletal muscles are an apt example. The following model is proposed as fitting physiological facts for this system.

The muscles must form a prime mover engine, in that for any time schedule of body displacement (illustratively, constant speed schedules) the loads on the muscles are indeterminate. The muscle engines therefore must always be in an idling state, ready to respond with output horsepower to meet load demand. Such engine cycles are generally run by control of the thermo-dynamic process that supplies the energy transformation. In the present instance of a chemical oxidation process, the fuel flow, the oxygen flow, or the level of an inhibiting combustion product could be the factor controlling the rate of energy transformation. It is clear that the tissue is amply supplied with fuel (sugar) at regulated levels, and the major combustion product, carbon dioxide, is absorbed in an ample sink. Thus it appears that the most plausible control element is the oxygen supply, particularly since there is little oxygen storage in the system. It is therefore proposed that the local flux of oxygen to the muscle tissue is controlled by the microcirculation functioning in an active control mode.

From our own earlier experimental work (1), the work of Lewis (2), and Krogh (3), and various comments culled from microcirculation conference reports of the past ten

years, it appears that the highest frequency of local power control is confined within a band approximating one cycle per 1-2 minutes, which we have loosely referred to as a 100 second cycle. Since the active oxygen exchange elements -- from effective oxygen exchange area considerations -- are the capillaries, and most of them -- from blood flow considerations -- are essentially impeded, the 100 second power cycle represents an effective intermittent opening and closing of the capillaies in this time domain. In truth, the intermittent oxygen flow through capillaries may consist only of an intermittent red blood cell flow and not serum flow, so that the flow variation may not necessarily be due to mechanical opening and closing. It is likely that the overall cycling process is known in physiology as vasomotion.

The process of equivalent opening and closing is not random, as evidenced by locally coherent thermal power cycles appearing at every point in and on the body (i.e., as demonstrated in fluctuations in skin and internal temperature). Since the thermal cycles from point to point are not highly correlated, there is apparently little local control of the resistance beds. However, the resistances of larger aggregates are not indeterminate as is indicated by cyclic coherence in oxygen consumption at the mouth, i.e., a 100 second cycle is present in ventilation and metabolic rate. Thus the local opening and closing cycle appears quasi-coordinated into a non-linear limit cycle ring oscillator that propagates through the system.

The muscles and microcirculation supply elements, the capillaries, are not acted upon in a more rigidly scheduled firing order familiar to prime mover engineering. Instead there appears to be a loose but well coordinated statistically determined firing order, linked from region to region, which is continuously adjusting to the power demands of the system. This means that for a given activity level characterized by a velocity pattern, the power demand is adjusted to the force loads on the system.

The system resistance as a whole has a determinate slowly varying mean state, with individual regions indeterminate and available to adjustment to a best fit of conflicting inputs. Thus the system operates generally in a resistance control mode. The nature of the control algorithm can only be guessed at. It may involve subtle cues of fatigue, coordination by electrical signals and chemical byproduct concentrations.

For example, we have proposed (1) a hypothetical mechanistic scheme in which the local capillary is normally closed but opens for a limited time when a specific signal is presented. The muscle fibers, the transforming motor element, on the other hand it is proposed, will use up all the oxygen at whatever rate the surrounding tissue permits. These two actions can create the conditions for a local instability.

Specifically, an elementary unit of the system may be defined as consisting of a local group of muscle fibers, which are sufficient in extent to represent not only the electrical firing from a single nerve fiber, but of all those adjacent motor units that cooperate to produce a coordinated nervous wave (see Adrian (4) for discussion of such cooperative motor units activity). This thus serves to define, even if vaguely, a motor element that can be fully coordinated in an electrical sense, from the level of intermittent individual muscle fiber discharge up to saturated and coordinated waves of muscle activity. In prototype, the motor element may be viewed as disposed in a cylindrical form. The muscle fibers in such a bundle alternate with capillaries (see, for example, Krogh (3). These capillaries are connected in a network shunting from arterial (oxygen rich, high pressure) to venous (oxygen poor, low pressure) blood. On the approach side, the arterial side, the capillary networks are supplied by small arteries, the arterioles, which possess a muscle motor unit, a sphincter, which by opening and closing, can control flow to the capillaries. The predominant pressure drop takes place at the arteriole level, nominally through the arteriole sphincters, though there may be other additional closure mechanisms. It is likely that total blood flow is controlled by sphincters, but the red blood cell fraction may be otherwise controlled, likely electrically. The stage is thus set for control action of the oxygen

flow. (In earlier descriptive form, it has been discussed by Krogh (3).

There is a flux of blood axially along the capillaries, among the muscle fibers. There is in addition an oxygen flux from the capillaries out to the tissue and thence to the active muscle fibers. This forms a flux stream orthogonal to the blood flux stream. Now, according to the present hypothesis the muscle fibers are an active sink that will utilize oxygen at whatever rate its boundary permits. Thus, the muscle fibers do not determine the rate governing reaction, which must be determined instead by a 'diffusion' rate across the intervening tissue geometry. However, the capillaries are active. They are not all full of red cells. In fact, most of them are free of, or low in, red blood cell flow. (Following Krogh, it is common to regard that most of the capillaries are considered to be closed at any time). Thus, as an equilibrium force balance, one might expect that with a given number of effective open capillaries, a certain cross-channel equilibrium concentration of oxygen would exist in the tissue, ranging from a nominal 19% oxygen concentration in arterial blood down to near zero for interstitial fluids. Depending on the geometry, this would represent a specific equilibrium oxygen flux into the muscles, and thus its existing equilibrium oxidation rate. There would similarly be an equilibrium returning carbon dioxide counterflux. There could be more than one model of the equilibrium point, depending on the nature of the boundary equilibrium at the muscle fibers and as determined by the operating points of the metabolic reactions, i.e., the distribution would tend toward an equilibrium following each change in effective capillary opening distribution.

The one major open element in this description is the effective number of open capillaries. The question is what makes them open or close, or since they are normally closed, what makes them open for limited times, and in particular, what forms the 100 second nominal timing phase? It is suggested that a component that enters into the cross-channel flux is responsible, although this component may be carried in the axial channel flow. It is likely neither oxygen nor carbon dioxide, since these sub-

stances acting only passively would come to spatial and temporal equilibrium. It is also not likely any other passive intermediary, since this too would tend to equilibria. It cannot be the oxidation kinetics, since these are too fast and also can only tend toward equilibrium. Therefore, as Krogh also sought, there must be some switching, or escapement element for opening or closing capillaries. It is not ruled out that either a second escapement or a spring return is used for the opposing action. Krogh understood the problem quite well and it motivated his search for a vasodilating agent.

Our search for the escapement has suggested adrenaline for the most plausible agent. It is a powerful vasodilator in muscle and its time of action seems correct. It is reputedly a calorigenic agent as well. The problem is to work out a suitable hypothetical model for the local 100 second cycle. Some possibilities are the following:

1. There is a centrally produced cyclic stream of adrenaline into the blood from the adrenals. This may be delivered into the blood at a near 100 second rate to form a predominant timing phase. The pulsed adrenaline wave in the blood can regularize a 'twinkling' in the capillary number by being used up, or tied up by the number of capillaries that open on signal from it. The rate of adrenaline flow could determine the twinkling rate of capillaries and therefore the oxygen flow.

2. A second possibility is that the adrenaline is maintained in the blood at very slowly changing levels. Its flow rate is still used to open a definite number of capillaries. However, the two minute cycle is locally determined. In a closed capillary, the red cell supply has dropped appreciably and the muscle fibers are leaching the oxygen from the surrounding tissue. The timing phase is the time constant associated with this diffusive sink (similar to drainage from a single water well in a field). As the oxidation reaction goes on, its combustion byproducts pile up as carbon dioxide and various intermediaries. One of these, perhaps carbon dioxide or lactic acid building up to a threshold level, then triggers the capillary to open, recharging the capillary with blood and the region with oxygen.

3. Somewhat more specifically, Lundholm (5) has suggested that adrenaline acts to increase the lactic acid production in the cells with a resulting increased diffusion into the surrounding tissue, and that it is the lactic acid in the tissue fluid which produces the vasodilation. It is also possible that adrenaline acts simply to increase the cell oxidation rate, which would have the same effect. Interestingly enough, other metabolic byproducts have been similarly postulated to mediate blood flow in active organs. (Berne, for example, has proposed adenosine for the heart).

However, our key thought, that regardless of the local mechanism for control of blood flow, it is the oxygen choke that controls the metabolism level, has generally been well regarded.

For a single flow distribution system to permit local cyclic demand according to local power need likely requires that it be an adaptive control system in more than one sense. Up to this point, we have discussed the control in the 100 second time domain. There is evidence for regulation and control functions at other time domains, faster and slower.

At a faster time domain, there is an axial jitter in the red cell flux, likely related to what Krogh (3) called plasma skimming. At a rate of several cycles per second, there is a fluctuation in the number of blood cells per second passing a point in a given capillary. (This has been viewed in Bloch's movies of the microcirculation, see (6) for illustration; or see (7) for a popular view of the microcirculation and (8) for references on the microcirculation). At a branch point, the fluctuations appear in the division of cells between the two branches, although in longer time the stream will tend to divert from one branch to the other. It is likely these slower processes that represent Krogh's plasma skimming and one aspect of the 100 second cycle. It may be that this adaptive control cycle is built up from the higher frequency blood cell jitter, and thus not to be found in actual sphincter controlled opening and closing of arterioles. At present it has not been possible to

distinguish among the various processes.

It seems clear that the high frequency jitter is mediated by electrical forces. The 100 second cycle appears more likely mediated by an electro-chemical or more properly, a hormonal-electrical mechanism that digitally (i.e., in quantized fashion) monitors the red blood cell flux. It thus appears that the individual cell embarks on a trip through a capillary net very much like a ball in a pin-ball machine. The 'pins' are electrical-chemical interactions at the wall. The walls tend to act like electrical valves. In addition, pursuing the pin ball analogue, there may be sectional closure switchings, also electrically mediated, that more formally control passages or constrictions. It is a combination of such elements that provide an as yet unknown algorithm for an adaptive control that meters the oxygen, which is tied to the red blood cell carriers to the local muscles. One surmises that an electrical feedback system furnishes information on regional flow settings.

At a slower time scale, there is evidence that there exists an adaptive zonal control over the blood flow. This may be viewed as follows: The muscle motor elements fire only with a determinate statistical number per unit time, i.e., their number 'twinkles' at a 100 second time domain. While such action appears stochastic its propagation is not. There are conflicting demands of motor units in the vicinity that must be satisfied, and then there are the conflicting demands among major systems, i.e., the heart, liver, brain, kidney, GI tract, skeletal muscles, and the skin. To satisfy the systemic circulations, it appears likely that there is another ring oscillator model of control in the nervous system, at the level of the hypothalamus, that controls a near seven minute blood flow division among these various circulations. It appears plausible that the division is affected by resistance, say at the level of the arteriole sphincters. Thus it is likely that the control of blood flow is affected through this seven minute cycle. The flow shifts are most prominent in the circulation to the skin, and are probably known elsewhere as well (such as in the kidney). Seven minute temper-

ature cycles at the hypothalamus correlated with metabolism have suggested the likelihood of deep body temperature control as taking place at the hypothalamus. Thus it may be that the ring division of blood flow takes place on the basis of providing a control of heat exchange. (See experimental data in (9). Any zone thus has a mean blood flow, and mean oxygen flow provided to it, which, at slow operative levels, is sufficient to supply zonal oxygen need.

In addition to those adaptions of cyclic supply according to conflicting functions and modalities, there is yet another longer time adaptive growth control of the architecture of the distribution system which should be considered. One might question whether this can be considered adaptive control especially within the context of this symposium. Yet, it surely is when one considers that there is a viability in living systems which is characterized by a reversible adaption of distribution system numbers and sizes in time. From this point of view, growth adaption is certainly adaptive control to various modalities of living.

In the case of the microcirculation, or more generally also the arterial supply, growth control is reflected in the developmental architecture of the system. To describe the flow distribution system requires a geometric-topological architectural model. The need for such a model was originally stressed by Young (1809). As reported by Aperia (10), Young considered that the system of vessel ramifications...follows on the whole the same laws throughout the entire organism...After a certain independent course every vessel ramifies into two branches of the next stage. Thereby, a simple course for the length as well as for the cross-section of the different stages is stated. Corresponding pieces of the same stage of ramification show the same physical conditions."

In (1), a model was proposed that fits the anatomy, namely that a main arterial branch develops embryologically down the 'center' of each functional unit (the limbs are viewed as an excellent prototype), and that a topologically similar prototype is supplied at each subsequent level of subdivision. The prototype topological element

appears to be an elongated cylinder which is then divided into m sectors and n parallel slices. This subdivision into m n segments quickly transforms the large elongated cylinder into m n small pseudo-cylinders which can then be similarly subdivided in turn. This satisfied the topological needs for this system in providing it with flow distribution of a sufficient number of elements. The subdivision proceeds from the aorta with an internal diameter in the range of centimeters, to a normal large artery in the range of a centimeter, on down to arterioles in a range near 30 microns (o.003 cm.). A major essential property appears to be that the mean velocity is approximately constant in all arteries, which tends to fix the diameter at each subdivision. It is conceivable that the tubes grow in size to fulfill this condition by some sort of acoustic prescience..(Although biologists may commonly think in terms of hydrodynamic erosion, it is more likely that vibrational 'noise' acting on the local cellular wall structure may be a growth stimulus). However, the oxygen flux geometrically demands a proportioning between the diameter of the blood vessel required to supply the oxygen flux and the diameter per unit length of supplied tissue so that there is an apparent conflict between a first power law of artery diameter and length of the subdivision required for geometric similarity, and a two-thirds power law required topologically by gas distribution requirement. This is resolved in a fashion that would be understandable to the more practical minded plumber.

Tube runs are used in (i.e., they grow to) fairly customary lengths for each diameter, suitable for each level of subdivision. Any needed adjustments are made by branching around the main topological tree. Thus the tube runs which have not changed their length much between branches can be represented by a gross scatter (in a logarithmic presentation) around a first power law of variation of diameter with length of runs (11). A set of design laws for the distribution system can follow that will permit growth or degradation of supply tubes which can adapt to local use. Need for change might be illustrated in a demand for mild modification of the distribution system at various levels in response to a new pattern of muscular exercise.

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