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FLOW AND PRESSURE REGULATION IN THE CARDIOVASCULAR SYSTEM

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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,[5-8] textbooks,[9-12] or reviews.[13-23] Principles or descriptive fragments are offered here which may contribute to a model.

1. While the operating state of any causal chain 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-electric coupling, cellular complexes are competent to develop autonomous engines,[24] 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 embryonic heart discharges into tissue; the new blood flow courses as in a porous medium; it returns to the heart.[25] 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 semipermeable 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.[10,26]

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 (5g) 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[21]). 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[27] (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.[3,8,27] 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 LeChatelier'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 available 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."[20] Some eight rudimentary relations in the CV system under steady-state conditions are

$$M = h\Delta Q_{ox} \tag{1}$$

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,[28,29] 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.[30]

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.[31] Disregarding these detailed changes, a nominal constant h (4.8 kcal/ℓO_2) may be assumed for steady-state activity.

$$\Delta Q_{ox} = Q_b \Delta C \tag{2}$$

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,[7,28,30-32] the blood flow continues to change its distribution through local beds with a settling time of the order of seven minutes.[9,31,33]

$$Q_b = \Delta v/\tau \tag{3}$$

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 a 1-2 minute cycle of heart beat.[7,32]

$$R = (P_a - P_v)/Q_b \tag{4}$$

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 system 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 systemic 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,[10] 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).

$$\Delta p = \Delta v / C_a \tag{5}$$

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,[26] 40-60 mm Hg when young, 50-70 at old age as the compliance diminishes.

$$\Delta p \approx [(p_a - p_v)/RC_a]\ \tau \tag{6}$$

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

$$p_{sa} \approx \text{constant} \tag{7}$$

For most mammalia, the (mean) systemic arterial pressure is nominally 100 mm Hg.[26]

$$p_v \approx 0 \tag{8}$$

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.[9-11] 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.[23] (It is a fixed fraction of rest beat period in small mammals, and near constant for large.[34])

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.,

$$X = X_{00} + X_0 + X_1$$

X = any variable.

X_{00} = a developmentally programmed 'basic' (i.e., with a genetic base) component (if any) of the variable.

X_0 = 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).

$$\overline{(X)}_{00} = X_{00} + \overline{(X_0)}_{00}$$

$$\overline{(X)}_0 = X_{00} + \overline{(X_0)}_0 + \overline{(X_1)}_0$$

$$\overline{(X)}_1 = X_{00} + \overline{(X_0)}_0 + \overline{(X_1)}_1$$

$(\overline{X})_{00}$ = time average at rest (i.e., it is the current status at rest). When lacking data, $(\overline{X})_{00}$ may measure X_{00}. (No activity measure)

$(\overline{X})_0$ = time average over a long period (e.g., months), representing the current status. (Average activity measure)

$(\overline{X})_1$ = time average over a period of sustained steady state at current activity. (Current activity measure)

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

$$\tau = \tau_{00} + \tau_{po} - \tau_{so} - \tau_1$$

The existing heat period is made up of a developmental component τ_{00}, 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:

$$(\overline{\tau})_{00} \propto W^{1/4} \tag{1}$$

The intrinsic period τ_{00} of the isolated heart is a mammalian parameter that varies with animal weight W (The 00 weight of the animal is also developmentally programmed); from shrew to whale, it only changes from 800 to 8 beats per minute (bpm).

$$(\overline{Q_b})_{00} \propto W^{0.85 \pm 0.05} \text{ or } (\overline{q_b})_{00}$$

$$= [(\overline{Q_b})_{00}/W] \propto W^{-0.15 \pm 0.05} \tag{2}$$

This whole organism (or weight specific) relation for Q_b (or q_b), is *the developmentally programmed demand flow of tissue*.[26,35] 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/100g, 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/100g 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.[19,37]

A common belief is that the basal homeotherm state exhibits near constant heat production (and blood flow) per unit surface area M/A.[11] Note that

$$A \propto W^{2/3} \tag{3}$$

i.e., *surface area is nearly proportional to the 2/3 power of weight*,[8,36] implying a certain general geometric mammalian similarity. One might thus expect blood flow to be proportional to $W^{2/3}$ (Klieber[38] 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,[26,35] 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.

$$p_{voo} \approx 0 \tag{4}$$

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[9,39]) 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,[36] 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.[40] The resting aorta blood velocity $(\overline{V})_{oo}$ is a near-constant (about 15-20 cm/s). 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.

$$(\pi/4)\, D^2\, (\overline{V})_{oo} = (\overline{Q_b})_{oo} \propto W \qquad (5)$$

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

$$(\pi/4)\, (D/L)^2\, (\overline{V})_{oo} L^2 \propto W \qquad (6)$$

a law for the aortic length.

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_0 and mean pressure

$$(\overline{p_{sa}})_{oo} = 2\sigma_0\, (S/D) \qquad (7)$$

13. The metabolic concomitants of the law of the tissue are quite similar to those for blood flow

$$(\overline{\Delta Q_{ox}})_{oo} \propto W^{0.80 \pm 0.05} \text{ or } (\overline{\Delta q_{ox}})_{oo}$$
$$= [(\overline{\Delta Q_{ox}})_{oo}/W] \propto W^{-0.20 \pm 0.05} \qquad (8)$$

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 *an oxygen consumption law of the tissue*; and also

$$(\overline{M})_{oo} = (\overline{h})_{oo} (\overline{\Delta Q_{ox}})_{oo} \qquad (9)$$

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 dies. The 00 response of the heart is to grow in size ($\propto$ weight^{36}) so it can deliver a minimum $(\Delta v)_{oo}$ ($\propto W^{1.10}$). Δv must be at least as great.

$$\Delta v \geqslant (\overline{\Delta v})_{oo} = (\overline{Q_b})_{oo} \tau_{oo}$$

One can also imagine a 'design' resistance R_{soo} that develops on the basis of a minimum renal filtration pressure p_{koo}.

$$\overline{(R_s)}_{oo} \geqslant R_{soo} = (p_{koo} - p_{voo})/\overline{(Q_b)}_{oo}$$

$$p_{sa} \geqslant p_{koo} \approx 60 \text{ mm Hg}$$

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.[40] They have aorta rest velocity, $\overline{(V)}_{oo}$. 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. Semipermeable 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[41]; 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. Figure 1 – Q_b versus ΔQ_{ox}[8,22,26,42] – seems to be independent of athletic status, and nearly weight specific (Athletes may operate at a lower rest point than non-athletes.[23]); 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[31] 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.[42,43]

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[27]; but lesser net change over a near 60-day weight cycle); if 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.

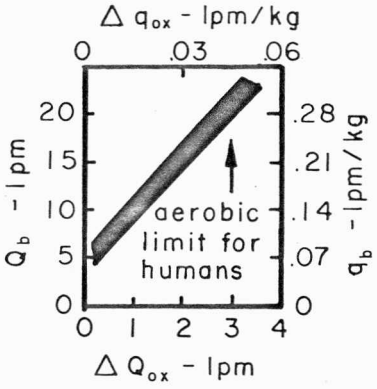

Fig. 1. Generalized human blood flow – oxygen uptake curve (independent of status).

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.[22,23] 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.)

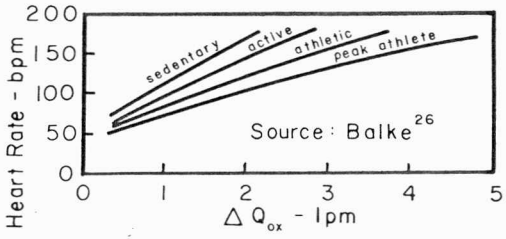

Fig. 2. Rate change with status.

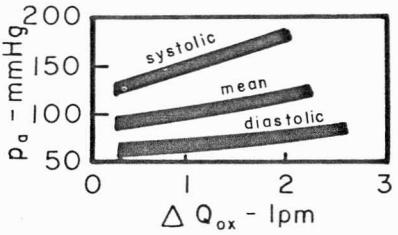

Fig. 3. Normal effects of exercise[22].

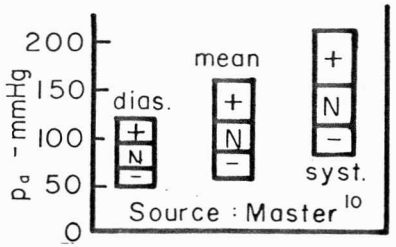

Fig. 4. Rest pressure, hypo (–) -, normo (N) -, hyper (+) -, tensives.

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},[28,30,44,45] and a 7-minute settling time for Q_b.[31,33] The former is also concomitant with red cell fluctuation in the capillaries,[46] and in a cyclic O_2 tissue pressure.[47]

There is some variation of heart rate, beat by beat, at a given activity (Scher,[7] Olmstead[32]), 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[10,48] (or Topham[7]) upon exercise or 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,[10] pp. 462, 199), heart rate rises with about a two-second delay. This is probably related to a ventilatory response.[45] 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,[10] 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_b, 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."[48]). As an independent issue, we consider high systemic pressure as governed independently from the fluid exchange systems.

Adding another noncontradictory 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 ($\bar{p}_{sa}$) 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.[48] (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[9] 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,[17] 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[49] found an average mean pulmonary pressure of 25 mm Hg at rest for human students living at 10,000 ft. During vigorous supine exercise, mean pressures were 35-115 mm Hg. One athletic girl showed 165/95. Steers at 13,000 ft, who had mean pulmonary pressures of 25-35 mm Hg at 5,000 ft, showed 55-110 mm Hg after six weeks. At nine weeks, deaths that occurred were due to congestive heart failures. (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,[5-8] 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 or 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.

$$v_b = C_{sa}\,[p_{ra} + Q_b R_s] + C_{sv}\,[p_{ra} - p_i]$$

$$+ C_{pa}\,[p_{pv} - p_i + Q_b R_p] + C_{pv}\,[p_{pv} - p_i]$$

$$Q_b = \frac{v_b - p_{ra}[C_{sa}+C_{sv}] - p_{pv}[C_{pa}+C_{pv}] + p_i[C_{sv}+C_{pa}+C_{pv}]}{C_{sa}R_s + C_{pa}R_p}$$

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 interpleural pressure as constant (e.g., $p_i = -4$ mm Hg), then we may write

$$Q_b = \frac{v_1 - p_{ra}C_s - p_{pv}C_p}{C_{sa}R_s + C_{pa}R_p} = \frac{p_{sa} - p_{ra}}{R_s}$$

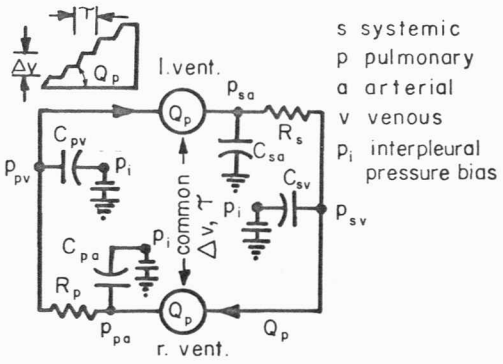

Fig. 5. Simplified equivalent linear network for the cardiovascular system.

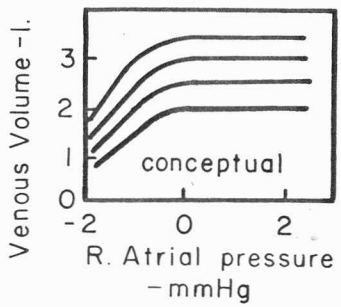

Fig. 6. Filling curves of systemic veins (at different autonomic excitations).

Differentiate to determine the sensitivity of change of p_{ra} and p_{pv} to change in Q.

$$\frac{\Delta Q}{\Delta p_{pv}} = \frac{-C_p}{C_{sa}R_s + C_{pa}R_p}$$

$$\frac{\Delta Q}{\Delta p_{ra}} = \frac{-C_s}{C_{sa}R_s + C_{pa}R_p}$$

$$C_s \approx \frac{100\text{ cc}}{40\text{ mm}} + \frac{100\text{ cc}}{2\text{ mm}} = 52.5\ \frac{\text{cc}}{\text{mm}}$$

$$C_p \approx \frac{100\text{ cc}}{30\text{ mm}} + \frac{100\text{ cc}}{5\text{ mm}} = 23\ \frac{\text{cc}}{\text{mm}}$$

$$C_{sa} = \frac{100\text{ cc}}{40\text{ mm}} = 2.5\ \frac{\text{cc}}{\text{mm}}$$

$$C_{pa} = \frac{100\text{ cc}}{30\text{ mm}} = 3\ \frac{\text{cc}}{\text{mm}}$$

$$R_s = \frac{100\text{ mm}}{7\text{ lpm}}$$

$$R_p = \frac{8\text{ mm}}{7\text{ lpm}}$$

$$\frac{\Delta Q}{\Delta p_{ra}} = \frac{-52.5}{(2.5 \times 100)/7 + (3 \times 8)/7}$$

$$\frac{\Delta Q}{\Delta p_{pv}} = \frac{-23}{[\,''\,]} = \frac{-7\text{ lpm}}{12\text{ mm Hg}}$$

Using human constants, these sensitivities indicate the change in venous pressures that would result from quasistatic changes in flow (here at

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 determined 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 00 component).

The circuit analysis, of what will occur if there are various flow demands put on the volume, shows

$$Q_b = \frac{v_3 - C_s p_{ra}}{R_s C_{sa} + R_s C_{pa}} = \frac{v_3}{[\,'']} - \frac{p_{ra}}{R_s C_{sa} + R_p C_{pa}} \approx \frac{v_3}{[\,'']} - \frac{p_{ra}}{R_s C_{sa}/C_s}$$

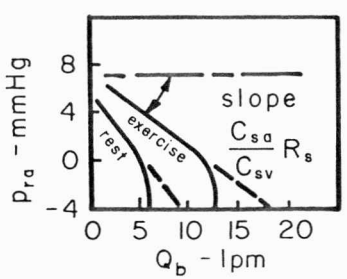

Fig. 7. Right atrial "venous return" curves.

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 a 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[17]), 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

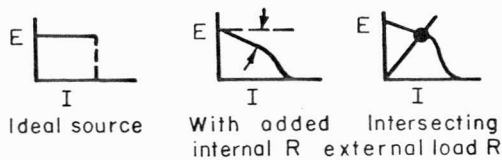

Fig. 8. Illustrating a 'pump' characteristic.

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 characteristic, 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.

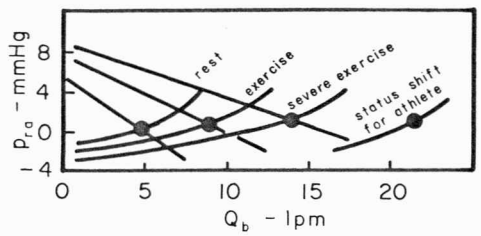

Fig. 9. "Cardiac output" curves.

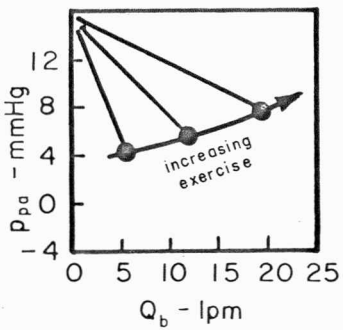

Fig. 10. Left atrial "venous return" curves.

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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References

[1] R. Schoenheimer, *The Dynamics of Body Constituents* (Harvard U.P., Cambridge, Mass., 1942).
[2] W. Cannon, *The Wisdom of the Body* (Norton, New York, 1939).
[3] A. Iberall in C. Waddington (Ed.), *Towards a Theoretical Biology*, 2. Sketches (Aldine, 1969); A. Iberall and W. McCulloch, Trans. ASME, J. Basic Eng. **91**, 290 (1969).
[4] A. Iberall and S. Cardon, Ann. N.Y. Acad. Sci. **117**, 445 (1964).
[5] F. Grodins, Quart. Rev. Bio. **34**, 93 (1959).
[6] A. Guyton, *Cardiac Output and Its Regulation* (Saunders, Philadelphia, 1963).
[7] E. Reeves and A. Guyton (Eds.), *Physical Basis of Circulatory Transport* (Saunders, Philadelphia, 1967).
[8] E. Bloch, S. Cardon, A. Iberall, D. Jacobowitz, K. Kornacker, L. Lipetz, W. McCulloch, J. Urquhart, M. Weinberg, F. Yates, "Introduction to a Biological Systems Science," NASA CR 1720 (1971).
[9] D. Gregg in C. Best, N. Taylor (Eds.), *The Physiological Basis of Medical Practice* (Williams and Wilkins, Baltimore, 1961).
[10] R. Rushmer, *Cardiovascular Dynamics* (Saunders, Philadelphia, 1961).
[11] T. Ruch and H. Patton, *Physiology and Biophysics* (Saunders, Philadelphia, 1965).
[12] R. Berne and M. Levy, *Cardiovascular Physiology* (Mosby, St. Louis, 1967).

[13]E. Landis and J. Hortenstine, Physiol. Rev. **30**, 1 (1950).
[14]B. Folkow, Physiol. Rev. **35**, 629 (1955).
[15]C. Heymans and E. Neil, *Reflexogenic Areas of the Cardiovascular System* (Churchill, 1958).
[16]L. Eichna and D. McQuarrie (Eds.), Physiol. Rev. **40**, Suppl. 4 (1960).
[17]W. Hamilton and P. Dow (Eds.), *Handbook of Physiology*, Sec. 2 Circulation (Williams and Wilkins, Baltimore, 1962,3,5), Vols. I-III.
[18]S. Mellander and B. Johansson, Pharmocol. Rev. **20**, 117 (1968).
[19]S. Mellander, Ann. Rev. Physiol. **32**, 313 (1970).
[20]J. Herd, Ann. Rev. Physiol. **32**, 289 (1970).
[21]O. Gauer, J. Henry, and K. Behn, Ann. Rev. Physiol. **32**, 547 (1970).
[22]A. Carlsten and G. Grimby, *The Circulatory Response to Muscular Exercise in Man* (Thomas, 1966).
[23]V. Karpman and G. Kukolevskiy, "The Heart and Sports," NASA TTF-662 (Feb. 1971).
[24]B. Goodwin, *Temporal Organization in Cells* (Academic, New York, 1963).
[25]F. Mall, Amer. J. Anat. **5**, 227 (1905).
[26]P. Altman and D. Dittmer (Eds.), *Respiration and Circulation* (FASEB, 1971).
[27]A. Iberall and S. Cardon, Bioph. J. Abst. **8**, Soc. Abst. MD1 (1968); S. Cardon and A. Iberall, Curr. Mod. Bio. **3**, 237 (1970).
[28]C. Lenfant J. Appl. Physiol. **22**, 675 (1967).
[29]S. Nicolaïdis, Ann. N.Y. Acad. Sci. **157**, 1176 (1969).
[30]A. Iberall, Trans. ASME, J. Basic Eng. **82**, 92, 103, 513 (1960).
[31]D. Costill, J. Appl. Physiol. **28**, 251 (1970).
[32]A. Iberall and S. Cardon, NASA CR 219 (May 1965).
[33]L. Brouha, P. Smith, R. DeLanne, and M. Maxfield, J. Appl. Physiol. **16**, 133 (1960).
[34]E. Lepeschkin, Ann. N.Y. Acad. Sci. **127**, 170 (1965).
[35]A. Iberall and W. Weinberg, Biophy. Soc. Abst. **11**, 161a (1971).
[36]J. Holt, E. Rhode, and H. Kines, Am. J. Physiol. **215**, 704 (1968).
[37]R. Forsyth, A. Nies, F. Wyler, J. Neutze, and K. Melmon, J. Appl. Physiol. **25**, 736 (1968).
[38]M. Klieber, Physiol. Rev. **27**, 511 (1947).
[39]A. Iberall and S. Cardon, NASA CR 141 (Jan. 1965).
[40]A. Iberall, Math. Biosci. **1**, 375 (1967).
[41]W. Redisch, F. Tangco, and R. Saunders, *Peripheral Circulation* (Grune and Stratton, 1957).
[42]B. Saltin, G. Blomqvist, J. Mitchell, R. Johnson, K. Wildenthal, and C. Chapman, Circ. Suppl. VII to *XXXVII-XXXVIII*, VII-1 (1968).
[43]B. Ekblom, P. Åstrand, B. Saltin, J. Stenberg, and B. Wallström, J. Appl. Physiol. **24**, 518 (1968).
[44]L. Goodman, Trans. IEEE, Biomed. Eng. **13**, 67 (1966).
[45]P. Dejours, *Respiration* (Oxford, 1966).
[46]S. Cardon, C. Oestermeyer, and E. Bloch, Microvasc. Res. **2**, 67 (1970).
[47]W. Whelan and P. Nair, Am. J. Physiol. **218**, 973 (1970).
[48]B. Bevegård and J. Shepard, Physiol. Rev. **47**, 178 (1967).
[49]R. Grover, Ann. N.Y. Acad. Sci. **127**, 632 (1965).