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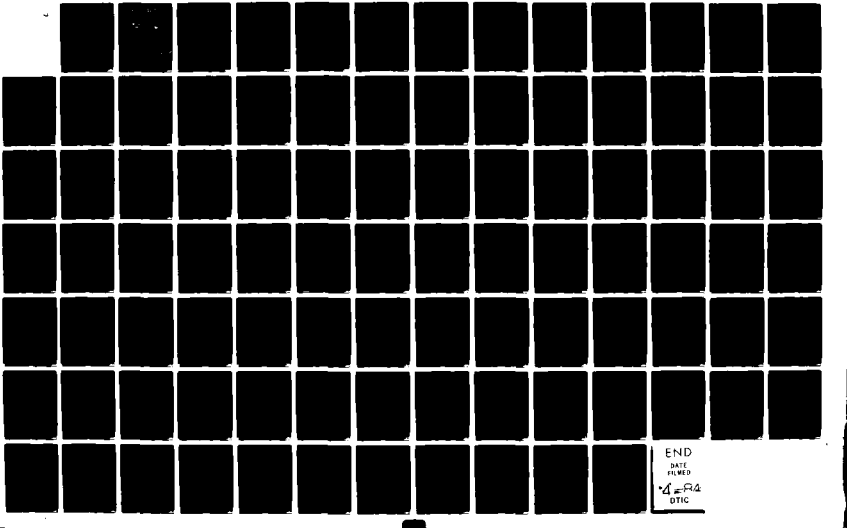

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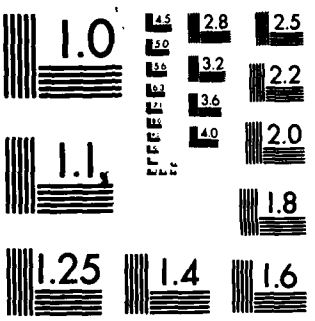

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A NON-DIMENSIONAL ANALYSIS OF CARDIO-VASCULAR RESPONSE TO COLD STRESS: PART I, IDENTIFICATION OF THE PHYSICAL PARAMETERS THAT GOVERN THE THERMO-REGULATORY FUNCTION OF THE CARDIO-VASCULAR SYSTEM.

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NAVAL MEDICAL RESEARCH AND DEVELOPMENT COMMAND

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Whether in combat-type situations, or during peace-time, Man constantly strives to increase the envelope of human performance capabilities. One environmental factor that appears to seriously impede such capabilities is the ambient temperature within which the performance takes place. Cold stress and/or the consequences of hypothermia can lead to adverse effects that range from severe impairment of physiological function to death, itself.

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The prevailing belief today is that vascular changes and tissue hypoxia are directly responsible for all types of local cold injury, and that variation in the clinical features or manifestations reflects variation in the nature of the insult and the host response. With this in mind, this study has examined the human cardiovascular system in terms of its four basic elements: The fluid (blood), the pump (Heart), the flow pipes (vascular system), and the control mechanisms (intrinsic factors, the central and autonomic nervous systems, and the endocrine system). Then, cardiovascular thermoregulation has been described in terms of how each of these elements responds to cold stress, with the ultimate intent of performing a non-dimensional analysis of this response. As a first step towards such an analysis, some 400 physical and chemical parameters that govern the thermoregulatory function of the cardiovascular system have been identified. These can then be grouped into dimensionless variables that: (i) shed considerable light on the physics of the problem at hand; (ii) constitute the basis for making simplifying assumptions in the formulation of subsequent mathematical analyses; and, (iii) bring to the surface the important parameters that need to be measured when performing experiments on physiological responses to environmental insults.

TABLE OF CONTENTS

A Non-Dimensional Analysis of Cardiovascular Response To Cold Stress

PART I: Identification of the Physical Parameters that govern the Thermoregulatory Function of the Cardiovascular System.*

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Introduction

In principle, the physiologic response to cold stress is rather straightforward: By means of a variety of feedback control regulatory mechanisms, the human organism attempts to decrease heat loss to the environment, while at the same time increasing the heat produced by its various subsystems. These might be termed first-order effects, or responses that transpire as a direct consequence of, and in an effort to protect the organism from, exposure to extremely cold temperatures. While intended to stabilize body core temperature with the ultimate intent of keeping the organism alive, these first-order responses do, unfortunately, have associated with them, second-order consequences, or, "spin-offs", if you will, that significantly affect man's ability to perform or function effectively in a cold environment. So dramatic are some of these consequences that the human body--in an attempt to keep itself from freezing to death--may, ironically, very well kill itself by another mechanism, such as uncontrolled dehydration, frost-bite, gangrene, cardiac arrest, renal failure, liver failure, and a variety of

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*Note: This work was accomplished while the author was in residence at the Naval Medical Research Institute, Bethesda, Maryland, as a summer faculty Research Fellow under the ONR/ASEE Program.

other ailments or afflictions that may be precipitated by the human response to cold stress.

Because man's performance is so greatly restricted in the cold environment, and because so many pathologic conditions may result from the human response to cold stress, and because so little is known about either the physiology of temperature regulation or the means for counteracting the adverse consequences of exposure to very low temperatures, this study was initiated. Its goal is to establish a rational basis for ultimately developing a comprehensive program to study, evaluate, and, hopefully, solve a very serious problem.

The Role of the Cardiovascular System in Temperature Regulation

The average student of physiology is generally well-versed and trained to understand the metabolic function of the cardiovascular system. Blood is, indeed, the river of life--bringing nutrients, oxygen and other biochemical supplies to all the cells of the body while continuously removing carbon dioxide and other toxic waste products. By comparison, the thermoregulatory function of the cardiovascular system receives much less emphasis, and the student comes away from a physiology course with little appreciation for how important this role really is in terms of the sustenance of life.

When one envisions the anatomical configuration of the vascular network of pipes and channels through which the blood flows as it courses through the body, and compares this anatomy with, for example, the radiator of an automobile, the potential for thermoregulation afforded by the cardiovascular system becomes immediately obvious. Like water in a radiator, blood in the physiologic system can absorb the heat

generated by the complex chemical reactions of life; and, like water in a radiator, blood can carry (convect) this heat to the surface of the organism to be expelled to the environment. Indeed, various estimates suggest that as much as 95% of the heat generated by the body at any given time flows to the surface (skin) through vascular convection. Conversely, this thermoregulatory role can be reversed when heat is to be conserved by the body. Again, acting like the thermostat in the radiator of an automobile (which keeps the engine coolant away from the heat-dissipating surface area when the engine is cold), vascular smooth muscle tissue can completely shut off (or significantly reduce) flow to the periphery when this becomes necessary to maintain core temperature.

Even its metabolic function is not totally independent of the role of the cardiovascular system in thermoregulation. Many of the processes which are called upon to generate additional heat at a time of need are controlled by biochemical constituents (hormones, enzymes, substrates, "activating" factors, and so on) which are brought to their site of utilization by the mass transport capabilities of this river of life. Thus, although the human cardiovascular system is by no means the only regulator of body temperature, it is certainly the most important one in the sense of decreasing heat loss to the environment, and it plays a prominent role also in those processes whereby additional heat is produced during cold stress. Moreover, its very temperature, as monitored by the hypothalamus, acts further as a triggering mechanism for many thermoregulatory responses. For these and many other reasons, cardiovascular response to cold stress deserves careful attention--which is the rational for the analysis that follows.

The choice of a preliminary non-dimensional approach exploits a very powerful technique for grasping the fundamental features and essential physics of a problem before attempting a more complicated mathematical formulation. That is to say, the approach first identifies as many as possible of the control variables known to affect or be involved in determining the value of a certain parameter of state (say, core body temperature, T_c); and then it groups these into dimensionless quantities that represent ratios of forces, time scales, and so on. The values of these ratios allows one to draw significant conclusions concerning the relative importance of each of the original control variables in affecting the parameter of state under consideration. While shedding considerable light on the physics of the problem, such conclusions also constitute the basis for making simplifying assumptions in the subsequent mathematical analysis--and--they bring to the surface the important parameters that need to be measured when doing experiments on physiological responses to environmental insults.

Bearing all of this in mind, the cardiovascular system may be identified in terms of four basic elements: The Fluid (Blood), the Pump (Heart), the Flow Pipes (Vascular Channels), and the Control System (Central Nervous System, Autonomic Nervous System, Endocrine System, and Intrinsic Factors)-- and cardiovascular thermoregulation may be viewed in terms of how each of these responds to cold stress. Taking body core temperature, T_c, to be the <u>dependent</u> variable, our first objective is to identify as many as possible of the independent control variables that affect T_c through the cardiovascular system; in particular, through the four basic elements of the cardiovascular system as they relate to total blood flow and its distribution in the body. Let us examine

them one by one as we seek to establish our list of control variables that influence cardiovascular response to cold stress.

The Fluid: Blood

There are three basic things one needs to know about Blood in order to assess its role in control of body temperature:

(i) To what extent is the fluid capable of carrying heat?

(ii) To what extent is the fluid capable of, or actually carrying biochemical constituents that are involved in thermoregulation via alternate physiologic processes (metabolic function)?

(iii) With what ease can the fluid be pumped through the vascular system (one of the determinants of flow)?

(i) The ability (or lack thereof) of blood to carry heat depends upon at least the following variables:

a) Its own temperature, T_B, °C, relative to the temperature, T_E, of the environmental surroundings. Heat transfer is a physical process that is driven by a gradient in temperature between two contiguous regions in space. The transfer normally takes place from the region of higher temperature to the region of lower temperature, with a rate that depends on the temperature difference, $T_B - T_E$. Thus, if $T_E > T_B$, heat is transferred to the fluid; if $T_E < T_B$, heat is transferred to the environment from the fluid; if $T_E = T_B$, an equilibrium situation prevails; and depending on $T_B - T_E$, more, or less heat per unit time will pass between the fluid and its environment.

b) Its thermal conductivity, k_t, in Btu/hr-ft-°F, or

cal/sec-cm-°C, or Watts/cm-°C. This physical property of materials defines the heat flux (i.e., heat transferred by conduction per unit area of contact between two contiguous regions in space) per unit temperature gradient between the regions. The thermal conductivity depends, in turn, upon the specific heat, c_v(Btu/lb_m-°F or cal/gm-°C) of the fluid at constant volume, the dynamic viscosity, μ_a (Poise=dynes-sec/cm^2, or, grams/cm-sec) of the fluid at a given rate of shear, and a dimensionless proportionality constant, i (called the "arrangement factor"), which takes into account the <u>way</u> in which energy is stored in the fluid, according to the relation:

$$k_t = i c_v \mu_a$$

Multiplying both sides of the equation above by fluid mass density, ρ_f, (gms/cm^3) yields:

$$\rho_f k_t = i c_v \rho_f \mu_a \quad \text{, and, rearranging,}$$

$$\frac{k_t}{\rho_f c_v} = \frac{i \mu_a}{\rho_f} = \alpha$$

The quantity, $\rho_f c_v$, having units of cal/cm^3-°C, is defined to be the thermal capacitance of blood, and, when multiplied by total blood volume, V_B, gives the total thermal capacity, C(cal/°C) of the fluid:

$$C = \rho_f V_B c_v$$

The quantity, α, having units of cm^2/sec (the same as kinematic viscosity, $\nu_f = \mu_a/\rho_f$) is called the thermal diffusivity

of the fluid. Thus,

$$\alpha = \nu_f = \frac{k_t V_B}{C} .$$

Finally, introducing the dimensionless specific heat ratio, $\gamma = \frac{c_p}{c_v}$, where c_p is the specific heat of the fluid at constant pressure,

$$k_t = \frac{\mu_a c_p}{\gamma} , \text{ or, } \frac{c_p \mu_a}{k_t} = \frac{\gamma}{\ell} = Pr,$$

the Prandtl Number, which is a very important parameter in heat transfer.

c) Its mass density, ρ_f (gms/cm^3), to the extent discussed in (b) above and later in this report.

d) Total Blood Volume, V_B(liters), to the extent discussed in (b) above and later in this report.

e) Blood pressure, p, (dynes/cm^2 or mm Hg).

f) Where radiation may be important, the dimensionless emissivity, ε, of the fluid.

g) Where convection may also play an important role, the convection conductance, or coefficient, h, expressed in terms of the units Btu/hr-ft^2-°F and sometimes called the surface or film coefficient.

h) The mean velocity of blood flow, v (cm/sec), to the extent that there is a time scale associated with the propagation and transfer of thermal energy to or from a conducting medium, and mass across a membrane. The velocity of blood flow and its convective interactions with the vascular surface are discussed further in sections (ii) and (iii) below, as well as in later sections dealing with the pump, the flow pipes and

the control system. Our concern here is more with specific blood properties and with the way in which these may be affected by the chemical composition of the fluid, its thermodynamic state, and time, t. Unfortunately, such effects are still largely unexplored and not clearly defined, but worthy of much future research. In particular, physical variables associated with the non-Newtonian, anisotropic, viscoelastic characteristics of blood need to be examined in greater detail to the extent that they influence the ability of the fluid to transport heat. Some of these variables are listed below.

i) The dimensionless non-Newtonian index, n, of the fluid. As a fluid, blood shows stress-strain-rate behavior that is characteristically Pseudoplastic. That is to say, it obeys a constitutive equation of the form:

$$\tau = k_c \dot{\xi}^n$$

where τ = fluid shearing stresses (dynes/cm^2), $\dot{\xi}$ = Strain Rate in the fluid (sec^{-1}), k_c = the consistency index of the fluid (the units of this parameter are defined in terms of the variables in the equation above), and n = the dimensionless non-Newtonian index of the fluid. If the fluid is Newtonian, n = 1, $k_c \rightarrow \mu_a$, and the equation above reduces to the famous linear stress-strain-rate relationship:

$$\tau = \mu_a \dot{\xi}$$

Equating the two relationships for stress, $k_c \dot{\xi}^n = \mu_a \dot{\xi}$, allows one to define an "apparent viscosity", μ_a, for non-Newtonian

fluids:

$$\mu_a = k_c(\dot{\xi})^{n-1}$$

The "apparent viscosity" defines the resistance to flow that a fluid "appears" to offer at a given rate of shear. For Newtonian fluids (n=1) this resistance is constant ($\mu_a = k_c$ = constant), independent of the shear rate. For pseudoplastic fluids (of which blood is an example) this resistance decreases with increasing shear rate, a behavior characterized by values of n less than unity.

j) The consistency index, $k_c\left(\frac{\text{dynes - sec}^n}{\text{cm}^2}\right)$ of blood, as defined in section (i) above. This is a measure of the "viscous" nature of the fluid, although "viscosity", per se, has no real meaning for a non-Newtonian fluid.

k) The yield stress, τ_y, of blood, expressed in dynes/cm^2. It is rather well-known fact that blood also displays characteristics of a Bingham Plastic fluid, in the sense that deformation and flow are manifest only if the shear stress exceeds some critical value, τ_y, called the "yield stress" of the material. It is further known that the presence of a yield stress may be attributed directly to the protein Fibrinogen, since not only does τ_y vanish in de-fibrinogenized blood, but, also, τ_y increases in direct proportion to the concentration, [F], in mg% (mg/100 ml whole blood) of Fibrinogen in the fluid. One may add the latter, then, to the list of variables being developed for further analysis.

l) One may also add to the list the Hematocrit, H, of blood--

defined to be the percentage by volume of Red Blood Cells in whole blood. Both the non-Newtonian index, n, and the consistency index, k_c, are very sensitive functions of Hematocrit. The non-Newtonian index, n, decreases linearly (i.e., becomes more and more pseudoplastic) with increasing hematocrit, H, according to the relation:

$$n = 1.00 - C_1 H$$

where C_1 is a dimensionless, species-specific constant. The consistency index, k_c, increases exponentially with hematocrit, but in a manner that depends also on the concentration in the fluid of the sum of Fibrinogen, [F], plus the Globulins, [G]. This sum may be designated as Total Protein, [P], minus Albumin, [A], written TPMA, since:

$$[P] = [F] + [G] + [A]$$

The variation of k_c with H and TPMA follows the relationship:

$$k_c = C_2 e^{C_3 H} e^{C_4 \frac{TPMA}{H^2}}$$

where, again, C_2, C_3 and C_4 are species-specific constants. C_3 is dimensionless, C_4 has units of a reciprocal concentration, ml/mg, and C_2 has the same units as k_c(dynes-sec^n/cm^2). Note that for high Hematocrits, $\frac{TPMA}{H^2} \to 0$ (H in per cent), $k_c \to C_2 e^{C_3 H}$, and Hematocrit dominates the fluid behavior. For low hematocrits, $e^{C_3 H} \to 0$, $k_c \to C_2 e^{(TPMA) C_4 / H^2}$ and the TPMA concentration plays a more prominent role in the fluid mechanics of blood.

Hematocrit is also an important variable to the extent

that red blood cells carry oxygen, which is an important raw material for generating additional heat during exposure to cold stress. We may thus add to our growing list the partial pressure of oxygen in blood, pO_2, in dynes/cm^2 or mm Hg, and the Hemoglobin concentration [Hb], gm% or grams per 100 ml of whole blood.

m) To complicate matters <u>still</u> further, blood also exhibits time-dependent properties characteristic of the class of fluids termed thixotropic. That is to say, under cyclic loading the resistance to deformation offered by the fluid seems to decrease not only with increasing shear rate (a pseudoplastic effect) but also with time as the number of loading cycles increases (a thixotropic effect). Thixotropy can be attributed to the physical characteristic of stress-relaxation that such visco-elastic materials exhibit. One parameter used to define stress-relaxation, which follows a general relationship of the form:

$$\frac{\tau}{\tau_\infty} = 1 - e^{-\lambda t}$$

is the relaxation time constant, λ, which, like shear rate, has units of reciprocal seconds, sec^{-1}. Note that as $t \to \infty$, $\tau \to \tau_\infty$, some asymptotic limiting value which is less than τ at any given time, t (as is obvious from the form of the governing equation).

Pseudoplastic behavior is a function of the <u>spatial</u> gradient in shear to which a fluid is subjected; whereas Thixotropic behavior is a function of the <u>temporal</u> gradient in

shear to which the fluid is exposed. Thus, corresponding to the parameters k_c and n which define fluid behavior in terms of the ratio of stress to spatial strain rate, one can also define a viscoelastic complex modulus, $E_r(t)$, as a parameter which defines fluid behavior in terms of the ratio of stress to temporal strain rate, $\dot{\varepsilon}$:

$$E_r(t) = \frac{\tau(t)}{\dot{\varepsilon}(t)}$$

If the temporal strain rate applied is sinusoidal, $\dot{\varepsilon}(t) = |\dot{\varepsilon}(t)|e^{j\omega t}$, the resulting stress will be of the form: $\tau(t) = |\tau(t)|e^{j(\omega t-\phi)}$, where ϕ is some phase lead angle. Then:

$$E_r(t) = \frac{|\tau(t)|}{|\dot{\varepsilon}(t)|} e^{-j\phi} = |E_r(t)|\{\cos\phi - j\sin\phi\}$$

The quantity: $\frac{|\tau(t)|}{|\dot{\varepsilon}(t)|}\cos\phi$ is called the Dynamic Elastic Modulus, $E_d(t)$ of the viscoelastic material, and,

The quantity: $\frac{|\tau(t)|}{|\dot{\varepsilon}(t)|}\sin\phi$ is called the Dynamic Viscous Modulus, $E_j(t)$ of the viscoelastic material.

The magnitude $|\dot{\varepsilon}(t)|$ can be taken to be equal to fluid strain rate $\dot{\xi}$, giving the complex modulus the same units as fluid viscosity, but keeping it time dependent. Similarly, the Dynamic Elastic Modulus and the Dynamic Viscous Modulus have time-dependent values with units of viscosity. The phase angle, ϕ, is a function of circular frequency, ω (radians/sec), which, in turn is a function of linear frequency, $\omega = 2\pi f$. This introduces still another variable to our list, i.e., the

pulse rate, f (cycles per second or beats per minute) at which blood is being driven through the cardiovascular system.

The frequency-dependent complex modulus for blood defines its thixotropic behavior, which includes such features as stress-relaxation, creep and hysteresis.

n) To the extent that they may affect the heat-carrying capacity of blood, the concentrations of certain chemical constituents should also be added to the list of variables affecting the thermoregulatory response of the cardiovascular system to cold stress. These will be discussed further below, but are mentioned here, also, in passing. They include hydrogen ion concentration (alkalinity or acidity, pH), and the concentrations of several endocrine hormones, central nervous system factors, electrolytes, enzymes, blood gases and nutrients.

By now it should be obvious that the alteration of a single factor or parameter in physiologic systems is not always associated with just one resulting effect. For example, alterations in the mechanical properties of blood contribute to its thermoregulatory function in <u>all three</u> of the categories identified earlier--they affect the ability of the fluid to store and exchange heat efficiently with body tissues, they affect its mission as a mass-transport carrier, and they affect the ease with which the fluid can be pumped. The challenge to the researcher, however, is to distinguish between the <u>first-order</u> effects that <u>directly</u> result from the alteration being examined, and <u>second-order</u> effects that are spin-offs or consequences of the first-order results. This is a concept frequently overlooked by investigators, to wit: imagine a row

of dominoes lined up and standing close to one another. If one knocks over the first domino, he or she will start a chain reaction that will eventually cause all of the dominoes to fall. But all the individual did was to knock over the first domino (first-order, or primary effect); the others fell as a consequence of that action (second-order, or cascading effect). Indeed, the individual never even touched or, for that matter, even was aware of the existence of the other dominoes in the line. Frequently, in physiological research, an investigator will observe several outcomes of a particular experimental procedure-- and report these as if they are all due to the specific procedure (even though some of them may be consequences of, rather than due to the procedure). This is one aspect of such research that frequently confuses the issue and makes the understanding of physiological response mechanisms more complicated than it may need to be. It also seems to be particularly prevalent in the literature that deals with man's response to the cold environment--at least as far as this author has been able to ascertain.

(ii) The extent to which blood is capable of, or actually carrying biochemical constituents that are involved in thermoregulation via alternate physiologic processes depends on at least the following variables:

a) The concentration, $[S]_B$ mass/unit volume, of biochemical species [S] in the blood, relative to its concentration $[S]_E$ in the extravascular environment. As is heat transfer driven by a gradient in temperature between two contiguous regions in space, so is mass transfer driven (in general) passively by a

gradient in species concentration between two contiguous regions in space. The transfer normally takes place across a capillary membrane from the region of higher concentration to the region of lower concentration, at a rate that depends on the concentration difference, $[S]_B - [S]_E$. Thus, if $[S]_E > [S]_B$, mass tends to want to be transferred from the extravascular space into the blood (and will be if conditions otherwise allow it--see later). On the other hand, if $[S]_B > [S]_E$, mass will tend to be transferred from the blood into the extravascular space, and if $[S]_B = [S]_E$, an equilibrium situation will prevail. In each case, depending on $[S]_B - [S]_E$, and assuming no active transport processes or driving forces other than a chemical concentration gradient, more, or less mass per unit time will pass between the fluid and its environment.

The kinds of mass involved when one speaks of thermoregulation are: Endocrine Hormones; Central Nervous System Chemical Releasing Factors (CRF); Various Electrolytes, Certain Enzymes and/or Co-Factors; Blood Gases; Hydrogen ions (pH); Nutrients (Proteins, Fats Carbohydrates); and other by-products of metabolism (e.g., Nitrogen, Carbon Dioxide, Lactic Acid, etc.). Thus, at any given time, S may stand for:

1. Thyrotrophin Releasing Hormone (TRH, from Hypothalamus),
2. Corticotrophin Releasing Factor (CRF, from Hypothalamus),
3. Growth Hormone Releasing Factor (GHRF, from Hypothalamus),
4. Growth Hormone Release Inhibiting Hormone, or Somatostatin, (GHRIH, from Hypothalamus),

5. Adrenocorticotrophic Hormone (ACTH, from Pituitary),
6. Thyrotrophin (from Pituitary), (TSH=Thyroid Stimulating Hormone),
7. Somatotrophin, or Growth Hormone (GH, from Pituitary),
8. Antidiuretic Hormone, or Vasopressin (ADH, from pituitary),
9. Insulin (from Pancreas),
10. Glucagon (from Pancreas),
11. Aldosterone (from Adrenal),
12. Deoxycorticosterone (from Adrenal),
13. Cortisone (from Adrenal),
14. Hydrocortisone, or Cortisol (from Adrenal),
15. Corticosterones "A", "B", or "S" (from Adrenal),
16. Epinephrine, or Adrenalin, or Adrenine (from Adrenal),
17. Norepinephrine, or Noradrenalin, or Arterenol (from Adrenal),
18. Thyroxin (from Thyroid Gland),
19. Triiodothyronine (from Thyroid Gland),
20. Thyrocalcitonin (from Thyroid Gland),
21. Parathormone (from Parathyroid Glands),
22. Calcitonin (from Parathyroid Glands),
23. Renin (Enzyme from the Kidneys),
24. Angiotensin I and II (in Blood),
25. Serotonin (from Gastrointestinal Tract),
26. Dopamine (an intermediary in the manufacture of epinephrine and norepinephrine from Tyrosine),
27. Dopamine-Beta-Hydroxylase (an enzyme that converts

Tyrosine into the precursor of Dopamine, Dopa),

28. Blood Gases - Oxygen and Carbon Dioxide,

29. Hemoglobin,

30. Lactic Acid,

31. Hydrogen ion concentration (pH),

32. Plasma Electrolytes: Calcium, Chlorine, Magnesium, Potassium, Sodium, Phosphorus,

33. Blood Urea Nitrogen (BUN),

34. Blood Carbohydrates, Glucose,

35. Histamine and Immunoglobulins IgA, IgG and IgM,

36. Plasma Proteins: Albumins, Globulins, Fibrinogen, Total, and Amino Acids,

37. Buffering Ions: Phosphate, Sulfate, Bicarbonate, Ammonium,

38. Enzymes: Phosphatases (Acid, Alkaline), Transaminases (Serum Glutamic-Oxalacetic Transaminase, SGOT, Serum Glutamic-Pyruvic Transaminase, SGPT), Dehydrogenases (lactic, LDH, isocitric, ICD, glucose-6- α-hydroxybutyric, HBD, Maleic, MDH, Glutamic, GDH), Amylase, Lipase, LPP, Aldolase, Creatinine Phospokinase, CPK, ornithine Carbamyl Transferase, OCT, Guanase, Ceruloplasmin, Cholinesterase, etc.,

39. Lipids and Fatty Acids, Free Cholesterol, Esterified Cholesterol, Total Cholesterol, Triglycerides, Phospholipids, Total Lipids,

40. Trace Elements: Copper, Zinc, Manganese, Iron, Chromium, Iodine (PBI), Cobalt, Molybdenum, Cadmium, Selenium,

Lithium, Fluoride, Sulfur, etc.,

41. Bilirubin, Creatine, Creatinine,

42. Vitamins and Coenzymes: A, B_1 (Thiamine), B_2 (Riboflavin), B_3 (Niacin), B_5 (Pantothenic Acid), B_6 (Pyridoxine), B_{12}, Folic Acid, Biotin, Para-amino Benzoic Acid (PABA), C (Ascorbic Acid), D, E, K, Choline, Inositol, Rutin, Hesperidin,

43. Any other biochemical constituent concerned with the maintenance of body temperature. Blood must be capable of picking up, transporting and delivering these substances to their respective "target organs" or sites of action, and dropping them off as efficiently as possible during the one or two seconds that it spends in an average capillary (where all transport processes take place). To the extent that such transport processes are affected by cold temperatures is still not clearly understood. It might be noted further that changes in blood chemistry that invariably accompany physiologic responses to cold stress also affect the flow properties of the fluid, as discussed more fully both earlier, and in the sections that follow.

b) The Diffusion Coefficient, D_s of the fluid, expressed in the same units as Kinematic viscosity, i.e., having dimensions of a $(\text{length})^2$ per unit time. Just as the <u>thermal conductivity</u> defines the <u>heat</u> transferred by conduction, per unit area of contact between two contiguous regions in space, per unit <u>temperature</u> gradient between the regions, so does the <u>diffusion</u>

coefficient define the rate of transfer of mass by chemical diffusion, per unit area of contact between two contiguous regions in space, per unit chemical concentration gradient between the regions. The diffusion coefficient is a measure of the "ease" with which chemical species S can make its way through blood offering an effective resistance (Kinematic viscosity) D_s to particle transport. Being an important constant characterizing the mobility of S in blood, D_s also depends on temperature, the Universal Gas Constant, R, hematocrit and the concentration $[S]_B$. Dependence on the latter is via a so-called "activity factor," β, which multiplies $[S]_B$ to account for concentration variations resulting from particle-to-particle interactions in other-than-dilute solutions. The quantity $\beta[S]_B$ is called the activity of the solution. It may be thought of as the "effective concentration" as opposed to the actual concentration of species S in blood.

c) To the extent that species S may be carrying an electric charge, the electromotive diffusion coefficient, D_s^*, which is related to the ordinary diffusion coefficient, D_s, by the relation:

$$D_s^* = Z \frac{FD_s}{RT} [S], \text{ and which has units}$$

of coulombs (charge) - seconds per unit volume. The quantity F is the Faraday Constant (96,500 coulombs per mole of monovalent ions), Z is the ionic valence of species S, R is the universal gas constant (8.31 Joules/mole - °K), and T is temperature in degrees Kelvin. In the same sense as an

activity factor, β, is associated with the ordinary diffusion coefficient, D_s, described in (b) above, a dielectric constant, ϵ, is also associated with the electromotive diffusion coefficient, D_s^* --and for the same reason, i.e., to correct the mass transport equations for other-than-dilute solutions. The electromotive Diffusion Coefficient is a measure of the quantity of mass transferred per unit surface area, per unit time, when a unit voltage difference or gradient drives charged particles across the area under consideration.

d) To the extent that turbulence might be present in the flow, the eddy diffusion coefficient, D_E,

e) To the extent that transport in Blood may be by means of specific carrier molecules, the concentration [C] of such molecules in the fluid, their degree of saturation, their geometric configuration, their mobility, their state of deformability, their degree of hydration, and their affinity for the proper substrate are all variables that need to be considered. For example, Albumins and Globulins in blood are essential carrier molecules of the hormone Thyroxin. Other highly non-polar compounds tend to be insoluble in aqueous solutions and need to be "carried" in blood by polar molecules that act as "taxi cabs" for these compounds. The <u>ability</u> of carrier molecules to "do their thing" is greatly influenced by their stereospecificity for the proper substrate; and this stereospecificity, being mostly geometric in nature, is very sensitive to temperature. As little as a degree centigrade one way or the other could cause elongation, compression,

warping, or other configurational changes that could render these "taxis" incapable of carrying the proper "passengers". And if these "passengers" are essential ingredients of the organism's response to cold stress, the inability of blood to carry them to their intended destination could (and probably does) have grave consequences.

f) In cases where the chemical substances required for thermoregulation <u>are</u> soluble in aqueous solution, one must examine further the extent to which this solubility is, itself, affected by temperature. This can be quantified by several related parameters, which include:

1. The <u>solubility</u> of a given solute, S, in blood, defined to to be the quantity of solute (usually a solid or gas, and usually expressed in grams or moles) which will dissolve in a given quantity of solvent (also expressed in grams, usually 100, or moles) to produce a completely saturated solution at a specified temperature. It is a well known fact that solubility is very temperature-sensitive. For example, in an everyday sense, most everybody realizes that sugar dissolves <u>quicker</u>, and more <u>of</u> it (per unit volume of solvent) dissolves in <u>hot</u> coffee than in <u>iced</u> tea;
2. Closely related to the solubility of solids or gases in fluids is the corresponding property that defines the <u>miscibility</u> of liquids with other liquids;
3. Directly proportional to the number of moles of solute which is dissolved in a definite weight of solvent, is a

corresponding lowering of the vapor pressure of the solvent--a phenomenon known as Raoult's Law;

4. Due to the lowering of the vapor pressure of the solvent, there is a corresponding (and virtually one-to-one) elevation of the boiling point and depression of the freezing point temperature of the solvent;
5. The Solubility Coefficient, which is defined to be the ratio of species solubility in blood to species solubility in the surrounding aqueous environment;
6. The Partition Coefficient, which is defined to be the ratio of species solubility in oil to species solubility in water;
7. The osmotic pressure of blood, π (mm Hg, or psi), which is defined to be the hydrostatic pressure that must be applied to prevent water from leaving a region of low [S] to flow to one of high [S] in response to a concentration gradient in [S]. Osmotic pressure is directly proportional to the concentration difference $[S]_B - [S]_E = \Delta[S]$, being equal to 1 atmosphere when $\Delta[S]$ is equal to 1 mole per liter of solution;
8. Dissociation Constants, for soluble Electrolytes;
9. The Energy of Hydration, for soluble Electrolytes; and,
10. The activity Coefficient, for soluble Electrolytes.

The role of blood as a mass transport carrier is well-documented, but its effectiveness in this role (especially as it relates to carrying biochemical constituents that are essential for thermoregulation) as a

function of temperature is not clearly understood. Organs and tissues depend for their very survival on fast chemical transport processes that bring nutrients and oxygen into the cell while removing carbon dioxide and waste products from the cell. These mass transport processes are quite temperature-dependent. Furthermore, the various processes and biochemical reactions must be catalyzed by chemical constituents whose geometric configuration (the very basis of their ability to catalyze reactions) is quite temperature sensitive. So, too, are the very reactions, themselves.

(iii) Literally all of the variables examined thus far in sections (i) and (ii) above affect as well the ease with which blood can be pumped through the vascular system. In particular, decreases in temperature have effects on the fluid that tend to make it more difficult to pump. That is to say, when temperature falls,

a) The dynamic viscosity, μ_a, of the fluid increases,

b) Fluid mass density increases,

c) The kinematic viscosity, ν_f, of the fluid increases,

d) Non-Newtonian fluid dynamic properties become more pronounced,

e) The fluid consistency index goes up,

f) Fluid yield stress, τ_y, tends to go up,

g) The relaxation time constant, λ can decrease by as much as 50 to 150%, which means that the relaxation and recovery time of the viscoelastic fluid (which is equal to $1/\lambda$), can increase dramatically,

h) The Elastic and Viscous Moduli may increase, and,

i) The resistance to flow offered by the fluid can become considerable.

Such increased resistance to flow has a double-edged sword effect: On the one hand, by making it harder to pump the fluid, the increased flow resistance slows it down and also insures that less fluid will reach the extremities under conditions of cold stress. This is good. It acts to discourage heat loss in the periphery at low temperatures, and encourage such loss in the core regions of the body. That is, blood spends more time, and therefore has more time to release more heat, in the core regions of the body; and the effectiveness of internal heat transfer processes that act to maintain core temperature are generally improved. But... on the other hand, there are serious consequences to this type of increased flow resistance...for it puts an increased burden on the pumping requirements of the heart! The harder it is to pump fluid through the vascular system, the harder the heart has to work to get blood from the left ventricle through the systemic circulation to the right atrium, and from the right ventricle through the pulmonary circulation to the left atrium. Thus, this aspect of thermoregulation is not without some cost to the organism--in increased pumping requirements and, perhaps, in alterations of transport processes that could also affect other physiologic functions--such as muscle performance, for example, where adequate perfusion rates are necessary for proper performance. This may be somewhat speculative at this point, but certainly worthy of future study.

The Pipes and Channels: Vascular System

There are four basic things one needs to know about the vascular

system in order to assess its role in control of body temperature:

(i) To what extent do the walls of this system allow heat to be transferred across them?

(ii) To what extent do the walls of this system allow mass transport of biochemical constituents that are involved in thermoregulation via alternate physiologic processes?

(iii) With what ease does the vascular system allow blood to be pumped through it?

(iv) How does the vascular system regulate the distribution of blood flow pathways during conditions of cold stress? That is, how much opportunity does the vascular system give blood to lose (or gain) heat, to what extent, and at what rate?

(i) The ability (or lack thereof) of heat to be transferred across the walls of the vascular system depends upon many of the same parameters that were described earlier in our discussion of the ability of blood to carry heat. Thus, of importance are:

a) The temperature of the vascular wall, T_w, relative to both the temperature of blood, T_B, and the extravascular temperature of the environmental surroundings, T_E;

b) The thermal conductivity, k_w, of the vascular wall;

c) The specific heats, c_v^* and c_p^*, of the vascular wall; and their respective ratio, $\gamma^* = c_p^*/c_v^*$;

d) Wall mass density, ρ_w;

e) Wall Thermal Diffusivity, α_w

f) The unit surface conductance, film coefficient, or convection coefficient, h_w, of the vascular wall, in Btu/hr-ft^2-°F. This

particular heat transfer coefficient defines the heat flux (i.e., heat transferred by convection from a bounding surface to a fluid in motion, or, across a flow plane within the interior of the flowing fluid) per unit area of contact between the bounding surface and the fluid, per unit temperature difference between these two contiguous regions in space. A detailed analysis of heat transfer due to convection reveals that it is basically a combination of conduction and radiation, both of which are generally influenced by the fact that the fluid is in motion. If the radiation contribution is negligible, then one may write:

$$\text{Heat flux due to Convection} = h_w(T_B - T_w) = \text{Heat flux due to conduction} = -k_t \left\{\frac{\partial T}{\partial r}\right\}_w$$

where $\left\{\frac{\partial T}{\partial r}\right\}_w$ is the dimensional temperature gradient measured at the blood-endothelial lining interface of the vascular lumen. Thus,

$$h_w = -\frac{k_t \left\{\frac{\partial T}{\partial r}\right\}_w}{T_B - T_w}$$

and the unit surface conductance is recognized to be the gradient of dimensionless temperature at the surface. Being proportional as well to k_t, it, too, depends on the physical properties of the fluid: specific heat, thermal conductivity, dynamic viscosity, arrangement factor, mass density, thermal capacitance, thermal capacity, kinematic viscosity, thermal diffusivity and specific heat ratio--all of which have already been discussed. However, since h is also influenced by the

fact that the fluid is in motion, it depends further on the fluid velocity and, perhaps even more importantly, on the velocity gradients at the wall surface (i.e., on the velocity profile of blood flowing through a vascular channel). Finally, h is also quite sensitive to the geometry of the Vascular Wall.

Multiplying both sides of the equation above by Vascular internal diameter, D, yields:

$$\therefore \quad \frac{h_w D}{k_t} = \frac{-D\left\{\frac{\partial T}{\partial r}\right\}_w}{T_B - T_w} = \text{Nu, the Nusselt Number, which is another very important parameter in heat transfer.}$$

Introducing also the dimensionless Reynolds Number, $Re = \frac{\rho_f v D}{\mu_a}$, one can define further a dimensionless Stanton Number as the product of:

$$(\text{Prandtl Number})^{-1} \times (\text{Nusselt Number}) \times (\text{Reynolds Number})^{-1}$$

$$= St = \left(\frac{c_p \mu_a}{k_t}\right)^{-1} \frac{h_w D}{k_t} \left(\frac{\rho_f v D}{\mu_a}\right)^{-1} = \frac{h_w}{c_p \rho_f v} = St$$

The product of Reynolds Number and Prandtl Number alone is called the Peclet Number: $\frac{\rho_f v D}{\mu_a} \frac{c_p \mu_a}{k_t} = Pe = \frac{\rho_f c_p v D}{k_t}$

We shall have occasion to get back to these and other dimensionless parameters later in this report;

g) To the extent discussed in (f) above, the velocity profile, v(r) of blood flowing through a vascular channel, expressed as axial velocity as a function of tube radius, r;

h) To the extent that it affects the velocity profile, heat, and mass transfer processes, one is concerned with whether flow in the vascular system is laminar or turbulent, as

determined by the value of the Reynolds Number, $Re = \rho_f v D/\mu_a$, or, in its non-Newtonian form,

$$Re = \frac{\rho_f v^{2-n} D^n}{\frac{k_c}{8}\left(\frac{6n+2}{n}\right)^n}$$

i) Geometry of the vascular wall, to the extent that it affects the various heat transfer coefficients, mass transfer, flow behavior, and other events related to thermoregulation. Geometry addresses the following variables:

1. Internal vascular diameter, D, in units of length,
2. Cross-Sectional Area, A, of Vascular Lumen, $(\text{length})^2$,
3. Cross-Sectional <u>contour</u> of vascular lumen,
4. To the extent that the cross-sectional contour may not be circular, or otherwise simple in geometry, the hydraulic diameter of the vessel, defined to be four times its cross-sectional area divided by the length, P, of its perimeter: $4A/P = D^*$,
5. Tube wall thickness, a, (as an insulator and mass transport barrier),
6. To the extent that it affects transition to turbulence, and other transport processes, tube wall surface roughness. Three parameters are usually required to define surface roughness: they are ζ, which is a measure of the <u>size</u> of the roughness projections and has the dimensions of a length (sometimes ζ is presented in dimensionless form as a fraction of internal tube diameter, ζ/D), ζ^*, which is a measure of the <u>arrangement</u>

or spacing of the roughness elements and also has the dimensions of a length, and m, which is a form factor, depending upon the shape of the individual roughness elements (m is a non-dimensional quantity).

Tube wall surface roughness is usually accounted for implicitly by specifying a friction factor, f_R (dimensionless) that is determined experimentally so as to make analytically predicted flow through rough tubes equal to actually measured flow through the same tubes. In addition to being dependent on wall roughness, the friction factor also varies with the Reynolds Number of the flow, $f_R = f_R(Re, \frac{\zeta}{D}, \frac{\zeta^*}{D}, m)$. For laminar flow through smooth ($\zeta = \zeta^* = m = 0$) pipes:

$$f_R = \frac{64}{Re} \quad , \quad 0 \leq Re \leq 2000 \text{ (Hagen-Poiseuille Formula)}$$

For turbulent flow through smooth pipes:

$$f_R = \frac{0.316}{(Re)^{1/4}} \quad , \quad 2000 \leq Re \leq 100{,}000 \text{ (Blasius Formula)}$$

In the transition range between laminar and turbulent flow,

$$\frac{1}{\sqrt{f_R}} = -0.86 \ln \left\{ \frac{\zeta/D}{3.7} + \frac{2.51}{Re\sqrt{f_R}} \right\} \text{ (Colebrook Formula)}$$

For completely turbulent flow in rough tubes, values of f_R can be found tabulated as functions of the relative roughness, ζ/D, and the mean Reynolds Number of the flow, Re.

7. The presence or absence of pores in the vascular wall

surface and their geometry (cross-sectional contour, mean diameter, cross-sectional area, symmetry, length, smoothness, wall configuration, degree of patency, spatial orientation, number, etc.). Especially important here, as far as mass transport is concerned, is how pores in the vascular surface are affected by temperature. There is strong evidence that suggests that ions and other polarized substances that have very low solubility in lipids traverse capillary walls through water-filled pores. Any significant alteration in pore-geometry, or in the physical properties of the material which fills the pore (such as, e.g., changes in temperature) can have potentially detrimental mass transport consequences. For a more thorough discussion of the physics of mass transport across biological membranes, the reader is referred to the report: "Principles of Mass Transport Across Biological Membranes," by Schneck, Daniel J., Virginia Polytechnic Institute and State University, College of Engineering, Department of Engineering Science and Mechanics, Biomedical Engineering Program, Technical Report Number VPI-E-83-07, March 15, 1983, Blacksburg, Virginia 24061.

8. Symmetry, or lack thereof, of the vascular cross-section,
9. Length of blood vessels, a parameter related to such physical events as flow development, end effects, pulse wave reflections, and total pressure drop required to drive the fluid through the vessels,

10. Axial configuration or shape of the walls of the blood vessels, i.e., do they taper, are they parallel, do they converge or diverge, is there any significant curvature to them, are there branches, bifurcations, and so on--and if so, what is the radius of curvature, R_v, of the vascular wall, or the branching angles, θ? For a more complete discussion of the effects of tube geometry on flow through blood vessels, the reader is referred to the report: "Ischaemia In The Heart Due To Atherosclerotic Mechanisms, Flow Anomalies and Vascular Spasm," by Schneck, Daniel J., and Davis, Roy B., III, Virginia Polytechnic Institute and State University, College of Engineering, Department of Engineering Science and Mechanics, Biomedical Engineering Program, Technical Report Number VPI-E-82-17, July 1, 1982, Blacksburg, Virginia 24061.

11. Degree of Patency of the Blood Vessels lumen. Three considerations are important here:

    The extent of occlusion of the vascular lumen due to arterio-atherosclerotic plaques and lesions, or other forms of wall thickening;

    The degree of extravascular compression exerted on blood vessels by surrounding tissues; and

    The level of tone of smooth muscle tissue in the vascular wall.

The presence or absence of vascular pathology can be quantified by standard clinical techniques and by

additional physical parameters, some of which have already been mentioned (tube wall thickness, cross-sectional configuration, etc.) and others which shall be addressed below (vascular pulse-wave transmission, viscoelastic wall properties, etc.). These can also serve to assess the role of extravascular compression on blood vessel patency. Vascular spasms and wall tone adds to our list of variables not only the mechanical properties of smooth muscle tissue and how these are affected by temperature (see iii and iv below), but also the level of activity (firing rates) of the sympathetic f_s (spikes per second) and parasympathetic, f_p, nervous systems, and the concentration in smooth muscle tissue of epinephrine, norepinephrine and acetylcholine. The endocrine hormones have already been mentioned.

12. Orientation and distribution of blood vessels in the physiologic system,

13. Number of patent blood vessels available at any given time, including those forming anastomoses and collateral pathways that affect both the distribution and course of blood flow through the system.

j) Where radiation may be important, the dimensionless emissivity, ε_w, of the wall.

k) As a corollary to the mean velocity of blood flow and the dynamics of the fluid flow, one needs to consider as well the dynamics of the wall motion of vascular vessels, as such motion relates to both mass and heat transfer. This is

discussed further below.

l) Total Surface Area, A_v, of the vascular system available for both heat and mass transfer. This parameter is to the Vascular System what total blood volume, V_B, is to the fluid system.

m) Viscoelastic physical properties of the wall. These will be discussed further in sections (iii) and (iv) below, but are mentioned as well here, in passing, to the extent that they, too, affect the extent to which the walls of the vascular system allow heat to be transferred across them. Physical Properties include: Stimulation Coefficients, Generalized Poisson Ratios, Generalized Static Young's Moduli, Pulse-Wave Propagation Speed (Phase Velocity), Constitutive Relationships, Tissue Dashpot (viscous) constants, Tissue series and parallel spring (elastic) constants, stress-Relaxation Time Constant, Relaxation Modulus,Strain Retardation (Creep) Time Constant, Creep Compliance, Hysteresis, Amplitude Magnification Factor, Phase Angle, Dynamic Modulus of Elasticity, Complex Elastic Modulus, Complex Compliance, Storage Modulus, Viscous Modulus, Impedance Function, Complex Viscous Modulus, Stress Retardation Time Constant, Strain Relaxation Time Constant, Resonance Frequency, Linear Thermal Expansion Coefficient, and the Joule Coefficient.

n) Last, though certainly not least, the various derivatives with respect to <u>time</u> (not only space) of tube wall temperatures. This is another of those variables that is frequently overlooked in physiological research, i.e., the time-rates-of-change, or <u>rate-dependence</u> of the system's response character-

istics to environmental stress.

ii) Mass transport across biological membranes is a very complex process that is quite temperature sensitive. In the first place, one must establish whether the transport is passive or active (i.e., requiring energy--another temperature-sensitive issue). Second, one must distinguish between transport through pores in the membrane versus transport through the membrane material itself. Third, one must consider whether the transport processes are driven by body (at-a-distance) forces or by surface (contact) forces. Fourth, one must examine carefully the presence or absence of facilitators of transport, i.e., carrier molecules (even though the transport mechanism may be purely passive), enzymes, coenzymes, etc. and, finally, one needs to be aware of what factors may encourage, or inhibit, the mobility of the material being transported. All of these, in turn, introduce additional considerations that are much too numerous and detailed to be covered in this report--but which are dealt with at some length in the previously cited report by Schneck (Principles of Mass Transport Across Biological Membranes, VPI-E-83-07, 1983). What is done here is simply to list those parameters that govern mass transport, with the reader being referred to VPI-E-83-07 for further details. Thus, of importance are:

a) Total Surface Area, A_v (length^2) of Vascular System,

b) Fraction of Surface Area A_v that is Pore-Free (in percent), A_o,

c) Fraction of Surface Area A_v that consists of Pores (in percent),

d) Effective Diffusion Coefficient, D_e, (length)^2/unit time,

e) Surface Diffusion Coefficient, D_K^*, (length)^2/unit time,

f) Ordinary Diffusion Coefficient, D_S, (length)^2 per unit time,

g) Electromotive Diffusion Coefficient, D_S^*, coulombs-sec/(length)^3,

h) Osmotic Pressure-Filtration Coefficient, P_0, (length)^2/unit time,

i) Hydrostatic Pressure-Filtration Coefficient, P*, dynes/cm^3,

j) Active Transport Permeability Coefficient, P_A, in units of velocity,

k) Osmotic Permeability Coefficient, P_{H_2O}, length per unit time,

l) Eddy Diffusion Coefficient, D_E, (length)^2/time,

m) Permeability Coefficient For Ordinary Diffusion, P_s, length per unit time,

n) Permeability Coefficient For Electromotive Diffusion, V_s, $\frac{\text{coulombs}}{\text{unit time}}$,

o) Number of Pores, c, per unit membrane area,

p) Pore Diameter, d, in units of length,

q) Specific Vascular Wall Conductance, g, (coulombs)^2/Joule-area-time,

r) wall Reflection Coefficient, or Staverman Factor, b, dimensionless,

s) Magnetic Permeability, p*, in gausses per oersted,

t) Activity Factor, β, Dimensionless,

u) Vascular Wall thickness, a, in units of length,

v) Volume Fraction of Water, ϕ_w, in Vascular Pores,

w) Mobility Constant, $\eta^* = FD_s/RTe$, (where e is the charge on an Electron), time per unit mass,

x) Dielectric constant, κ, Dimensionless,

y) Viscosity of pore fluid, μ_p, in poises,

z) Equilibrium Potential of Vascular Wall for species S, $\mathcal{E}_s$, volts,

aa) Osmotic Force Per Unit Volume For Species s, $\vec{\pi}$, force/volume,

bb) Tortuosity Factor for pores, δ^*,

cc) Coefficient of friction between vascular wall pore and solute, s_s,

dd) Coefficient of friction, s_f between vascular wall pore and pore fluid,

ee) Coefficient of friction between pore fluid and solute, s_p,

ff) Mass Density of pore fluid, ρ_p, in gms/cm^3,

gg) Specific Resistivity, $\rho^* = \frac{1}{[S]\eta^* FeZ^2}$, of the vascular wall, in units of Joules-Meters-Second per Coulomb^2,

hh) Electrical Resistance of Vascular Wall = $R^* = \rho^* a/A_v$, in units of Joules-Second per (Coulombs)^2,

ii) Specific Conductivity of vascular wall = $\frac{1}{\rho^*}$,

jj) Electrical Permeability of the Vascular Wall = FD_s/aRT, in units of (coulombs per unit length) per (mass per second).

Many, if not <u>all</u> of the variables listed above are quite temperature-sensitive. Capillary pore diameter, for example, will increase in a hot environment and constrict, or decrease in a cold environment--enhancing mass transport on the one hand, while inhibiting such transport on the other. The mobility constant, η^* (w above) is inversely proportional to temperature, as is the viscosity, μ_p, of the pore fluid. Mass density, ρ_p, of the pore fluid also varies as 1/T, and virtually all of the other factors

that control transport across the walls of the vascular system have some dependence on temperature. Again, the reader is referred to VPI-E-83-07 for more details.

(iii) The ease with which the vascular system allows blood to be pumped through it introduces variables related to the physical properties of the vascular wall, the degree of patency of the blood vessels, and the number of "paths of least resistance" available for fluid transport through the vascular system. This section deals primarily with the first of these considerations, the second and third being addressed in section (iv) that follows.

Blood vessel walls are characteristically nonlinear, visco-elastic materials with time-and-temperature-dependent physical properties. The nonlinearities can be attributed to the fact that the vascular wall is a complicated composite structure, consisting of three major constituents--Elastin, Collagen, and Smooth Muscle tissue--embedded in a mucopolysacharide matrix to form a multi-levelled (Endothelium, Intima, Media, Adventitia, Epithelium) architecture capable of distributing blood throughout the physiologic system. Each constituent has distinctly different chemical and physical properties, with collagen being the strongest (Modulus of Elasticity $\simeq 10^9 - 10^{10}$ dynes/cm^2) and Elastin being the weakest (Modulus of Elasticity $\simeq 10^6 - 10^7$ dynes/cm^2) of the three. Moreover, the large percentage of water (on the order of 50-75%) that permeates the vascular architecture, together with the complex, long-chain configuration of polarized molecular species that comprise the walls of blood vessels, give them time-dependent

or viscoelastic properties that are quite temperature-sensitive. In order to describe the physical behavior of materials such as the vascular wall, scientists have developed what are called "Phenomenological" mathematical models. These are various combinations of springs and dashpots (or viscous dampers, i.e., shock absorbers) which are not physical analogues per se of the actual physical structure of the material being modelled, but whose particular arrangement gives rise to a governing differential equation that accurately predicts or describes real material behavior as measured for that particular material. In other words, the material behaves as though it were comprised of the springs and dashpots that constitute the phenomenological model, and so the various spring constants and dashpot constants measured for this model can be used to characterize the physical properties of the material under consideration. Furthermore, by allowing these "constants" to be, in fact, functions of strain, strain rate, its various derivatives, time and temperature, the phenomenological models can predict not only viscoelastic behavior, but nonlinear behavior as well. Bearing all of this in mind, the vascular wall properties that describe its physical response characteristics include the following:

a) Smooth Muscle Stimulation Coefficients, q_i, $i = 0,1,2,3...N$, where N is the degree of nonlinearity being considered for any given model of smooth muscle tissue. These stimulation coefficients are functions of sympathetic (f_s), parasympathetic (f_p) and Endocrine ([S]) control of smooth muscle behavior, as well as muscle strain, strain-rate, time and temperature. In

the case of temperature, not only is it of concern in terms of affecting the response of smooth muscle to various stimuli, but, also, in very cold temperature environments smooth muscles may actually become paralyzed, rendering them helpless in terms of redistributing blood flow to parts of the body that need it. Smooth muscles, depending on their state of excitation as determined by q_i, control the vascular "tone" and hence patency of blood vessels. This is an important determinant of flow distribution, and, in turn, an important aspect of vascular response to cold stress (see below).

b) Generalized Poisson Ratios, σ_i, i=1,2,3,...N, which define the lateral response of a material subjected to a longitudinal deformation.

c) Generalized Static Young's Moduli, $\mathcal{E}_i$, i = 1,2,3,...N, which define the ratio of stress to strain in a material subjected to a static deformation (strain-rate or rate of change with respect to time of strain is zero). In the most general static case,

$$\text{stress} = \text{function of } [\mathcal{E}_i, \text{strain}, (\text{strain})^2, (\text{strain})^3, \ldots, q_i, \text{muscle geometry}, \sigma_i, t, T]$$

d) Speed of Propagation, or phase velocity, of a pulse wave through the vascular wall. This quantity, v_w, is sometimes given in terms of the vascular geometry and Static Young's Modulus by the simple Moens-Korteweg Formula:

$$v_w = \sqrt{\frac{\mathcal{E}_1 a}{D o_f}}$$

which, although greatly idealized, gives reasonable results and

provides a convenient estimate of $\mathcal{E}_1$ if the tube geometry (a,D) and fluid properties (ρ_f) are known.

e) Tissue Dashpot constants, B_j, j=1,2,3,... up to the number of viscous dampers required to model accurately the time-dependent response characteristics of the vascular wall (i.e., stress-relaxation, creep, phase relationships, and so on). In most cases, one or two such elements are sufficient for all practical purposes.

f) Tissue Spring Constants, K_j, j=1,2,3,... up to the number of springs required to model accurately the elastic response characteristics of the vascular wall. In most cases, one spring in parallel with and one spring in series with a viscous damper constitute the building blocks or functional units of a phenomenological model, and the model is built up of such units. Moreover, whereas K_j may or may not be very sensitive to temperature, B_j is <u>very much</u> a function of T, since fluid viscosity increases quite markedly with decreasing temperature.

g) Stress-Relaxation Time Constant, λ_ε, generally given as a function of B_j and K_j. In one of the more simple cases, λ_ε may be expressed as:

$$\lambda_\varepsilon = \frac{\text{Viscous Damping Constant, } B_1}{\text{Series Spring Constant, } K_1}$$

and it provides a measure of the <u>rate</u> at which stress-relaxation occurs. This rate, too, is quite temperature sensitive, since relaxation times can increase by as much

as 50 to 150 percent at very low tissue temperatures.

h) Relaxation Modulus, $\mathscr{E}_R$, defined to be the time-dependent ratio of stress (which is "relaxing" with t) to strain, when the latter is maintained at some constant value, ξ_o, i.e.,

$$\mathscr{E}_R(t) = \frac{\tau(t)}{\xi_o}$$

Like the stress-relaxation time constant, the Relaxation Modulus is also very sensitive to temperature.

i) Strain-Retardation (Creep) time constant, λ_τ, also expressed as a function of B_j and K_j. In one of the more simple cases, λ_τ may be written in terms of the viscous damping constant, B_1, the series spring constant, K_1 and the parallel spring constant, K_2, as:

$$\lambda_\tau = \frac{B_1(K_1 + K_2)}{K_1 K_2},$$ and it, too, depends very much on temperature.

j) The Creep Compliance, $\mathscr{E}_c$, defined to be the time-dependent ratio of strain (which is "creeping" with t) to stress, when the latter is maintained at some constant value, τ_o, i.e.,

$$\mathscr{E}_c(t) = \frac{\xi(t)}{\tau_o},$$ and which also depends on temperature.

k) Hysteresis is an event attributable to the same characteristics of visco-elastic materials that give rise to such phenomena as stress-relaxation and creep. It refers to the fact that if a piece of vascular material is deformed from rest to some maximum value, and then the deformation

is released in some continuous fashion, the loading stress-strain curve is not the same as the unloading stress-strain curve, and the material does not return to its resting configuration for some time after the load is completely removed. In other words, at the instant the stress reaches zero again, the material retains a certain amount of stretch (at least for some time). Hysteresis can be characterized by three basic parameters:

1) The area, ψ, that lies between the loading and unloading stress-strain diagrams during any particular deformation cycle, or, more accurately, this area as a function of time for repeated cyclic loading. $\psi(t)$ represents strain energy dissipated as heat which is required to break up weak polar bonds that give the material a tight, "coiled-up" configuration when at rest. It is thus, in some sense, a measure of this configuration.

2) The elastic after-effect, or, strain, $\xi^*(t)$ remaining in the tissue at the end of each loading cycle. The "residual" strain remaining in the material after it has been unloaded is actually the difference between the "uncoiled" configuration of the long-chained polymers and their "coiled-up" configuration. Thus, it, too, is a measure of the tendency of the material to shorten further as a result of the formation of secondary polar bonds that collapse the internal molecular structure of

the tissue.

3) Because hysteresis results from the breaking of weak, polar bonds in the material, it obviously has an upper limit. Indeed, it has been observed that the shape and characteristics of the stress-strain behavior of vascular tissue tend to become fixed as the number of loading-unloading cycles increases. Thus, the total number of cycles, M, required to accomplish this is another measure of the hysteresis properties of the material.

All three parameters, $\psi(t)$, $\xi^*(t)$, and M depend very much on T.

l) If vascular tissue is subjected to a dynamic, cyclic loading (as, indeed it is <u>in vivo</u>), one observes a phase difference, ϕ, between the applied load and the resulting deformation. This phase angle can generally be expressed as a function of B_j, K_j, the circular frequency, ω, of the cyclic loading, and temperature. For one simple case (see Schneck, D.J., VPI report number VPI-E-83-20, June, 1983, page 74),

$$\tan \phi = \frac{(K_1/B_1\omega)}{\left[\left(K_1^2/B_1^2\omega^2\right) + \left(1 + \frac{K_1}{K_2}\right)\right]\frac{K_2}{K_1}}, \quad 0 \leq |\phi| \leq \frac{\pi}{2}$$

m) Similarly, under cyclic loading, the <u>amplitude</u> of the response is different from the amplitude of the disturbance, the two being related by an amplitude magnification factor, Q, that is also a function of B_j, K_j, ω

and t. For the same simple situation considered in (l) above, the magnification factor is found to be:

$$Q = \sqrt{\frac{\left(\frac{K_1}{B_1\omega}\right)^2 + \left[1 + \frac{K_1}{K_2}\right]^2}{1 + \left(\frac{K_1}{B_1\omega}\right)^2}}$$

The circular frequency for which $\omega\lambda_\varepsilon = \frac{K_2}{K_1 + K_2}$ is called the lower breakpoint frequency of the amplitude frequency-response characteristics of the tissue; the circular frequency for which $\omega\lambda_\varepsilon = 1$ is called the upper breakpoint frequency of these same frequency-response characteristics. The significance of these is explained in the previously cited report (VPI-E-83-20). Also, the maximum phase shift occurs when $\omega\lambda_\varepsilon = \sqrt{\frac{K_2}{K_1 + K_2}}$.

n) The <u>resonant frequency</u>, ω_d, is that frequency for which a driven system will have an infinite magnification factor, and it is equal to the natural frequency, ω_n, of the system. That is to say, if a system is driven at its natural frequency, it will resonate. In general, ω_n depends upon K_j, B_j and the mass of the system (and temperature to the extent that mass density and dashpot constants are temperature-dependent).

o) The Dynamic Modulus of Elasticity, defined to be the ratio of the range in stress to the range in strain for a material subjected to a time-dependent loading:

$$\mathcal{E}_D = \frac{\tau_{max} - \tau_{min}}{\xi_{max} - \xi_{min}}$$

For pure sinusoidal-type loading, the Dynamic Modulus of Elasticity turns out to be equal to the Static Young's Modulus times the amplitude magnification factor.

p) The complex elastic modulus of the material, $\bar{\mathscr{E}}$, defined to be the ratio of stress (as a function of time) to strain (as a function of time) when a material is subjected to a time-dependent loading. $\bar{\mathscr{E}}$ is then, by definition, also a time-dependent quantity, $\bar{\mathscr{E}} = \frac{\tau(t)}{\xi(t)}$, and, if $\tau(t)$ and $\xi(t)$ are both written in complex mathematical notation, $\bar{\mathscr{E}}$ can be written in terms of a real and imaginary part. The real part, $\bar{\mathscr{E}}_r(\omega)$, sometimes taken to be an alternate definition for the Dynamic Modulus of Elasticity, is more often termed the storage Modulus, and represents the (recoverable) energy stored in the viscoelastic material when it is deformed. The imaginary part, $\bar{\mathscr{E}}_i(\omega)$, is called the Viscous Modulus, and represents the (lost) energy dissipated when a visco-elastic material is deformed. It can be shown (see VPI-E-83-20) that the phase angle, ϕ, can be written: $\phi = \text{ArcTan} \frac{\bar{\mathscr{E}}_i(\omega)}{\bar{\mathscr{E}}_r(\omega)}$, and thus represents the ratio of the energy-dissipating characteristics of the tissue to the energy-storing nature of the material.

q) The reciprocal of the complex elastic modulus is called the complex compliance, $\bar{J}$, of the material, such that: $\bar{\mathscr{E}}\,\bar{J} = 1$.

r) The complex impedance function, $\bar{\mathscr{E}}_\mu$, defined to be the

ratio of stress (as a function of time) to strain rate (as a function of time) when a material is subjected to a time-dependent loading. $\bar{\mathcal{E}}_\mu = \frac{\tau(t)}{\dot{\xi}(t)}$ can be shown to be equal to $\frac{\bar{\mathcal{E}}}{j\omega}$ ($j = \sqrt{-1}$), so that a knowledge of either the complex elastic modulus or the complex impedance function (at all circular frequencies) suffice to describe completely the viscoelastic properties of vascular tissue. Incidentally, the quantity $\omega\bar{\mathcal{E}}_\mu$ is called the complex viscous modulus of the tissue.

s) The stress-retardation time constant, λ_p, which is numerically equal to the stress-relaxation constant, λ_ε, but which measures the rate at which tension builds up in the walls of an artery when the smooth muscle tissue actively generates an isometric tetanic contraction. In other words, whereas λ_ε governs the rate of passive release in stress, λ_p governs the rate of active build-up in stress--both rates being numerically equal for the same tissue.

t) The strain-relaxation time constant, λ_F, which is numerically equal to the strain-retardation (creep) constant, λ_τ, but which measures the rate at which the walls of an artery or other vascular vessel constrict when the smooth muscle tissue actively generates an isotonic contraction. In other words, whereas λ_τ governs the rate of passive extension of vascular tissue under load, λ_F governs the rate of active contraction under load--both rates being numerically equal for the same

tissue.

u) The linear thermal expansion coefficient, β_w, for the vascular wall, which defines how the linear dimensions of the wall change per unit change in temperature when the wall loading is held constant (an isotonic creep effect).

v) The Joule coefficient, η_w, for the vascular wall, which defines how vascular tone changes per unit change in temperature when the wall dimensions are held constant (an isometric relaxation effect sometimes called the Joule, or Gough-Joule effect).

w) Percentage by weight of the major constituents of the vascular wall, i.e., Elastin, W_E, collagen, W_c, and smooth muscle tissue, W_s.

(iv) The ability of the vascular system to regulate the distribution of blood throughout the physiologic system represents one of the most important aspects of the cardiovascular response to cold stress. Herein is represented a vital means for decreasing heat loss to the environment and conserving heat in the core of the body. Since one of the determinants of total heat loss is the area of contact between two contiguous regions, blood is redistributed during cold stress so that less area for heat transfer to the environment is made available at the skin surface, while more area for heat transfer to the body core is made available in the interior, more vital regions of the body. Furthermore, since heat transfer takes time, vascular alterations take place that

allow blood to spend more time in the core regions of the body and less time in the periphery. In fact, flow tends to be diverted away from the periphery, effectively increasing the insulation thickness of the organism; and, by a clever counter-current exchange mechanism, the blood managing to reach the peripheral regions of the body does so at a greatly reduced fluid temperature, such that the gradient driving heat out of the system is greatly reduced (while that driving heat into the core of the body is correspondingly increased). Thus, by arranging it such that less total fluid, at a much lower temperature, spending only a little bit of time, in regions as far removed from the periphery as possible, has a minimum amount of surface area and a maximum amount of insulation across which to transfer heat to the environment, the vascular system does its best to discourage heat loss from the organism during cold stress. These events, however, are not without some adverse consequences, such as dehydration, impaired motor function, edema formation, peripheral gangrenous necrosis, frost bite, cardiac overexertion, and others. They represent, therefore, still another example of how attempts by the human organism to survive environmental insults can actually lead to its demise from alternate repercussions of its compensatory mechanisms! In any case, the factors that take part in redistributing blood flow during cold stress are as follows:

a) A sustained peripheral venous and arteriolar vasoconstriction, which reduces blood flow to the extremities

and hence minimizes heat loss from the skin. Such vasoconstriction results from adrenergic sympathetic control of arteriomotor tone, and so is very dependent upon the firing rate, f_s, of sympathetic nerve fibers. Ironically, very intense cold (below -20°C or -4°F) may cause intermittent paralysis of vasoconstricting sympathetic fibers that control arteriovenous sphincters, thus leading to a syndrome known as Cold-Induced Vaso-Dilatation, or CIVD. This brings up the point that investigators examining cardiovascular response to cold stress (indeed, any physiologic process) must always be on the lookout for multi-phasic types of responses, which, in this case, may depend on:

1. Environmental Temperature, T_E,
2. The rate of environmental cooling, $\frac{dT_E}{dt}$, and its various derivatives, $\frac{d^2T_E}{dt^2}$, $\frac{d^3T_E}{dt^3}$, ...,
3. Time of exposure, t_e, to environmental temperature, T_E,
4. The presence or absence of wind, and its velocity, $\vec{U}$,
5. Ambient humidity ratio, in per cent,
6. The season of the year during which cold-exposure occurs,
7. The time of day when cold-exposure occurs,
8. The physical build of the individual exposed to cold stress, especially as it relates to subcutaneous fat

content (insulation), muscle mass (shivering mechanism), Height, Weight, and Anthropometric Measurements,

9. The physical condition of the individual exposed to cold stress, especially as it relates to musculo-skeletal function (ability to exercise), cardio-vascular function, endocrine function, central nervous system function and sympathetic nervous system function,
10. Food consumption (diet), including alcohol intake,
11. Oxygen and carbon dioxide intake and utilization,
12. Degree to which individual exposed to cold stress is clothed or otherwise protected from the elements, including the type of clothing being worn and its thermal properties,
13. The age of the individual,
14. His or Her sex,
15. Previous exposure to cold stress and/or predilection of the individual to anomalous thermoregulatory response characteristics,

and so on, and so on.

The effect of such peripheral vasoconstriction is to increase total peripheral resistance, which is defined to be the ratio between (the difference between Right Atrial Blood Pressure, or pressure in the vena cava, p_A, and Left Ventricular Blood Pressure, or mean aortic blood

pressure, $P_v = \frac{1}{2}(P_{systolic} - P_{diastolic})$ divided by the total cardiac output, C.O., i.e.,

$$\text{Peripheral Resistance, } R = \frac{P_v - P_A}{C.O.} .$$

Again, this is a biphasic response in that continued and sustained exposure to cold below -20°C or -4°F in T_E, or, 30°C in core temperature T_c reverses this process for reasons already cited. It might be further mentioned that an increase in R also puts an overload on the heart, which is a dangerous situation for prolonged periods of time. Moreover the pooling of blood in the core of the body, due to reduced flow to the periphery, leads stretch receptors located at critical points in the system to sense an excessively high extracellular fluid volume space. This triggers a sequence of responses that lead to dehydration (excessive urination being an example of such) <u>without</u> compensatory thirst mechanisms coming into play--because the organism "thinks" it is expelling <u>excess</u> fluid, not fluid required for normal homeostasis.

b) Peripheral <u>venous constriction</u> acts as a shunt to selectively channel venous return blood through <u>deep veins</u> back to the heart, rather than through more superficial veins which promote heat loss. Known as the "Venous Shunt" Response, this also forces venous return of cooler blood to take place in association with, or in proximity to central arteries carrying warmer blood. The ratio is usually one artery to two adjacent veins. What

happens now is that warm blood travelling towards the periphery gives off heat to the adjacent cooler blood heading back towards the heart. The net effect of this Arterio-Venous Countercurrent heat exchange is two-fold: First, arterial blood temperature falls as it gives off heat to the venous blood, en route to the extremities--the arterial blood thus arrives near the body surface at a much lower temperature than it would otherwise, the difference in temperature, $T_B - T_E$, is thereby significantly reduced, and, with it, the rate of heat loss to the environment; and, second, venous blood temperature rises as it picks up heat from the arterial blood, en route back to the heart, thereby helping to maintain body core temperature at its desired level. This arterio-venous countercurrent heat exchange mechanism, then, which results directly from Adrenergic-Sympathetic control of venomotor tone, acts to keep as much heat as possible from getting to the extremities (by cooling the temperature of the blood reaching the cutaneous capillary beds), and to conserve heat centrally by taking it from arteries going towards the periphery and transferring it into veins going back towards the heart.

This thermoregulatory response, too, is not without some potential adverse consequences. For one thing, lack of heat in peripheral tissues can lead to the formation

of ice crystals in the extracellular fluid, causing the latter to become hypertonic with respect to the intracellular fluid, causing the cells to shrink, shrivel-up and die, causing frost-bite and all kinds of additional undesirable pathologic conditions. For another thing, impaired cellular metabolism caused by excessively cold temperatures, such as destruction of the mitochondria, can result in gangrenous necrosis and a variety of other problems. Remember, though, that these are secondary to the primary thermoregulatory response mechanism, which is the venous shunt.

c) Peripheral capillary vasoconstriction (skin, muscles, ears, nasal mucosa) causes a build-up in back-pressure that forces open superficial arterio-venous anastomoses (AVA's), thereby reducing heat loss at the expense of intermittent ischaemia. Blood flow is shunted by these AVA's away from the closed peripheral capillary beds and into deeper veins, where the processes described in (b) above can also come into play. These AVA's also keep arterial blood warmer by not letting it get to the skin surface to lose heat. Instead, the intent is for it to flow just close enough to the ischemic tissue to give off enough local heat to prevent frost-bite, but not near enough to the skin surface to dissipate heat to the environment. Depending on how long the ischaemia lasts, the effects of decreased blood supply on organ function may or may not be significant.

d) Peripheral Arteriolar Constriction can completely shut off the supply of blood to many capillary beds at once. Such diverting of blood away from the periphery effectively increases the total insulation of the body by making the heat have to travel further to reach the skin surface before being dissipated. It also contributes to all of the mechanisms discussed in (a), (b) and (c) above, and has many of the same consequences.

e) Peripheral vasoconstriction, arterio-venous anastomoses, and venous shunts succeed in reducing the heat transfer area between the body and its environment, while increasing the area between internal heat transfer surfaces. In this way, the loss of heat to the environment is discouraged at the expense of storing more heat within the organism, by mechanisms already discussed.

f) These same mechanisms also allow less time for heat transfer to take place at the surface of the body because they act to minimize the quantity of blood that reaches the periphery, and the length of time it spends there en route back to the heart. Conversely, the fluid (and more of it) spends more time in the interior regions of the body, and thus has ample opportunity to give off more heat to the core. This has the added benefit of causing the blood that does reach the periphery to do so at a much reduced temperature, which further discourages heat loss.

g) In a less sophisticated context, all of the mechanisms

described above also conserve heat by redistributing as much of the flow as possible to simply keep it away from the body surface. The fluid cannot lose heat to the environment if it is simply kept from coming into contact with the environment. In principle, it is just that simple!

h) Finally, it has already been mentioned that peripheral vasoconstriction also increases the effective insulation thickness of the organism. Thus, viewed in terms of the heat transfer relationship:

Heat Flow = (Thermal Conductivity) × (Heat Transfer Area) × (Temperature Difference between Fluid and Surroundings) × (The reciprocal of insulation thickness)

We find that during cold stress, the role of the vascular system is to reduce the heat transfer area, reduce the temperature difference between the fluid and its surroundings, and increase the effective insulation--all of which act to reduce heat flow.

The Pump: Heart

The one single aspect of cardiac function that relates to thermoregulation is cardiac output, C.O. , generally expressed in liters per minute. In assessing the role of the heart in control of body temperature, one therefore is concerned with those factors that ultimately manifest themselves as alterations in cardiac output and, in the cost to the organism of generating such an output. Cardiac Output is defined

to be the product of Heart Rate (cycles per minute, f) and Stroke Volume, S.V., in liters of blood leaving the left ventricle per cardiac cycle:

$$C.O. = f \times S.V.$$

Stroke Volume, in turn is defined to be the difference between the volume of the left ventricle at the end of the filling phase of the cardiac cycle (end-diastolic-volume, EDV,) and the volume of the left ventricle at the end of the emptying phase of the cardiac cycle (end-systolic-volume, ESV):

$$S.V. = EDV - ESV$$

Our attention is thus focussed on:

(i)	Factors that affect Heart Rate,	Cardiac Output
(ii)	Factors that affect End Systolic Volume,	
(iii)	Factors that affect End Diastolic Volume,	
(iv)	Factors that affect Coronary Perfusion Rate,	Cardiac Input
(v)	Factors that affect Net coronary Arterio-Venous Difference in Oxygen Tension	

(i) Heart Rate is determined by the pacemaker activity of the sino-atrial (SA) Node, by the rate at which impulses propagate through the atrial and ventricular musculature (conduction velocity, u), by the state of health of this musculature, and by the delaying activities of the atrio-ventricular node (AV-Node). The SA-Node is a self-paced signal generator whose intrinsic firing rate can be modified up or down by the sympathetic nervous system (chronotropic effect of f_s), the parasympathetic nervous system (pressor effect

of f_p), and certain endocrine hormones. These will be discussed further in a later section on cardiovascular control. During cold stress, heart rate increases at first but then begins to decrease linearly with both temperature, T_E, and time of exposure, t_e, due to an intrinsic slowing of pacemaker activity in the sinus node, a slowing of conduction velocity, u, and slowing of myocardial contraction velocity (i.e., prolongation of systole). These show up, along with other characteristic changes, in the Electrocardiogram, which is a measure of the electrical activity and signal transmission characteristics of the myocardial neuromusculature. Of particular interest are more sophisticated types of electrocardiography (ECG), such as those that are measured on the heart itself (intracardiac ECG), those that measure simultaneous multi-lead ECG signals, and those that are analyzed by computer. The types of measurements taken from an electrocardiographic signal may be classified into five broad categories as follows:

a) Intervals (time) between characteristic wave patterns. The ECG trace normally consists of a series of deflections each designated by the letters, P,Q,R,S,T and, sometimes, by additional subdivisions labelled A,H,T_c,R',U and V. Thus, one speaks of a:

   1. P-wave interval, representing the time required for atrial depolarization;
   2. Q-R-S-complex interval, representing the time required for ventricular depolarization;
   3. T-wave interval, representing ventricular repolarization;

4. P-R Interval, representing atrio-ventricular conduction time;

5. P-Q interval, representing atrio-ventricular conduction time when a Q-wave is present;

6. Q-wave interval, representing the propagation of the sino-atrial signal through the interventricular septum;

7. R-wave interval, representing, basically, the time required for the SA signal to propagate through the right ventricular musculature;

8. S-T-segment, representing complete cardiac depolarization (isoelectric) following systolic contraction;

9. P-R-Segment interval = {P-R or P-Q interval} - {P-wave interval} which represents the A-V Node Delay Time;

10. S-Wave interval, representing completion of ventricular depolarization;

11. R'-Wave interval: If more than the Q,R and S deflections are present in the ECG, the upward deflection following S is labelled R', a downward deflection following R' is S' (if necessary, R" and S" may follow);

12. U-Wave Interval, representing membrane after-potentials;

13. Q-T Duration or "Electrical Systole;"

14. Corrected Q-T Duration, $Q\text{-}T_c$ = {Q-T} - {Q-R-S} = S-T segment = {S-T interval} - {T-Wave interval};

15. S-T interval, measured from the end of the R'-wave to the end of the T-wave;

16. Q-S interval, sometimes used synonymously with Q-R-S;

17. R-R interval = Total time for one cardiac cycle, sometimes designated P-U or P-P intervals; and,

18. Less common designations, such as P-A, H-V, H-Q, H-S, etc., for which the reader is referred to the literature.

b) Slopes of the various characteristic deflections enumerated above, together with their amplitudes, maxima and minima.

c) Total areas under the curves and intervals defined in (a) above, together with the location of the base-line axes of the curves.

d) Orientation and general wave shape of the ECG, such as whether or not it is inverted, skewed, raised or lowered relative to the isoelectric base-line, etc., and,

e) Biological Signal Analysis of Electrocardiogram, including:

1. Fourier Frequency Spectrum Analysis;

2. Signal noise analysis;

3. Determination of a probability density function p(X), yielding, for a given value of voltage, X, the probability that the ECG signal will attain this value at any arbitrary time;

4. Determination of a probability distribution function P(X), yielding, for a given value of voltage, X, the probability that the ECG signal will be less than or equal to X at any arbitrary time;

5. Determination of a probability range function, $\int_{X_1}^{X_2} p(X)dX$ yielding, for any two values of voltage, X_1 and X_2, the probability that the ECG signal will fall inside

the range between X_1 and X_2 at any arbitrary time;

6. Determination of an autocorrelation function, yielding information about the extent to which voltage measured by a single ECG lead at a given time depends upon voltage measured by that same lead at some other time; (time correlation);

7. Determination of various cross-correlation coefficients, which evaluate the extent to which the voltage measured in one ECG lead at a given time is related to the voltage measured in any other ECG lead at the same time (space correlation);

8. Determination of all of the various moments of both the ECG signal itself and its corresponding frequency or power spectral density function. These include the:

   Mean Value (first moment with respect to voltage of the probability density function),

   Deviation $(x_i - X_{mean})$, i=0,1,2,3,...,

   Mean Square (Second Moment),

   Variance (Mean of the Deviations Squared),

   Standard Deviation (Square-Root of the variance),

   RMS Value (Root-Mean-Square of X_i),

   The Mode (Value of X_i that appears most often),

   Skewness (third moment),

   Kurtosis, or Flatness Factor (fourth moment divided by second moment squared),

   Median (Value of X_i for which there are as many values above X_i as there are below X_i),

Width Factor (standard deviation divided by the mean), and so on;

9. Determination of Power Spectral Density Functions for the ECG signal;
10. Development of a deterministic mathematical equation for the signal, itself.

Changes in the electrocardiogram have been observed during cold stress and they can be correlated with such problems as heart block, irregular rhythm, atrio-ventricular dissociation, missing and/or premature beats, strain or enlargement of cardiac tissue, damage or disease from myocardial infarction and ischaemia, heart irritability and ectopic focii, hypertension, shunts or septal defects, intraventricular conduction delays, altered ion flux across sarcolemmal membranes, and atrial or ventricular tachycardia, bradycardia and fibrillation.

ii) The end systolic volume of the heart is determined by the "contractility" of the myocardial musculature, by the volume from which contraction begins (end diastolic volume, see iii below), and by the length of time allowed for contraction to take place (the systolic time interval).

Myocardial contractility is a somewhat abstract concept that is measured more by its manifestations in terms of cardiac output, than by its specific anatomical or physiologic basis. In a strict sense, it is a term used to describe the ability of the heart to generate power, as determined by the force-velocity and tension-

length characteristics of cardiac muscle. In that respect, one needs to know the same kinds of things about cardiac muscle as were of interest when smooth muscle was discussed earlier (see the discussion of the Vascular System, section iii)--since the nonlinear viscoelastic behavior of both types of tissue can be defined by specifying stimulation coefficients, poisson ratios, Young's Moduli, compliances, etc. However, whereas it would be nice to know all of these things in order to evaluate heart function in general, and the effects of cold in particular, they are not easy to measure, especially in vivo. Thus, alternative means have been developed to assess myocardial contractility on the basis of the results of such contractility, which manifest themselves as:

a) Heart sounds, caused by vibrations involving the heart chambers, valves, and contents, and the presence of turbulence in flowing blood. These can be measured by techniques employing phonocardiography, through which sounds associated with the following events can be recorded and evaluated:

   1. Closure of the Mitral and Tricuspid valves (first heart sound) between the atria and ventricles of the left and right sides of the heart, respectively;
   2. Sudden deceleration of the mass of blood within the ventricles;
   3. Closure of the Aortic Valve (second heart sound);
   4. Closure of the Pulmonary Valve;
   5. Partial "rebound" of the mitral valve (third heart sound) after the first surge of blood rapidly fills the ventricles during early diastole;

6. Mitral Regurgitation;

7. Sudden "reopening" of the mitral valve (fourth heart sound) during rapid filling of the ventricles in late diastole (atrial systole);

8. Opening "snaps" of the mitral valve in cases of mitral stenosis;

9. Left-to-Right septal shunt defects;

10. Heart murmers, mostly associated with excessive fluid turbulence;

11. Korotkoff Sounds (cardiac and vascular), and others.

b) Intraventricular blood pressure--both mean, maximum during systole, and total amplitude.

c) Rate of change of Ventricular Pressure with respect to time, i.e., the so-called "$\frac{dp}{dt}$" characteristics of the left ventricle during the isovolumetric contraction phase of the cardiac cycle. This is presumably related to the rate at which tension is developed in the myocardial musculature, and is measured maximally when the semi-lunar valves first open.

d) Systolic Emptying Time, usually involving three measurements:

1. Total Electromechanical Systole, from the onset of the QRS complex (electrical signal just starting out from the AV node) to the closure of the aortic valve (second heart sound);

2. Left Ventricular Ejection Time, from the beginning of the ventricular pressure upstroke (before mitral valve actually closes) to the dichrotic notch of the carotid artery pressure tracing (just after the aortic valve

actually closes); and,

3. Pre-Ejection Period, which is electomechanical systole (1) minus Left Ventricular Ejection Time (2).

The single most important determinant of systolic emptying time, and hence of ESV, is cardiac contractility, which, too, is controlled via the inotropic effect of the sympathetic and endocrine systems (see later). During cold stress, myocardial contraction velocity is slowed and there is a tendency for prolongation of systole. Associated with this is a decrease both in myocardial contractility and in left ventricular compliance.

e) Maximum Velocity of Contractile Element Shortening, measured from the instantaneous relationship between rate of change in tension ($\frac{dp}{dt}$) and isovolumetric pressure in the left ventricle;

f) Heart size and, in particular, the size of the individual chambers as measured, for example, by Angiocardiography;

g) State of Health of myocardial musculature, as determined by the electrocardiogram or by the presence in serum of the enzymes:

1. Lactic Dehydrogenase (LDH)
2. Creatine Phosphokinase (CPK), and
3. Glutamic Oxaloacetic Transaminase (GOT)

in above-normal quantities (indicating leakage out of myocardial intracellular fluid due to membrane damage). Of particular significance are the Isoenzyme forms of CPK, which include the three dimers: CPK-MM, CPK-MB, and CPK-BB.

h) Acceleration of the blood leaving the ventricles, which is a measure of the impulse imparted to the fluid by the contracting myocardium;

i) Peak flow velocity measured at the root of the aorta, which is a measure of the kinetic energy imparted to the fluid by the contracting myocardium, and, too, of the fluid momentum;

j) Stroke Power, approximated by the product of mean ventricular pressure $\{\frac{1}{2}\{p_{\substack{\text{max.} \\ \text{systolic}}} + p_{\substack{\text{min.} \\ \text{diastolic}}}\}\}$ and stroke volume {EDV - ESV} divided by systolic emptying time:

$$\text{Stroke Power} = \frac{\bar{p}_{\substack{\text{mean} \\ \text{ventricular}}} \times \text{S.V.}}{t_{\substack{\text{left ventricular} \\ \text{ejection time}}}}$$

k) Efficiency of Cardiac Muscle Contraction, defined to be the ratio of the work actually done by the muscle to the sum of the heat of activation (maintenance heat), the heat of shortening, and the work done.

l) Efficiency of Energy Conversion into Stroke Volume, defined to be the ratio of pressure-volume work ($\bar{p}_{\substack{\text{mean} \\ \text{ventricular}}} \times$ S.V.) to the sum of pressure-volume work plus strain energy lost.

m) Efficiency of other processes that lose energy in producing a stroke volume, such as metabolic activity required to maintain and repair myocardial cells, energy expended in the electrocardial wave of excitation, auxiliary chemical reactions, blood turbulence, and energy dissipated as interfascicular tension.

n) Efficiency of the cardiac cycle, defined to be the product of

(k), (l) and (m) above.

o) Efficiency of energy conversion from stroke power to fluid kinetic energy, defined to be the ratio of fluid kinetic energy to stroke work, $\bar{p}_{\substack{\text{mean} \\ \text{ventricular}}} \times$ S.V.

p) Efficiency of the heart, defined to be the ratio of useful stroke power to total power input (see later).

q) Weight and mass of the heart.

r) Rate of Oxygen Consumption by myocardial musculature; and,

s) The Respiration Quotient, defined to be the ratio of carbon dioxide produced by tissue metabolism to oxygen consumed in the same metabolism.

iii) The end diastolic volume of the heart is determined by the venous return to the right side of the heart, the filling pressure in the atria, the compliance of the ventricles, the strength of atrial contraction ("contractility" of atrial systole), and the total time of filling (ventricular diastole). Total filling time depends both on heart rate (cycles per minute) and on what percentage of the cardiac period is devoted to ejection (i.e., on myocardial contractility as discussed above). During cold stress, heart rate tends to decrease linearly with temperature, thus increasing the period of the cardiac cycle. Coupled with a slowing of myocardial contraction velocity, i.e., prolongation of systole, however, the two tend to offset each other to keep the filling time about the same. Inadequate systolic emptying and a corresponding increase in left ventricular end-diastolic pressure, together with an increased ventricular distensibility, tend to raise the end

diastolic volume. Again, however, the inadequate emptying tends to cause the stroke volume to stay essentially unchanged, i.e., both EDV and ESV go up by corresponding amounts. The relatively constant stroke volume and the decreasing heart rate cause total cardiac output to fall during cold stress. This could be further complicated if the rising EDV causes the ventricular musculature to go into a state of decompensation, where the Starling Mechanism becomes non-functional and stroke volume begins to drop off dramatically with increasing EDV.

iv) The Heart gets its energy basically from the blood supplied to it via the coronary circulation. Because of their unique location and pathways through the depressions of the heart, the coronary arteries receive 70-90% of their major supply of blood during the diastolic phase of the cardiac cycle. Extravascular compression of capillary beds during ventricular systole causes coronary flow to be momentarily interrupted, or even briefly reversed. Thus, anything (such as cold) that acts to increase the period of time that the ventricular musculature remains relaxed, is of benefit to the coronary perfusion rate and, ultimately, to the myocardial muscles themselves. Going one step further, sympathetic nerve stimulation tends to dilate the coronary arteries and reactive hyperemia due to increased carbon dioxide production also helps to maintain coronary flow at levels required for metabolic purposes. On the other hand, a systemic drop in blood pressure (hypotension due to hyperoxia), a rise in central venous pressure and a drop in ventricular oxygen consumption rate all act to reduce coronary inflow, as do changes in the blood and vascular system already

discussed earlier. The net effect is that coronary flow may go up, down, or remain unchanged during cold stress, depending on a number of factors.

v) Coronary perfusion rate is one of the factors that determines how much oxygen gets to the myocardial musculature. It is, of course, affected not only by the variables discussed in (iv) above, but also by the state of health of the blood vessels (patency, athero-arterio-sclerotic lesions, vascular spasms, etc.) and their geometry. The supply of oxygen to the myocardium, together with its ability to extract and utilize same from the blood determines, in turn, how much stroke power can ultimately by generated during the cardiac cycle. That is to say, in general, some 3 kilogram-meters of work can be performed for every cubic centimeter of oxygen that can be extracted from blood. Thus, the input power to the heart can be written as:

$$\text{Power In} = \underbrace{\left\{ [O_2]_{\substack{\text{Arterial} \\ \text{Blood}}} - [O_2]_{\substack{\text{Venous} \\ \text{Blood}}} \right\}}_{\substack{\text{Arterio-venous Oxygen} \\ \text{Concentration Difference,} \\ \text{in cc/liter of blood}}} \times 3 \frac{\text{kg-m}}{\text{cc } O_2} \times \begin{matrix} \text{Coronary Perfusion} \\ \text{Rate in Liters per} \\ \text{Minute} \end{matrix}$$

The output power is then: (Power In) × (Efficiency of Cardiac Muscle Contraction) × (Efficiency of energy conversion into stroke volume) × (efficiency of other processes that lose energy in producing a stroke volume).

As already mentioned, cold stress generally causes tissues to require more oxygen and so one finds that more oxygen is extracted

from hemoglobin. Ironically, however, the consumption of oxygen by the ventricular musculature falls during cold stress and there is a corresponding build up and retention of lactic acid in the tissue. This further reduces myocardial contractility and also contributes to a slowing (bradycardia) of the heart. In the limit it could ultimately lead to severe dysrhythmia, ventricular fibrillation, cardiac arrest, heart failure, and finally, death! In an effort to prevent this, mother nature has provided the cardiovascular system in man with the last of the four basic elements of the whole network--namely, the control system. While not strictly considered to be an integral "part of" the cardiovascular system per se, the various elements that control this system play an important enough role in its response to cold stress to be discussed separately in assessing and evaluating this response.

The Control System: Intrinsic (i.e., inherent characteristics of blood, the vascular channels and the heart) and Extrinsic (i.e., due to the autonomic, central nervous and endocrine systems).

Control of cardiovascular function is directed mainly at four basic variables: Cardiac Output, Total Blood Volume, Blood Pressure, and the Distribution of Blood (Peripheral Resistance) in the system; and it is accomplished by mechanisms that are either based on the inherent physico-chemical properties of the cardiovascular tissues themselves (intrinsic), or that can be traced to the effects on cardiovascular tissues of other organ systems in the body (extrinsic). Some important intrinsic control mechanisms include:

(i) The Frank-Starling Mechanism, which is based upon the length-tension characteristics of cardiac muscle fibers. Their ability to generate progressively larger forces the more they are stretched allows these fibers to compensate for increased venous return (larger EDV) by generating more systolic power. This insures that as much fluid will be pumped out of each ventricle, as comes in, a necessary condition for maintaining continuity between two pumps that are arranged in series, and is referred to as Heterometric Autoregulation.

(ii) A Self-Paced Sino-Atrial Node, which may be based on the permeability characteristics of the excitable tissue that lies in the upper portion of the right atrium. As the venous return from the systemic circulation dilates the right atrium, it stretches the delicate membrane of this sensitive SA node, causing it to discharge at some threshold level, and leading to atrial systole. This starts the cardiac cycle and the rate of venous return thus controls the heart rate intrinsically.

(iii) Myogenic Activity of Vascular Smooth Muscle Tissue, which is a smooth muscle response characteristic similar to the Myotatic, or stretch reflex in striated skeletal muscle. That is to say, when one stretches skeletal muscle, it generates (via the muscle spindle apparatus) a contraction (e.g., the tendon jerk). In a similar fashion, when one stretches vascular smooth muscle, as, for example by increasing blood pressure, blood volume, or both, it, too, responds by contracting. This acts to maintain blood flow to an organ relatively constant under normal conditions, and is sometimes called autoregulation.

(iv) Extravascular compression, which is a function of the permeability of capillaries. The theory here is that an increase in blood pressure, blood volume, or both, stretches the vascular tissue and thus permits net transfer of fluid from the intravascular space to the extravascular space. This transfer thus raises the fluid pressure in the extravascular space, thereby compressing the blood vessels and reducing the flow. It also causes a drop in intravascular blood volume, the increase of which may have been what started the problem to begin with.

(v) The effects of local metabolites on vascular smooth muscle. It is known, for example, that oxygen, carbon dioxide, lactic acid, potassium, adenine nucleotides, decreased pH, and various other products of metabolism inhibit smooth muscle tone. They thus lead to vasodilation when they accumulate in local regions (such as, for example, reactive hyperemia following brief periods of arterial occlusion) and vasoconstriction some of the other time.

(vi) Changes in blood and/or vascular tissue properties as a function of thermodynamic variables (temperature, pressure, etc.), metabolic rate, age, and chemical composition. These have been touched upon throughout this report and will not be dealt with to any further extent here.

(vii) Homeometric Autoregulation, which is that property of the heart by which it maintains a nearly constant end diastolic pressure even if the aortic pressure or venous return increases. It is believed that intrinsic release of myocardial catecholamines may be partly responsible for this.

(viii) A slowly responding atrioventricular node. The propagation

of the excitation impulse through the ventricular musculature is delayed at the A-V node, and the time of delay controls ventricular filling (EDV). Intrinsic alterations in the excitability and conducting properties of this node (the most dramatic of which would be a total A-V block) thus have dramatic effects both on heart rate and stroke volume.

(ix) Homeometric autoregulation is also responsible for the increased tension which is found in papillary muscles with increasing contraction frequency, although the basic mechanism involved is not clearly understood. One theory suggests that it may be due to a corresponding rise in intercellular calcium, paralleling the staircase effect which is observed in striated skeletal muscle when it is stimulated at gradually increasing frequencies.

(x) The oxygen-Reserve Mechanism, based on the fact that mass transfer is a function of the difference in concentration that exists for a species S distributed across a biological membrane. Normally, each 100 cc of arterial blood entering a capillary network contains approximately 19 cc of oxygen, of which 5 cc are removed on the average during routine metabolism, (arterio-venous difference equals $\frac{5 \text{ ml } O_2}{100 \text{ ml Blood}} = 5$ vol. %). During exertion, tissues use up oxygen at a higher rate. Thus, the concentration gradient driving O_2 <u>from</u> the blood <u>to</u> the cells increases, allowing the tissues to extract more oxygen from the blood and leading to a widened arterio-venous-oxygen-difference. Moreover, blood coming back <u>to</u> the lungs with less oxygen, by the same mechanism, is able to extract more oxygen from the alveoli, so the concentration of O_2 in the blood itself also tends to go up. The net result, known as the

oxygen-reserve mechanism and based on the intrinsic metabolic rate of tissues, is that during exertion, both the concentration of oxygen in blood increases while the concentration of oxygen in tissues decreases, so that the concentration gradient for O_2 transport to the tissues is greatly enhanced. Obviously, the reverse trend is manifest during periods of idleness. The oxygen-reserve mechanism is particularly important in the coronary circulation.

(xi) Arterio-Venous Anastomoses. These collateral vascular pathways, normally closed, can be forcibly opened by increases in blood pressure (like a pressure-relief valve). In this way, the distribution or flow of blood may be diverted from constricted vascular beds through emergency by-pass shunts which close again as the downstream pressure falls.

There are others, but they are not as important as those listed above, and they are rather poorly understood and/or documented. From the point of view of thermoregulation, control of cardiovascular function from extrinsic sources is of much greater interest, and we address here those parameters related to neural control via sympathetic and parasympathetic pathways, and humoral control via the endocrine glands, the kidney, abdominal tissues and local secretions.

The activity of autonomic effector neurons depends on the nature of the afferent information that reaches them from peripheral inputs. This information is generally integrated into an "afferent input profile" by the central nervous system, which then calls for a coherent autonomic nervous system response. Responses are generally called for to control blood pressure, blood temperature, blood chemistry, blood volume,

peripheral resistance, and cardiac output. Some of the more important extrinsic control mechanisms affect:

(i) Heart Rate (SA Node, Sympathetic Tachycardia, Parasympathetic Bradycardia)

(ii) Myocardial Contractility (Sympathetic Inotropic Effect, Vagus Nerve negative Inotropic Effect);

(iii) Peripheral Resistance (Sympathetic Vasoconstriction, Parasympathetic Vasodilation in the head, viscera, and genitalia);

(iv) End Systolic Volume (Myocardial Contractility) and End Diastolic Volume (Chronotropic Effect) of the heart;

(v) The speed of propagation of impulses through the heart (Sympathetic enhancement, Parasympathetic depression);

(vi) The refractory time of cardiac muscle (sympathetic decrease);

(vii) The velocity of muscle shortening (sympathetic acceleration, parasympathetic deceleration);

(viii) The synchrony of muscle shortening (enhanced by sympathetic nervous system activity);

(ix) The filling pressure of the ventricles (increased as a result of the Sympathetic inotropic response);

(x) Ventricular Distensibility (Sympathetic Increase, Parasympathetic Decrease);

(xi) Atrial contraction (end diastolic volume), (enhanced by sympathetic stimulation, depressed by parasympathetic activity);

(xii) The tension developed by the myocardium (sympathetic increase);

(xiii) Ejection Time (ESV), (sympathetic decrease);

(xiv) Filling Time (EDV), (sympathetic increase through decreased

ejection time, parasympathetic increase through bradycardia); and,

(xv) Maximum systolic ventricular pressure (increased by the inotropic effect of the sympathetic nervous system).

The input profile is generated by the central nervous system in response to information received from various receptors located strategically throughout the physiologic system. Among the more important ones are:

(i) Mechanoreceptors (stretch and/or baroreceptors):

a) Right and Left Internal Carotid Artery Sinus stretch receptors that send, via the sinus Nerve of Hering feeding into the IX'th cranial (Glossopharyngeal) Nerve, pressure information to cardiovascular regulatory centers in the medulla of the brain. The firing frequency, f_B, of these baroreceptors is proportional not only to the magnitude, p, of arterial pressure, but also to the rate-of-change with respect to time, $\frac{dp}{dt}$, of such pressure according to the relationship:

$$f_B = G_1 \frac{dp^+}{dt} + G_2 \frac{dp^-}{dt} + G_3[p(t) - p_t],$$

where p_t is the threshold pressure required to fire the receptor, G_1, G_2, and G_3 are sensitivity coefficients, and the super-scripts + and - are used to designate rates of increase (+) or decrease (-) in pressure. Since these have associated with them different sensitivity constants, G_1 and G_2 respectively, the reader will note that the sinus receptors respond differently to rates of pressure increase than they do to pressure decrease (a hysteresis effect). Furthermore, G_1, G_2,

and G_3, as well as p_t vary with the level of mean pressure, and f_B tends to be higher under cyclic loading than it is under steady-state loading.

b) Aortic Arch stretch receptors, located at the bifurcation of the Brachiocephalic artery into the right-subclavian and right common carotid arteries, and at the entrance to the left common carotid artery in the aortic arch. These baroreceptors are connected to the medulla by the Xth Cranial Nerve (The Vagus), which receives its information from the Aortic Depressor Nerve. Both the Aortic and Carotid Baroreceptor Reflex Systems work primarily through the arteriolar system to regulate peripheral resistance, and hence, blood pressure. The minimum firing threshold, p_t, of these receptors is approximately 40 mm Hg and they appear to respond to blood pressure up to a maximum of about 200 mm Hg. Some evidence suggests that under cold stress, the reflexes involving aortic baroreceptors, carotid bodies, and sympathetic vasoconstrictor fibers remain generally intact, but are significantly slowed due to alterations in propagation velocities. Thus, sudden changes in blood pressure could result in substantial adverse consequences before the organism could take the necessary steps to adjust.

c) Pulmonary Arterial Baroreceptors, located in both main branches of the Pulmonary Artery, allow the respiratory pump (ventilation) to adjust in response to changes in right ventricular output (pulmonary arterial pressure) that result from alterations in venous return to the right atrium. The

relationship between a rise in pulmonary pressure and ventilation is an inverse one, with an approximately 20% transient change in ventilation accompanying each 1 cm H_2O change in pressure. During cold stress, the breathing rate is reduced to minimize respiration losses (opposite of panting) that are associated with the volume of air moved to-and-fro across the moist surfaces of the upper respiratory tract. Pulmonary Artery baroreceptor reflexes are more pronounced in the respiratory system than they are in the circulatory system, becoming significant in the latter only if arterial pressure changes exceed 60 mm Hg.

d) Cardiac Mechanoreceptors, located in the left and right atrium, the coronary sinus, the epicardium and the left and right ventricles. Of these, the atrial receptors (whose effects are similar to but considerably weaker than those of the carotid sinus) appear to be most active, especially with respect to their effects on heart rate, renal vasculature, and atrial systole in response to rates of change of blood pressure in the atria. Ventricular receptors signal changes in systolic tension, which, if strong enough, can produce reflex bradycardia and hypotension. Normally, little information reaches the central nervous system from epicardial receptors, but these, too, if properly stimulated, can produce bradycardia, hypotension and a reduction in respiration.

(ii) Chemoreceptors:

Arterial chemoreceptors in the aortic arch and the carotid bodies are sensitive to changes in the partial pressures of oxygen

and carbon dioxide, to pH, and to certain abnormal fluid constituents, such as carbon monoxide. Cardiovascular responses (which are mediated through the diencephalon) to hypoxia plus hypercapnia include:

a) Bradycardia (due to increased vagal suppression of and reduced sympathetic excitation of the sino-atrial node);

b) Increased arterial blood pressure (due to sympathetic constrictor nerve activity);

c) Increased total peripheral resistance due to vasoconstriction;

d) Increased constrictor effects in all major beds, including muscle, skin, gastrointestinal, and renal beds, and,

e) Increased secretion of catecholamines.

Respiratory responses, for which the carotid bodies are three to six times more effective than the aortic body receptors, include the stimulation of ventilation with a reduction in pO_2 or a rise in pCO_2.

(iii) Thermoreceptors (temperature sensors):

a) Hypothalamic thermoreceptors appear to monitor blood temperature directly, with the Pre-Optic Anterior thermoregulatory center apparently responding to heat stress and the Posterior thermoregulatory center responding to cold stress.

b) Cold sensors in the spinal cord are intimately connected with the posterior hypothalamus and take part actively in the shivering response that involves activation of motor neurons. Strong stimulation of many somatic and visceral groups also evokes a spinal-reflex-induced increase in heart rate, blood pressure, regional constrictor effects, and secretion of

adrenal catecholamines.

c) Peripheral cutaneous temperature sensors in the skin (Krause's end-bulbs respond to cold, Raffini Corpuscles respond to warmth) also have intimate connections with both the anterior and posterior hypothalamus.

d) Mucosal Peripheral Sensors on the Tongue and in the nose, the latter providing sensory information via the Trigeminal, or V'th Cranial Nerve, are important in relation to diving and nasal circulatory reflexes.

e) Central visceral thermodetectors, the most important of which lie in muscles, the gastrointestinal tract, the kidney, the urinary tract, and the ventricular wall, all provide input to the central nervous system that ultimately manifests itself in some cardiovascular response to cold stress.

(iv) Osmoreceptors located in the supraoptic nuclei of the floor of the third ventricle of the brain lead to the release of ADH from the posterior pituitary, with its concomitant effects on both the cardiovascular system and the kidney nephron. In this way, extracellular fluid volume in general, and blood volume in particular, are controlled.

(v) Lung Inflation Receptors, or pulmonary stretch receptors are sensitive primarily to changes in transpulmonary pressure, and communicate with the central nervous system through the Vagus Nerve. Increased pulmonary stretch tends to suppress cardio-inhibitory effects from the stimulated chemoreceptors, as well as peripheral sympathetic constrictor tone in all major peripheral beds. It also renders the sympathetic constrictor mechanisms and

the autonomic mechanisms that control the heart rate less susceptible to incoming baroreceptor inputs during inspiration than during expiration. Respiratory centers in the brain can also influence vasomotor centers directly, even in the absence of respiratory movements.

Information about blood pressure, blood chemistry, blood gases, blood volume, blood temperature and environmental temperature sent to the central nervous system by the various transducers and pathways enumerated above ultimately finds its way to the vasomotor center of the brain. This center, located bilaterally in the reticular substance of the lower pons and upper medulla, maintains a partial state of contraction of blood vessels (called vasomotor tone) and controls both cardiac contractility and heart rate (through cardioaccelerator and cardioinhibitory centers). Depending on the response desired, the lateral part of the vasomotor center dominates cardiovascular function via sympathetic nerve fibers, or the medial part dominates via the parasympathetic fibers of the vagus nerve. The lateral and medial parts of the vasomotor center also inhibit one another reciprocally.

Tissues receive blood according to their metabolic requirements, their effect on body temperature, or their primary function relative to the life of the organism. For example, via a central ischemic reflex, a reduction of the blood supply to the brain leads to a rise in arterial pressure and a significant increase in sympathoadrenal activity, with a corresponding decrease in vagal activity. On the other hand, some tissues are not essential to life (e.g., the limbs), or exist in duplicate (e.g., kidneys, liver, lungs), or can still function under anaerobic or ischemic conditions (e.g., muscle), or are larger than they

need to be (e.g., stomach and intestines), or have very low metabolic requirements, or have substantial ischemic reserve capabilities, and so on. In these cases, the vasomotor centers distribute blood accordingly when a given situation requires a prioritization of available resources. It should also be mentioned that, while acting to control cardiovascular function, many of the receptors that generate input information for the central nervous system often have their own response characteristics affected by the very variables they are attempting to monitor. This is especially true in the case of temperature and stretch receptors. The response of stretch receptors depends very much on the mechanical properties of the tissue involved, which, in turn, are very dependent on temperature. Thus, we find, in general, that the response tends to get "sluggish" at lower temperatures. This illustrates the importance of realizing that an investigation of the cardiovascular response to cold stress should include, as well, the effects of cold temperatures on the associated mechanisms that directly or indirectly manifest themselves in altered cardiovascular function. Included might be such variables as nerve conduction velocities, parameters related to respiration, sensory receptor function, and so on--all emphasizing once more the intricate integration of all of the systems of the human organism into one functioning whole.

In addition to local (metabolites) and neural (acetylcholine, epinephrine, norephinephrine) chemical factors that control cardiovascular function, the performance of the heart and blood vessels also depends on humoral substances that are transported to various effector sites by the bloodstream. Some of the more imporatant ones are:

(i) Norepinephrine, secreted by the adrenal medulla in response to

sympathetic nerve stimulation via the posterior hypothalamus--produces vasoconstriction throughout the peripheral circulation (Vasopressor Action), is a powerful cardiac stimulator (Chronotropic and Inotropic Effects), produces coronary vasodilation, reactive bradycardia, increased systolic and diastolic blood pressure, increased peripheral resistance, and venoconstriction;

(ii) Epinephrine, also secreted by the adrenal medulla, is, in fact, the principal adrenal medullary secretion in man--Vasopressor Action, produces coronary vasodilation and transient dilation of the blood vessels of striated skeletal and cardiac muscle, Chronotropic Effect, Inotropic Effect, Activates phosphorylase activity in the heart, raises only the systolic blood pressure (vasodilator in skeletal muscle), reactive decrease in peripheral resistance, reflex tachycardia, bronchial dilator, prolongs contractile response of muscle, hyperglycemic agent, and increases secretion by the anterior pituitary gland;

(iii) Vasopressin (Anti-Diuretic-Hormone, ADH), secreted by the Neurohypophysis of the Pituitary Gland in response to signals received from the supra-optic and paraventricular nuclei of the hypothalamus--controls blood volume, osmotic pressure, vasopressor effect (constriction) on peripheral arteriolar and capillary beds, antidiuretic effect on kidney, and controls plasma volume;

(iv) The Kinins are small polypeptides that are split off from an α-globulin in plasma or tissue fluids by proteolytic enzymes. They are powerful vasodilators. Bradykinin is believed to be present in exocrine glands, but its physiologic significance is still a controversial issue;

(v) The enterochromaffin cells of the gastrointestinal tract and other abdominal structures give rise to a powerful smooth muscle stimulant and vasoconstrictor called Serotonin. This derivative of the amino acid Tryptophan is transported in the blood by Platelets and is commonly found in the brain and in other tissues. Since, depending on the state of the circulation, it may sometimes produce vasodilation, its role in vascular control is also somewhat poorly understood at present;

(vi) Renal Ischemia, low arterial blood pressure, or low sodium concentrations in blood cause the kidney to secrete Renin from its juxtaglomerular cells. Renin acts on the α_2-Globulins in blood to form the hormone Angiotensin II. Angiotensin exerts a powerful vasoconstrictor effect on the arterioles; it acts to encourage the release of Norephinephrine from adrenergic terminals and slow the reabsorption of same, and it stimulates increased secretion of Aldosterone from the Adrenal Cortex;

(vii) Histamine is released by damaged tissue to constrict the arterioles and dilate the veins;

(viii) Prostacyclin is manufactured in cell membranes. It is a powerful inhibitor of platelet aggregation and causes vasodilation in various vascular beds;

(ix) Prostaglandins (D_2,E_2,F_2) are also manufactured in cell membranes. In general, prostaglandins of the E-series are vasodilators and those of the F-series vasoconstrictors. They are synthesized from Arachidonic Acid, which is released from injured tissue;

(x) Thromboxane A_2, also released from cell membranes induces platelet aggregation and vasoconstriction.

In addition to these hormones and chemical activators themselves, one must be prepared to do chemical assays for precursors, substrates, enzymes and intermediate products associated with the manufacture of these compounds. For example, the biosynthesis of epinephrine in adrenergic nerve endings and the medulla of the adrenal gland proceeds from the precursor Tyrosine to DOPA (catalyzed by Tyrosine Hydroxylase) to Dopamine (catalyzed by Aromatic L-Amino Acid Decarboxylase) to the intermediate product, Norepinephrine, (catalyzed by the enzyme Dopamine-β-Hydroxylase), and finally, to the end-product, Epinephrine (catalyzed by the enzyme Phenylethanolamine-N-Methyltransferase). Similarly, Angiotensin I is a precursor of Angiotensin II, the enzyme involved being converting enzyme or Kininase II, and Kininogen is the precursor of lysin bradykinin (Kallidin, via the enzyme Kallikrein), which, in turn, is transformed into Bradykinin (enzyme is an aminopeptidase), which, finally, is metabolized into inactive peptides by Kininase I. And so the list may go on and on almost ad infinitum, the cut-off being more a function of an investigator's laboratory facilities and capabilities than of an exhaustion of available variables. Moreover, the responsiveness of cardiovascular tissue to all of these chemical control agents is quite temperature-sensitive. For example, when a cutaneous blood vessel is cooled from 37°C to 25°C, its response to sympathetic nerve stimulation or circulating catecholamines is augmented due to an increased affinity of the cell membrane of the cutaneous vascular smooth muscle cells for the vasoconstrictor substances.

The dual control of the cardiovascular system by extrinsic and intrinsic mechanisms allows for a wide range of adjustment. The heart rate can almost triple if necessary, to nearly 200 beats per minute.

So can stroke volume, from about 70 ml/beat to some 200 ml/beat by a 50% increase in end-diastolic volume and a 50% decrease in end-systolic volume. Thus, total cardiac output can skyrocket from the normal 5 liters per minute to as high as 35 or 40 liters per minute, a seven-fold increase! In the vascular system, flow rates may vary by a factor of 100 and capillary surface area by a factor of 7. Transport processes, likewise, can be greatly enhanced and chemical reactions accelerated. But it is important for the reader to be aware of the fact that the adaptations and control mechanisms discussed above have usually been investigated under highly artificial conditions. Hence, they may indicate only potential control mechanisms, or pre-dispositions for the responses suggested--since in the intact animal under stress (indeed, perhaps especially under cold stress) they may be, or are, often either overriden or modified by alternate control loops. There is just too much we still do not know, and perhaps all of the cardiovascular control pathways have not even been uncovered yet.

Concluding Remarks

The prevailing belief today is that vascular changes and tissue hypoxia are responsible for all types of local cold injury, and that variation in the clinical features or manifestations reflects variation in the nature of the insult and the host response. Problems with dehydration, impaired musculo-skeletal performance, metabolic disturbances, tissue necrosis, decreased mental proficiency, kidney and liver malfunction, and many other pathologic "correlates" of cold stress can be traced directly to consequences resulting from cardiovascular

responses to decreased environmental temperature.

As stated at the outset in this report, the physiologic response to cold stress is straightforward, in principle. But we then went on to identify some 400 parameters related to cardiovascular function alone (and, at that, the list is far from exhaustive) which may be affected by temperature, and in turn, may have associated with them potential adverse consequences. In other words--as is so often the case in the field of biomedical science--what is simple in principle, turns out to be not so simple to explain or understand. There is much, so very much, we do not know. There are processes which may not even have been discovered yet. There are subtleties that have yet escaped our attention. There are experimental boundaries that preclude our being able to study as comprehensively as we would like to, those physiologic pathways we know to exist; and there are analytic frontiers that must yet be expanded before mathematical techniques can yield more meaningful information. These are just some of the reasons that dimensional analysis has proven to be such a valuable aid in research. One can learn a great deal, without necessarily knowing--or even caring, at this point--all of the details associated with physical processes.

Thus, having identified the cardiovascular variables that are at least first order in the sense of thermoregulation, we shall go on in Part II of this series to group them into dimensionless parameters which govern thermoregulatory response. These are the parameters that should be addressed and measured in experimental investigations, and these non-dimensional quantities should shed some light on how the organism attempts to control body temperature.

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