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GENERAL DYNAMICS OF THE PHYSICAL-CHEMICAL SYSTEMS IN MAMMALS

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16. Abstract

Our previous report[1] reviewed the progress that we have made in understanding the principles upon which a global view of living systems might be based. Guided by that review we return in this report to the more detailed investigation of selected problems.

We have continued our investigation of human thermoregulation with a re-examination of physical foundations. Several discrepancies between generally accepted hypotheses and physical constraints were discovered. The difficulties are resolved by the introduction of two new hypotheses. A consistent steady-state model is described and suggestions for testing the hypotheses are made.

Having been invited by AIChE to present a paper on future directions for chemical engineers in biology, we offered as a unifying thesis our concept of homeokinesis, a general view of dynamically sustained processes, ever-beating in living systems at all levels. To provide chemical engineers with the deepest challenge, we described the physical-chemical problem of the chemical oscillator. We developed the issue from its lowest level, the origin of life, and attempted to relate it to the higher systems levels.

The work that we and others have done indicating the presence of blood glucose oscillations is still considered doubtful by some investigators. We have therefore carried out another experimental investigation of this subject. New data are presented which again substantiate the existence of such oscillations and which begins to explore possible mechanisms involved.

[1] "Introduction to a Biological Systems Science," NASA CR-1720, 1971.

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A. Introduction

In the late forties, while at the Bureau of Standards, the senior author made measurements on the thermal characteristics of the human body as a heat source, and found rapid changes in internal power. (The problem under investigation at the time was the heat load presented by a man in the confined space of a full pressure suit.) In 1950 a more detailed and quantitative study of the heat power was made, while studying clothing insulation, and reported in (1). From this quantitative study, there emerged a phenomenological picture of the overall metabolic dynamics in the complex homeotherm. It was found that rest metabolism, or constant activity state metabolism were not constant, but were in a sustained steady state of oscillation.

On the basis of these and other experimental studies, we have pursued a continuing discussion on the nature of human thermoregulation. It would be misleading not to point to the sustained discussion of the same problem to be found among physiologists. Basically, the problem lies in their field. The only contribution of the physical scientist or engineer is to force a dialectic in which proper attention is paid to the physical-thermodynamic aspects of the problem.

A number of major physiological reviews of thermoregulation may be found in (2-10). The nonspecialized reader who wishes a quick textbook introduction to the subject can start with Chapter 54 of Ruch and Patton (11), and Chapter 68 of Guyton (12). Newburgh (3) and then (2) and (4-10) follow in good order.

Against the background of this earlier material, we will attempt to carry out as much of a new synthesis as we believe possible of the dynamics of the heat flux-metabolism produced, and of the temperature potentials, both internal and external, that are maintained within the body.

Preliminaries

By thermoregulation in the human, we shall refer to the near constancy of the time averaged steady state core temperature of the human when exposed to a wide range of ambient temperatures or engaged in a wide range of sustainable activities.

Metabolism and oxygen consumption. Lavoisier was responsible for identifying heat production in the body as originating from an equivalent oxidation of foodstuffs. One finds in Sechonov (13) an attempt at a detailed balance between heat production and food consumption. By Rubner's time (14), a detailed balance had been achieved among various foodstuffs. Carbohydrates provide a mean value of about 4 kcal/gm in the body (alcohol for example provides about 7 kcal/gm); protein also provides about 4 kcal/gm; digestible fat provides about 7 kcal/gm.

We derive a relation between food intake, oxygen uptake and metabolism. If we express food intake in terms of a respiratory equivalent, or respiratory quotient, we have the following tabulated results (Table 1.1).

Table 1.1

	O_2 equivalent - kcal/ℓ	CO_2 equivalent - kcal/ℓ	R.Q. = $\frac{\Delta Q_{CO_2}}{\Delta Q_{O_2}}$
Carbohydrate	5.1	5.1	1.00
Protein	4.5[1]	5.6	.80
Fat	4.7	6.7	.71
Average diet (postabsorptive, at rest)	4.83	5.89	.82

Thus, in a reasonably close approximation,

$$M \approx 4.83\ \Delta Q_{ox}$$

M = metabolism (kcal/unit time)

ΔQ_{ox} = oxygen uptake (ℓ/unit time)

The average R.Q. (ratio of volume CO_2 produced to volume O_2 consumed) is given by 0.82.

[1]This would be high if protein were completely oxidized, but in humans protein is only broken down to urea.

Oxygen consumption and activity. The complex biological system is a degenerate thermodynamic engine. Thus at rest (post food absorption, in an undisturbed mental state), one finds a certain normal oxygen consumption required to maintain the living process. In a human this is about 0.25 lpm (i.e., a metabolism of 1.2 kcal/min or 1700 kcal/day). This might be considered a 'normal' rest metabolism. (Actually when lying down, asleep, the metabolism may drop to about .15 - .20 lpm, or 1200 - 1400 kcal/day.)

On the other hand, at peak activity that can be sustained 'aerobically', the maximum oxygen consumption is about 3 lpm.

'Aerobic' oxidation will be assumed to take place in the body, when the lactic acid production is still similar to that at rest. It has been found from such activities as mountain climbing, high altitude flying, cold and hot climate performance, that peak consumptions of 3 lpm can be maintained. It may be noted that it is doubtful that athletes, who can reach peaks of 4 - 7 lpm, can maintain consumption levels greater than 3 lpm (Costill (15)).

Even though men can operate at chemical equilibrium over a thermodynamic cycle, the objective 'work' that the system can perform, or the objective 'efficiency' with which a task can be performed (the efficiency might be measured by such parameters as speed, performance units per unit time, etc.) is not established. In any case it is low. Most of the energy associated with oxygen consumption winds up as heat, very little as work. By learning and training, the system can improve its skills. For example, some individuals, after practice can run a mile in 12 minutes, a few in under 4 minutes; the 'champion' 50 years ago could run a mile in 4.5 minutes, today in 3.8 minutes. Among different mammalian species of the same weight, some can run a mile in 2 minutes, others in 10 minutes. Thus within a species, between species, at different historical epochs in the life character of a species, performance capability can change. This may be summarized by stating that the efficiency with which a system can 'wire' together its motor systems for some resultant performance is a variable. It can only be characterized by population statistics associated with saturation performance of some well trained task that fits the animal's motor system. (E.g., humans can walk-run, fish can swim, birds can fly.)

Thus we can only grade performance over one objective parameter, oxygen consumption, and to use that we should grade it by steps of well practiced 'natural' performance (such as walking while carrying moderate loads).

Specific oxygen consumption, metabolism, and blood flow. A common assumption is that the area specific metabolism (metabolism per unit area) is essentially a constant, because of a near constancy of surface temperature. A closer 'truth' is that the weight specific metabolism is essentially a constant, because the weight specific blood flow is nearly a constant. The two variables - blood flow and metabolism (or oxygen consumption) - are tied very nearly by the oxy-hemoglobin saturation core at body ph. This is very nearly the same for all mammalian species.

Specifically, it appears that

$$A = C_1 W^{2/3}$$

A = mammalian surface area

W = mammalian weight

C_1 = a constant, essentially geometric

$$(M)_o = C_2 W^{0.9}$$

$$(\Delta Q_{ox})_o = C_3 W^{0.9}$$

$$(Q_b)_o = C_4 W^{0.9}$$

$(M)_o$ = mammalian metabolism (at rest)

$(\Delta Q_{ox})_o$ = mammalian oxygen consumption (at rest)

$(Q_b)_o$ = mammalian blood flow

If centered at human data, one would select

$W = 160$ lb.

$(\Delta Q_{ox})_o = 0.25$ lpm

$(Q_b)_o = 6$ lpm

These relations hold approximately over the size range shrew to large whale, and more closely rat to elephant. However, it appears that small mammals, below a few pounds in weight, have a higher metabolism. It appears that there may be a minimum oxygen rate that all mammals consume. It is not clear whether small animals, such as the shrew, consume considerable oxygen because they are 'nervous' and 'jittery', or that they are 'nervous' and 'jittery' because they have to consume considerable oxygen. These possibilities are open to 'explain' small animal metabolism.

(While they are not mammals, it is interesting to note that small quiescent fish (e.g., 2 gm) consume about 0.1 cc per gm per hr (twice that in normal activity). Note that if the rate 0.1-0.2 cc per gm per hr is extrapolated to human size, 160 lb, an oxygen uptake of 0.12-.24 lpm is obtained.)

Although these relations might permit us to generalize results for many species, we intend to specialize the thermoregulation problem for the human. (For example, not all mammals lose heat in evaporation in the same way. Dogs pant, losing evaporative heat through the tongue; rats lose heat through the tail; whereas humans lose heat through sweat glands in the skin.)

Temperature regulation versus ambient temperature and oxygen consumption (phenomenology). The characteristics that have to be explained are the following:

Given an ambient environment, characterized by an effective temperature (air and walls) T_a and relative humidity, a nude (or lightly clad or normally clothed) human engaged in a practiced sustainable activity in which he is consuming oxygen at a rate ΔQ_{ox}:

We note the following nominal characteristics.

One may note that the blood flow (cardiac output) varies over a 3-4 to 1 range (e.g., 5-6 lpm to 21 lpm); while the oxygen consumption (and thus metabolism) varies over a 10 to 1 range (e.g., 0.25 lpm to 3 lpm). The 'equilibrium' time scales vary over a considerable range.

While blood is delivered intermittently, beat by beat with a near one second period, the carotid baroreceptor only regulates blood pressure over a period of the order of 5-10 seconds. However, task start-ups (e.g., starting to run at a steady pace, or stopping) show a change of oxygen consumption of the order of 100 seconds. This has been traced to dynamics of local microvascular beds, which somehow are coordinated throughout the body, presumably by some blood carrier. A concomitant change in regional blood flow takes place with a seven minute period, as regional blood flows change. However, thermodynamic equilibrium of the oxidation reaction does not seem to take place in less than three hours. Thus physically, one may regard this as the first steady state 'equilibrium' period.

The character, or status of the system cannot be determined in less than a day, principally because of the rest-wake cycle. Loosely one might characterize people as active, 'athletic', or sedentary. In both cases the average metabolism is much closer to the rest metabolism than to the metabolism during the highly energetic state. What distinguishes an athlete from a non-athlete is that on the average the athlete will engage in a certain amount of daily duty cycle at high activity. This activity changes the operating point of his cardiovascular system, both of the heart and of the microvascular control settings. This is not seen so much at the extremes of oxygen uptake - at rest or at 3 lpm exertion, but in a more favorable uptake in between. Also the athlete will show a lower heart rate for the same tasks.

The status of the system can be changed adaptively by activity or inactivity in a period of about 3 weeks. The changes are primarily in the capillary characteristics and tissue character. However, such adaptive changes, are not our present concern.

Loosely speaking, mammals will exhibit similar weight specific blood flow demand at rest and in activity. An approximate idea of the balances in rest and activity can be obtained as follows (Table 1.2):

Table 1.2

Vascular demand at rest in mammals

Tissue	weight specific demand-ml/min per 100 gm tissue	percent of total cardiac output
Organ tissue (note exceptions-heart for example is 120±30)	30-120 range; 75±30	30
Kidney	430±50	15±4
Glandular tissue	220±100	0.3
Skin	10±4	7±1
'Carcass' (approx. half is muscle)	20	50
Cardiac output	18±7	100

At rest -

Weight balance:

	organ		kidney		gland		skin		carcass		
	$\frac{.30}{75}$	+	$\frac{.15}{430}$	+	$\frac{.003}{220}$	+	$\frac{.07}{10}$	+	$\frac{.50}{20}$	$\approx$	$\frac{1.00}{18}$
or	11%	+	1%	+	0%	+	19%	+	69%	$\approx$	100%

Flow balance:

	.30	+	.15	+	.003	+	.07	+	.50	$\approx$	1.00

At peak sustained activity -

Flow balance:

$$.30 + .15 + .033 + \frac{12}{1}.07 + (\tfrac{1}{2} \times 50 + \tfrac{1}{2} \times \frac{6}{1} \times .50) = 3$$

Thus while organ demand-tissue demand is fairly constant (75±30 ml/min/100 gm tissue), there are exceptionally high specific demands made by glandular tissue (a negligible problem here) and kidney. However, one should note the low demands made by skin and 'carcass'. It is the basic large demand changes that can be made by skin (local skin flow can change by a factor of 200), and by muscle (we will regard 'half' the carcass as being muscle) that represent the active cardiovascular changes from rest to exercise.

Under activity, the organ flows change only moderately. The substantial change that takes place is largely in peripheral muscle and skin. Roughly speaking, at peak activity the number of capillaries open in muscle doubles, and the peak muscle flow can increase about 20 fold. Skin flow can increase 200 fold. It is this 20 fold increase of blood flow in muscle of about 15% of the body mass that represents the increase in blood flow.

However, we cannot assure the peak increase throughout the entire mass of skin and muscle. Thus in our estimated calculations we have shown skin and muscle demand brought up to the level of active heart as muscle. Thus skin, perfused at rest at 10 ml/cc/100 gm tissue and muscle (half the carcass) perfused at rest at 20, are both brought up to 120 (the value for heart). A valid order of magnitude of blood flow is so calculated at peak activity.

The limitation of peak sustained blood flow (i.e., to a 3-4 fold increase over rest) is not the result of saturation of the controls (control of blood flow does not take place at the capillaries, but at the arteriole level). It is due principally to the saturation of the metabolic charge for the effort of the ventilation muscles.

Basically metabolism, or oxygen uptake, is determined at the capillary level at the 100 second time scale. (The blood flow, at the 400 second time scale is a follower. It is reset by hypothalamic control at the arteriolar level.) However the capillaries are caught up in a dual role. Their opening is temperature sensitive. On the other hand, the large degree of proliferation of capillaries (a capillary, on the average is arrayed within 60μ of another capillary) makes them a heat exchanger.

Capillaries are wide open in the temperature range 35-37°C, and in process of opening at about 30°C. Thus the local bed has autoregulatory thermal characteristics in that zone in which temperature is changing, that is, the skin.

Heat pulsing in capillaries of skin affects the sweat glands. Thus both show a 100 second cycle. However, the blood flow is shifted at a 400 second level, particularly in skin. Thus large shifts in the external flux, via heat exchange, take place. This has a large concomitance with the regional heat loss by evaporation through sweat glands.

For the phenomenological aspects of thermoregulation, we note the following nominal characteristics (Figure 1.3):

We regard the 'first' problem in describing the thermoregulation of the mammal (here particularly the human) to be to account, by internal mechanisms and by consistency with internal results, for the very nominal near constancy of deep body temperature, for those regulated characteristics of metabolism, and for the known experimental variation of average surface temperature and evaporative (water) loss. The totality of data to be accounted for descriptively are somewhat speculative. However they have been framed on the following experimental facts and studies.

1. For men at rest, the average metabolism at 0°C (10 hr average for men sleeping nearly nude) is about 30% higher than at 20°C.

   We interpret this to be mainly a charge placed on the cardiovascular system to maintain the perfusion distribution at low temperature against intense vasoconstriction. Thus we assume that this 30% rise may likely occur at every activity level.

2. Based on weaker experimental evidence, there seems to be a similar rise in metabolic rate beyond the "neutral" (i.e., minimum metabolism) temperature for the higher temperature range.

   We interpret this to be mainly a charge placed on the cardiovascular system to maintain the perfusion distribution at high temperature, i.e., to maintain vasodilatation capable of pouring maximum amount of fluid out through sweat glands for evaporative cooling. We assume that this 30% rise may likely occur at every activity level.

3. We have selected the minimum metabolism points at each activity level to fall along the Scholander lines. At least for humans, we regard these Scholander lines not as textbooks do, as a 'chemically regulated'

metabolism which increases linearly with decreasing temperature, but as a behavioral locus (an activity-temperature 'comfort' line) of mean activity for each ambient temperature and insulation that an animal has available. The choice of activity satisfies some long term behavioral algorithm, which in our present discussion does not concern us. In the shorter thermodynamic scale (i.e., 3-4 hours) the central nervous system is viewed as clamping on an activity pattern. The data thus represent not only 'comfort' operation, but all states of thermodynamic equilibrium, up to its breakdown as a simple equilibrium oxidation.

4. At temperature extremes, the system fails. The physiological literature is weak on data. Thus we have had to surmise. Ten hour sleeping data in air have been found. Of course, in water exposure - data from water immersed fliers, and from the horrible Nazi data - in 0°C water immersion, death takes place rather quickly. A recent study on rats, who have little body capacitance, indicates rapid breakdown of the regulation at 20°C in water immersion. It was found that the breakdown occurs when the skin temperature drops below 25°C. This agrees with our temperature measurements in capillaries. Guided by physical intuition, we place the cold limitation in the vicinity of -10°C. We have similarly scaled the death by 'freezing' for other activities. For example, we can believe that a champion runner might sustain life at peak sustained activity while running, near nude, at -40°C to -50°C. (Difficulties might arise with freezing of 'sweat' or 'moisture' for specialized regions. However light shielding of these regions, which would not affect insulation, only the surface deposition of ice, could sustain the activity.)

5. At high temperature, heat prostration due to inadequacy of evaporative regulation occurs. We have the limiting losses occuring with 100% wetted surface. This occurs near ambient temperatures of 40° to 50°C. We assume that with increased activity the limit of survival shifts along some curve.

A Review of Physiological Views

The classical physiological views of human thermoregulation have wobbled between regulation of an internal center (e.g., the hypothalamus, generally as 'thermostat') and regulation of the surface temperature. In general both views have been accepted and specialized 'temperature transducers' (i.e., temperature-electrical pulse code in the CNS) are postulated. On the other hand, a 'set-point' is also postulated at some central region. Hammel (9) points out that since excitable nervous tissue is temperature sensitive "it is surprising, not that temperature is transduced by excitable tissue, but that the process appears to be achieved principally by specialized thermal detectors or receptors". Even though he visualizes the possibility of "cold-sensitive" and "warm-sensitive" neurons, he assumes "that the hypothalamic temperature, when transduced, becomes the regulated temperature", but that "the other body temperatures, as well as other factors, influence the thermoregulatory responses". He assumes that there is a reference temperature, with a neural basis, and that this virtual (i.e., not real) temperature provides the set point.

Carlson (6) characterizes a concept of hypothalamic regulation by

"The...concept may be summarized as postulating a thermally sensitive (anterior) area of the hypothalamus from which heat loss originates... A heat maintenance center (posterior), that is insensitive to the stimulus of temperature, relays cold receptor impulses, transducing these into shivering and increased heat production. An interrelation exists between the two centers - anterior inhibiting posterior".

Benzinger (10) claims that, as a result of his work,

"The action of the thermoregulatory system could now be expressed in terms of excitation and inhibition... Moreover, the 'set-point' of the regulatory system, previously a theoretical concept, was defined experimentally... and reproduced with high precision as a characteristic of the human thermostat ...with significant differences between individuals".

From a recent article in Science by Myers and Veale (16):

"According to the monamine theory of thermoregulation...serotonin (5-HT) and norepinephrine (NE) are released possibly as transmitters from the anterior hypothalamus in functional opposition to one another in order to control the temperature of an animal around a given set point... Acting within the same hypothalamic site, one amine activates the heat production pathway when the animal is cold, and the other stimulates the heat-loss pathway when the animal is warm. However, the theory does not account for the mechanism in the central nervous system whereby temperature is intrinsically set and maintained in most mammals at a constant level of 37°C or thereabouts".

They propose:

"The mechanism for this set point appears to depend on a constant and inherent balance between sodium and calcium ions within the posterior hypothalamus".

Our criticism is that none of the reviews have arrived at a satisfactory physical heat balance inside and outside the body, and their discussions of so-called 'regulatory' or 'feedback' or 'set-point' or 'thermostatted' mechanisms, all dealing descriptively with operation of relatively high frequency, do not make clear the physical requirements and the constraints they place on mechanisms. Instead, we will now propose one new and some slightly novel physical analysis that will show that most of the thermal response is nearly an autoregulatory response. We shall propose that 'sensing' (e.g., central or skin) or 'control' mechanisms (also central or peripheral) have arisen to augment and expedite the autoregulatory response.

Furthermore, we will propose, more generally, that essentially all control mechanisms have followed (in phylogenetic evolution) the autoregulatory function, generally concomitant with the rapid chemically reactive flow streams within living organisms. Sensors, we suggest, follow function, in evolution. When a function is there crudely, selection pressure, through mutation, will

select a genetically codable process that augments the function. It is 'precipitated' into the internal milieu.

Loosely, the cortex assigns a task to the body. Through nervous channels, it organizes and coordinates the muscle patterns that will be used in the task. (We are discussing this over an epoch for which thermodynamic equilibrium will be nearly established. This means a period of the order of 3-4 Hours). However this does not guarantee the thermodynamic engine capability to perform the task, as the following crude argument will show.

The cortex assigns a nominal velocity to the body and thus to the practiced muscle set. It does not assure the resisting force structure that will be discovered (e.g., walking over rough ground) in performing the task. However

$$P = \Sigma FxV$$

P = power ('shaft horsepower', here 'metabolism')

F = resisting forces

V = local velocities

$$P = M = C\,\Delta Q_{ox}$$

M = metabolic expenditure

ΔQ_{ox} = oxygen consumption

C = approximate constant relating heat power and oxygen consumption

Thus the muscles can attempt to deplete local tissue of oxygen.

In the physiological picture, the tissue is maintained at a fairly high partial pressure of oxygen, and it is nervous control which will determine how much oxygen will be stripped from the blood supply. For example, the arterial oxygen concentration (with a heme carrier) is about 19-20 vol. %. On the average, the venous exit at the end of the capillary exchange bed is about 15 vol. %, for an a-v difference of about 5 vol. %; but for an active 'muscle' like heart, the a-v difference is 15 vol. %.

We have offered an entirely different dynamic picture. Based on our own observations of a local heat pulsing in all tissue (that is, as measured by dT/dt, where temperature T is averaged over an appreciable size, approximately 1 mm, to span microvascular features), we find the heat production per unit mass or volume of tissue to be oscillatory. The highest coherent frequency of about 1 cycle per 100 seconds, we proposed, was a follower engine for muscle power. It is our contention that the muscle fiber is an unstable engine element. If supplied with oxygen it will take up as much oxygen as is available. Thus, we premise that the muscle fiber must be oxygen flow limited. This flow

takes place by transfer from the capillaries. We have also shown that red cell flow in capillaries is oscillatory (not the plasma flow, but the file of red cells). Thus, we suggest, muscle zones are nervously innervated to provide a velocity; the muscles use up local oxygen; a combustion by-product, say CO_2, or lactate, may then 'speak' to such 'amplifier' structures as the mast cells; these then 'speak' pharmacologically through 'histamine' (or by a chemo-electric gating control) to the capillaries. This is a very long speculative chain. One piece of evidence for it is the appearance of a low cyclic tissue pressure (Whalen (17)) with about the proposed period. Conventionally, physiological literature considers tissue pressure to be high (of the order of 15 mm Hg), whereas we believe that Whalen has shown a tissue pressure oscillating between 0-5 mm Hg, implying an active mechanism.

In our picture oxygen uptake, and thus metabolism, are followers of resistance to muscular effort.

Note that power consumption has essentially nothing to do with ambient temperature. As a first approximation this is true, as is indicated by data for the ambient temperature range 20-35°C.

However, in a loose sense, the body interior (its 'core') has to be thermoregulated. This task is assigned to an automatic (autonomic) nervous function. The physiologists have sought a specific site to act as a 'thermostat', a 'set-point' for a temperature controller and normally found it in the hypothalamus. However, as we will show, its sharp 'control' characteristics are more illusory than they realize. The important function that takes place is a redivision of blood flow between the core and the periphery to achieve the core thermoregulation. Nominally, the core acts such that, if any region gets too warm (e.g., by virtue of a high production of local heat in the two minute thermodynamic engine cycle), there is a follower action by temperature sensing at the hypothalamus and the local tissue to provide that region with more blood. This takes place at the arteriolar level at the 400 second time scale. (A direct proof of the long term adaptive nature of the vasculature was provided by an experiment reported by Hammel. A heater, in the 5-10 watt range, was implanted in a sheep. Its surface temperature was hot. After a period of weeks it was colder than surrounding tissue. The change in vasculature providing compensatory heat exchange.)

Thus, if an organ increases its activity (as we discussed for muscle), there is an increased red cell supply demanded in the capillaries and the internal organ heats up. This is sensed by the hypothalamus (e.g., the hypothalamus outlines the body in a thermal mixing sense) and possibly locally (speculatively through thermal sensitive hormone (chemical) signals, or nervous transducers). A resubdivision of blood takes place and cools the local region. This follower action supplies blood in proportion to the local 'action'. In the case of the skin, it is both the hypothalamus and the thermal sensitivity of the microvasculature and possibly skin temperature sensors that help to resubdivide the blood between core and skin.

Note the elegance of the system. The same blood carrier, possibly by the same hypothalamic algorithm, simultaneously subdivides its flow among capillary carriers (nutrient and non-nutrient shunts) to provide the oxygen follower, the

'oxygen choke', to run the local thermodynamic muscle engine; the local heating calls up more local blood perfusion to 'put the thermal fire out', unwittingly to be able to follow the increased oxygen demand; and at the same time it can follow the external skin heating to put the thermal fire out by supplying more blood flow, unwittingly providing a path to-get-rid-of the more difficult heat.

However an additional function is achieved. The increased surface blood flow has a corollary capability to transfer plasma - water - out of the capillaries. The transfer capability exists in all capillaries, but there is a specialization in surface transfer. In the human, there are sweat glands. The corollary of waves of heat flow via the perfusion blood heat exchanger is waves of evaporative transfer via the sweat glands. The sweat glands show a twinkling performance (in number opening per unit time per unit area) similar to the red cell file in capillaries.

The two processes, shifting flow and metabolic output to the periphery and shifting evaporative water exchange to the periphery, are concomitant. This remark does not characterize the phase. Phase relations arise because the consequences of the slow blood follower upon metabolism (400 seconds) and upon evaporation are dynamically interrelated in their effect upon the hypothalamus.

We return to the question of equilibrium and refer to Benzinger's review. In his data, Benzinger never makes clear when he has an equilibrium situation. Thus one must always analyze his data with great care. We suspect that, typically, Benzinger's results present dynamic data, likely averaged over the two minute processes, i.e., the fast changes that we suggest take place within two minutes are averaged over, so that their existence cannot be detected in his data.

Figure 1.5 is a composite of Benzinger's Figures 9B and 18 which represent respectively the "metabolic" or "chemical" response to cold of a water immersed subject and the sweating response to heat. It is implied in (10) that the metabolic response curve is to be considered to represent the metabolism vs. temperature even for a subject not immersed in water.

To Benzinger's physiological data we add one external physical law

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

where $\bar{T}_s$ is the mean skin temperature.

This law states that regardless of internal mechanism, the net heat produced must be carried off by an equivalent 'conductance'. This is essentially a statement of the first law of thermodynamics. We shall show that a plausible magnitude for h is 7 kcal/m^2/hr/^oC. We point out that this law holds only at equilibrium. For transient conditions a time dependent term must be added.

We now examine the data in Figure 3.5 to see if they satisfy the above relation. We find that if one searches, essentially by trial and error, he

can find sets of mean skin and temperatures, metabolism and evaporative heat loss which, when taken with others' results for ambient temperature, satisfy the relation. For example the combination $\bar{T}_s = 35^oC$, $T_r = 36.9^oC$, M = 40 kcal/m^2/hr, E = 45 kcal/m^2/hr yields $T_a = 36^oC$, close to a reported value of 35^oC (cf. Carlson (6) or Newburgh (3)). Such a combination represents an operating point around which the various parameters oscillate with an approximate two minute period. To illustrate, if T_r were to fall below 36.9^oC then E would fall, heat would be stored and T_r would go up, eventually overshooting 36.9^oC. Then E would rise, excess heat would be lost, and T_r would fall. Thus Figure 3.5 is a picture of dynamic thermoregulation. Operating points based on Benzinger's data can be found for $\bar{T}_s \gtrsim 33^oC$. Below this the so-called "metabolic response" is supposed to provide the regulation. However, as several investigators have shown, there is only a 20-30% rise in the equilibrium value of M between $T_a = 25^oC$ and 0^oC. Benzinger's data indicate a doubling or tripling of the basal metabolism to obtain operating points below $T_s \gtrsim 30^oC$. He gets this result apparently because his data are dynamic data - it has been shown that metabolism may vary by a factor of two or three on a two minute scale. The extrapolation of such data to determine equilibrium values is very risky. (This issue of dynamic vs. equilibrium data has been analyzed more fully in our NASA Report CR-141 (1c) but, unfortunately, recent reviews have not taken due notice of our work.)

Because he is evidently mixing dynamic and equilibrium data or concepts, Benzinger states (in (10), Figures 14, 15, 16) that the apparent existence of a "discordant" relation between sweat rate and skin temperature is "paradoxical and 'antihomeostatic'", although sweat rate and central hypothalamic temperature are "concordant". He states that when he started his 1958 work "It was expected that sweating would follow the average temperature of the skin in the classic tradition, with skin warm-receptors as the hypothetical origin of exciting warm-impulses and central temperature prescribing the action of 'thermoregulator' in some as yet undetermined manner. The experimental results did not support those expectations." He thus points out "In spite of the trite observation that man in a warm environment has a warm skin and sweats, an opposite relation was presently seen".

We have argued, since 1965, that Benzinger's data can only be understood as part of a dynamic model. We started from a model in which metabolism and evaportation were largely variable, and temperature moderately so. We have used Benzinger's data to augment our model to the extent that we realized that metabolism and evaporation are fundamentally tied together, not by a 'static' value for hypothalamic temperature, but in some large scale autoregulatory chain, with about a seven minute time scale.

Thus Benzinger's figures, providing dynamic data (Figures 14, 15, 16) prove the reality of the model that we offered him. Basically, as we have interpreted it, using our dynamic modelling and Benzinger's data, a nearly regulated hypothalamic temperature T_r always cycles a little (via dynamic regulatory mechamisms). As T_r drops, metabolism M rises and evaporation E falls, skin temperature T_s rises; T_r rises; M falls; E rises; T_s falls; T_r falls, etc.

There is still not a model for the regulation of the metabolism but, given its regulation, we shall show a novel view of the dynamics of evaporation. We believe this new model has important bearing on the character of fever. Further, we believe we can account for the average state of thermoregulation. The net effect of our modelling is to narrow the range of physiological mechanisms required to account for thermoregulation and its breakdown.

In particular, it is common to see the following equations written to account for thermoregulation.

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

for the heat transfer through the external boundary layer; and

$$M = C\ (T_r - \bar{T}_s)$$

for the heat transfer through the peripheral conductance. The second equation states that at equilibrium, the metabolic heat produced within the core is conducted through a peripheral layer between the near linear gradient of 'core' (T_r) to skin. We have offered evidence that this layer should be identified not as a 'skin' layer (to the fascia) but as a depth to the middle of the muscle layer.

We now submit that this second equation is incomplete. We expressed our preliminary uneasiness on the paradoxes in the heat flux and temperature potentials in (1c) (see pp. 29-34 of that report).

The basic novel idea we add is that the heat which is to make its passage via the peripheral 'muscle-skin' layer is not 'conducted' solely vis-a-vis a thermal gradient, but that a significant part of it may be absorbed in the passage as a subsurface 'evaporation'. The sweat glands act as if they penetrate well into the layer and the 'pot-boiling' of water takes place deep in the tissue. Thus we would write, for a second equation, in the limiting case of totally subsurface evaporation:

$$M = C\ (T_r - \bar{T}_s) + E$$

In this very rudimentary form, the two equations subtract, leading nearly, to

$$h(\bar{T}_s - T_a) = C(T_r - \bar{T}_s)$$

If we take $T_r \approx 37^{\circ}C$, $h \approx 7$ kcal/m^2/hr/$^{\circ}C$; $C = 10$ kcal/m^2/hr/$^{\circ}C$ for vasoconstricted tissue (e.g., in the cold); or $C = 30$ kcal/m^2/hr/$^{\circ}C$ for vasodilated tissue (e.g., in the warm) we get

$$\bar{T}_s = \frac{C}{k+C} T_r + \frac{k}{k+C} T_a$$

$$\bar{T}_s = 22 + .41\ T_a \quad \text{in the cold}$$

$$\bar{T}_s = 30 + .19\ T_a \quad \text{in the warm}$$

We plot these 'curves' and compare them with the experimental data (see Carlson (6), data from Hardy and DuBois (18) and Wezler (19)), Figure 6.

The close agreement suggests that the novel idea of the mechanism for 'blowing off steam' from below the surface as a major element in thermoregulation merits further physiological consideration. (A more sophisticated treatment is given in the next section.)

We recapitulate. Note that basically we used only minimal assumptions: one, a physical model of the equivalent conductance of an air boundary layer; two, a physical-physiological model that tissue vasodilates and vasoconstricts and thus presents limiting condustances of 'fat' and 'water'; three, the assumption of a core thermoregulated at 37°C; and four, a physical-physiological assumption that the evaporative heat can be abstracted mainly subsurface. We point out that, with regard to the last assumption, in the limit it intersects with a limiting physical assumption in which the psychrometric character of the entire body (i.e., its wet bulb-dry bulb depression) governs. This takes place when the 'entire skin' of the body is wetted. This state was explored by Kerslake and colleagues (20).

With these assumptions we have shown that skin temperature can be accounted for by essentially physical reasoning. Thus we are left with essentially two additional physiological 'facts' to establish; one, how or why the internal temperature is thermoregulated at 37°C; and two, how, when, or why tissue vasoconstricts or dilates. (In an earlier study (1h), we reported on an experimental observation from our laboratory. The microvasculature (capillaries) seemed to vasoconstrict or dilate in muscle, just as in skin, depending on temperature. Below 30°C muscle tissue temperature, the tissue was tightly constricted; it appeared blanched. Above 35°C, the tissue was highly vasodilated. We thus believe, aside from any chemical sensitivity that they may have, the capillaries are certainly sensitive to temperature.)

With this preliminary introduction, we can carry on our modelling.

B. Steady-State Thermoregulation

In this section we proceed to quantify some of the ideas presented in the Introduction. Here we are particularly concerned with the physical-physiological structure of the thermoregulatory system.

Understanding of the steady-state behavior of a system is a necessary prerequisite to study of the system's dynamic behavior. Thus for the present we confine our attention to developing a steady-state model of thermoregulation. The time required for the body to reach a thermodynamic equilibrium is on the order of three to four hours. Simple observation shows obvious changes in surface conditions for at least this long a period. Data obtained over shorter periods should be considered as dynamic and should be extrapolated to represent the steady-state only with great caution.

In order to identify and clarify the basic physical and physical-physiological issues involved in the steady-state thermoregulation we formulate the problem in the following way:

We consider that there are essentially two independent variables, the activity level of the subject (e.g., resting, walking, running) characterized by his metabolism (per unit total surface area) M, and the environmental conditions of the experiment, which can be essentially characterized by an "effective", or "operative", temperature. This effective temperature is a prescribed combination of the "air" temperature and the radiative "wall" temperatures. For our purposes we shall generally consider these two temperatures to be the same and indicate the "ambient" temperature as T_a. Other environmental factors important under some conditions are the relative humidity, wind velocity, size of the room in which the experiments are performed, and orientation of the subject. The effects of these factors will be considered at the appropriate points below.

Given the independent variables, one seeks to model the system in order to predict the observable dependent variables. Of interest are the deep body temperature T_r, the evaporative heat losses (per unit total surface area)E, and the mean surface skin temperature $\bar{T}_s$. (The metabolism M has a small dependence on T_a which we shall not try to model at this point. A qualitative view of this dependence was given in the Introduction.) The data which are available for the dependent variables were presented in Figure 1.3. These data represent averages over the published values (1c, 18, 21-25) of each variable at the given ambient temperature. All the data are for nude or nearly nude individuals subject to low wind velocity (about 15 ft/min) and low relative humidity (less than 30%) conditions. The temperature data are for resting subjects.

There are several noteworthy features. An important fact influencing realistic modelling is that, for a chosen activity, e.g., resting, the metabolism changes only about 30% over a wide range of temperatures. (The dotted lines in Figure 1.3a indicate educated guesses as to the equilibrium levels

at high activity and the limits of survivability.) Thus, the independent choice of activity essentially determines the metabolism. The evaporative heat loss shows an expected behavior. It is small at low temperatures and then "turns on" at about $\bar{T}_s \approx 34^oC$ ($T_a \approx 30^oC$, resting) and increases rapidly thereafter. The deep body temperature T_r is nearly constant at 37^oC. Explanation of this fact is one of the major objectives in modelling the thermoregulatory mechanisms.

This study has uncovered a number of inconsistencies in the previous modelling of thermoregulation. In order to distinguish sharply between relevant physical issues and essentially physiological issues, we will construct a semi-phenomenological model. Thus, we assume that the behavior of E and T_r are known (as given in Figure 1.3b and 1.3c) for resting, nude individuals, and we shall try to model $\bar{T}_s$. The physical problem is that of heat transfer equilibrium between the body and the environment, and can be described as a determination of the heat transfer coefficients for transfer through the skin (C) and transfer across the skin-to-air boundary layer (h). Clarification of C is a physical-physiological problem since the nature and structure of the skin and subcutaneous layers are involved. Understanding of h is essentially a physical problem dealing with heat transfer from a surface (skin) into a fluid (air). We shall treat the physical problem first.

Skin-to-Air Conductance - Theory of h

The first step is to determine empirical values of the heat transfer coefficient h which we are trying to model. We define h by

$$h \equiv \frac{M - E}{\bar{T}_s - T_a}$$

where now M and E have been modified by the following consideration. About one-tenth (0.1) of the metabolic heat is lost by evaporation through the breath and hence is not transferred across the skin. Thus the M and E above (and henceforth) actually represent (M - .1M) and (E - .1M) (that is, they represent the metabolic and evaporative heat transfers through and across the skin per unit total surface area). We solve the above equation for $\bar{T}_s$,

$$\bar{T}_s = T_a + \frac{M - E}{h}$$

Using the data in Figure 1.3 we can plot $\bar{T}_s$ vs. T_a for various values of h (Figure 1.7). The solid dots represent averages of the $\bar{T}_s$ data in the literature. We see that for h to be consistent with this data it must vary from about 7 $kcal/m^2/hr/^oC$ at $T_a \approx 45^oC$ to about 3 $kcal/m^2/hr/^oC$ at $T_a \approx 5^oC$.

The theory for h can be developed in a straightforward way. Three factors are of importance: radiation, free convection, and forced convection. The effects are essentially additive and the individual contributions can be found in standard references (e.g., 26, 27).

Radiation. The heat transfer coefficient due to radiation can be estimated in the following way. We assume the skin is a perfect black body - its emissivity is 0.99 (3, p. 81). If we take the radiative environmental temperature to be the ambient effective temperature T_a, then according to Stefan's law the body receives energy $s\tau_a^4$ per unit radiating area per unit time (s is Stefan's constant, temperatures τ are in ^oK) and emits energy $s\bar{\tau}_s^4$ per unit radiating area per unit time. The effective radiating surface is about three-fourths of the Dubois area and so the net heat radiated by the body per unit time is

$$H_r = 0.75 \times A \times s \times (\bar{\tau}_s^4 - \tau_a^4)$$

where $$s = 4.94 \times 10^{-8} \text{ kcal/m}^2\text{/hr/(}^o\text{K)}^4$$

Then, with $$h_r = \frac{H_r}{A(\bar{T}_s - T_a)}$$

we have $$h_r = 3.7 \times 10^{-8}(\bar{\tau}_s^3 + \bar{\tau}_s^2\tau_a + \tau_a^2\bar{\tau}_s + \tau_a^3)$$

If we now put $$\bar{\tau}_s = 273 + \bar{T}_s \ , \quad \tau_a = 273 + T_a$$

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

where T_a and $\bar{T}_s$ are in ^oC.

Using the data given in Figure 1.3 we plot the contribution of radiation to the total heat transfer coefficient (Figure 1.8). We see that h_r is in the range 3.3 to 4.4 kcal/m^2/hr/^{o}C for $0 \lesssim T_a \lesssim 50^oC$.

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

The analytical solution of free convection problems is very difficult and only the most simple problems have been treated. However there exists in the literature (cf. the bibliography (26)) a large body of experimental correlations which summarize the results of free convection experiments in both the laminar and turbulent regimes. The correlations are generally presented in dimensionless form. (One must exercise some caution in extending these results, for example, to bodies of larger physical dimensions than those for which the original correlations were obtained.) Three dimensionless numbers, or "groups", are used in correlating free convection data.

The Nusselt number Nu indicates, in some sense, the efficiency of the convection process, i.e., it compares the convective energy transport to the energy that would be transferred by simple conduction. Thus for a body char-

acterized by a dimension D, transferring heat into a medium of conductivity k, for which a heat transfer coefficient h is measured, we define

$$Nu \equiv \frac{hD}{k} .$$

Clearly, if one knows the Nusselt number one can easily calculate h.

The Prandtl number Pr is a dimensionless combination of some air properties, $Pr = c_p\mu/k = 0.71$, essentially a constant.

The Grashof number Gr represents the ratio of the buoyant force to the viscous force on an 'element':

$$Gr = \frac{gD^3\Delta T}{\nu^2\tau}$$

where the acceleration of gravity $g = 980$ cm/sec^2, the kinematic viscosity $\nu = .14$ cm^2/sec, $\Delta T = \bar{T}_s - T_a$, τ is the absolute temperature, and D is the same characteristic dimension as in the Nusselt number. (If the individual is situated such that distances between him and the walls are smaller than D, then one must replace D in the Grashof number by that smaller dimension (27, p. 181). Since this tends to decrease the buoyant force with respect to the inertial forces, the free convection may be substantially suppressed.)

Dimensionless analysis of the fundamental transfer equations (26, chap. 23) shows that Nu is a function only if the product Gr Pr. The nature of the relationship depends on the particular geometry of the situation.

To illustrate we consider two cases, the first with the individual in a horizontal position, the second with him in a vertical position. In both cases, for simplicity of modelling, we consider the person to be a cylinder of diameter about one foot and height about six feet. For horizontal cylinders we have experimental correlations (27, p. 177, 180) for h_{free} (in kcal/m^2/hr/^{o}C)

$$h_{free} = 1.10(\Delta T)^{1/3} \quad \text{for } 10^9 \lesssim Gr\ Pr \lesssim 10^{12} \text{ (turbulent)}, \ \bar{T}_s > T_a$$

$$h_{free} = 1.57(\Delta T)^{1/4} \quad \text{for } 10^3 \lesssim Gr\ Pr \lesssim 10^{12} \text{ (laminar)}, \ \bar{T}_s > T_a$$

and

$$h_{free} \approx 0.7(\Delta T)^{1/4} \quad \text{for } 3 \times 10^5 \lesssim Gr\ Pr \lesssim 3 \times 10^{10} \text{ (laminar)}, \ \bar{T}_s < T_a$$

(This last result is for a horizontal plate, but there is little difference between plate and cylinder results.)

For vertical cylinders, with D = 6 feet, we have the experimental correlations (27, p. 173):

$$h_{free} = 1.16(\Delta T)^{1/3} \quad 10^9 \lesssim Gr\ Pr \lesssim \text{(turbulent)},\ \bar{T}_s > T_a$$

and

$$h_{free} = 1.08(\Delta T)^{1/4} \quad 10^4 \lesssim Gr\ Pr \lesssim \text{(laminar)},\ \bar{T}_s > T_a$$

(We point out that these correlations were made from measurements on objects perhaps as much as a foot high. Their correct extrapolation to six foot heights is not assured.)

If we evaluate the Grashof number according to its definition, using $T_a \approx 300^oK$, and use Pr = 0.71 then

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

Thus, for horizontal positions, we should use the laminar regime results, while for vertical positions we should use the turbulent regime results.

Since the position of the subject is often not stated, or a variety of positions were allowed during the same experiment, the best we can do is to indicate limiting values in the possible range of h_{free}. The largest values of h_{free} come from the horizontal laminar results while the smallest come from the vertical turbulent results. When the skin surface is cooler than the environment we have only the one horizontal laminar result. We see that h_{free} never exceeds 3.3 kcal/m^2/hr/^{o}C and is never less than 1.6 kcal/m^2/hr/^{o}C. (We remind the reader that these estimates are made assuming sufficient space around the subject that the free convection is not suppressed.) Note that the values of h_{free} for the vertical and horizontal cylinders do not differ very much from each other. This numerical 'coincidence' is a consequence of a length to diameter ratio of about 6:1. Its significance to us is that, if the two 'extreme' orientations do not yield different values of h_{free} then we expect that those values of h_{free} should be fairly good for any orientation. Thus value of h_{free} averaged between the vertical and horizontal results is shown in Figure 1.8.

Forced Convection. When the air in the vicinity of the subject is driven by a pressure gradient then the heat convection from the surface is termed forced convection. For such cases the Nusselt number is correlated with the dimensionless Reynolds number

$$Re = \frac{DV}{\nu}$$

where D is a characteristic dimension, V is the air velocity, and ν is the kinematic viscosity of air. If we assume a body to be representable by a cylinder one foot in diameter then, regardless of whether the 'wind' is blowing parallel or perpendicular to the axis, we have D = 1 foot. The Reynolds number becomes

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

In the case of flow parallel to the axis of the cylinder we have (26, pp. 554-557)

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

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

In the case of flow perpendicular to the axis of the cylinder we have (26, p. 560)

$$h_{forced} = .34V^{.466} \qquad 0.4 \lesssim V \lesssim 40 \text{ ft/min}$$

$$h_{forced} = .20V^{.62} \qquad 40 \lesssim V \lesssim 400 \text{ ft/min}$$

$$h_{forced} = .06V^{.80} \qquad 400 \lesssim V \lesssim 2500 \text{ ft/min}$$

Thus there is little difference between results for perpendicular or parallel flow. The forced convection results for parallel flow are shown in Figure 1.8 for V = 16 ft/min, V = 450 ft/min (5 mph), and V = 900 ft/min (10 mph).

A mathematical problem of great complexity arises when both free and forced convection occur simultaneously. McAdam's(27, p. 258) suggestion that the higher value be used raises doubts when h_{forced} and h_{free} are of the same order as occurs in our problem. We would recommend that a 'vector' addition be employed and the total convection coefficient h_c be written as

$$h_c^2 = h_{forced}^2 + h_{free}^2$$

This gives heavier weight to a larger contribution yet treats equally equal contributions.

The total heat transfer coefficient h is the arithmetic sum of the radiative and convective contributions. This h is shown in Figure 1.8. We see that, for small velocities ($V \approx 15$ ft/min as attempted in many experiments), we have very nearly h = 7 kcal/m^2/hr/^oC across the entire temperature range regardless of the orientation of the subject.

This result is clearly inconsistent with the conclusion reached from Figure 1.7, that h should vary between 3 kcal/m^2/hr/^oC at $T_a = 5^oC$ and 7 kcal/m^2/hr/^oC at $T_a = 45^oC$.

The theory we have developed here does permit values $h \approx 3$ kcal/m^2/hr/^{o}C, but only under somewhat artificial conditions. For example, if the free convection were suppressed by closely confining the subject, and if the wind velocity were 'zero', and if the radiative wall temperatures were adjusted to reduce radiation, then one could obtain $h \approx 3$ kcal/m^2/hr/^{o}C. Most experiments reported in the literature were performed under more ordinary conditions, the major efforts apparently being made to maintain the temperature close to the desired value and to maintain low wind velocities. Given these conditions there remains a variety of subtle ways in which the heat transfer coefficient can still be affected.

Recall that the above heat transfer coefficients were computed on the assumption that a steady-state was reached, that the subject was essentially nude and extended (i.e., his entire surface area was exposed), and that wind velocities were small. If an experiment in a coal environment is not carried out over a long enough time the mean skin temperature may not have fallen to its final equilibrium value and the value of h will appear to be smaller than it really is. As we pointed out before, a time of at least three to four hours is required to achieve equilibrium. If the subject is partly or lightly clothed, or if he is allowed to shield himself or protect himself by curling up, or if the space around him is so confined that free convection is suppressed then the measured value of h will be less than the calculated value. We suggest that some or all of these effects have combined to produce values of h as low as 3 kcal/m^2/hr/^{o}C near $T_a \approx 5^oC$.

To test the theory, we performed an experiment at an environmental temperature of 19^{o}C, in an open space, with a male subject wearing only a brief bathing suit. After four hours a mean skin temperature of 26-27^{o}C was recorded. This is about 3^{o}C less than the value in Figure 1.3c. It is indicated with an (x) in Figure 1.7 and one notes that it lies nearly on the line $h = 7$ kcal/m^2/hr/^{o}C. Thus it is strongly suggestive of what we have been driving at, namely that a consistent basis for the development of a theory of h can be established directly from physical principles, and that the experimenter must understand critically factors affecting his experiment. We propose that further measurements of mean skin temperatures in ambient conditions below 20^{o}C should be made under the following conditions: (1) nude or nearly nude fully extended subject, (2) a minimum 3-4 hour exposure, (3) low wind velocity (less than 1 mph), (4) open space around the subject (i.e., distances to walls should be tens of feet). Only then can we be confident that a physically founded theory for h has been established.

Tissue Conductance - Theory of C

We turn now to the development of a consistent theory for the tissue conductance C. This is a physical-physiological problem the solution to which depends on a reasonable modelling of the active physiological mechanisms involved. That a problem exists is easily seen.

The traditional definition of mean tissue conductance $\bar{C}$ is (e.g., (24), p. 204)

$$\bar{C} = \frac{M}{T_r - \bar{T}_s} \quad .$$

It is clear that this definition is inadequate for $\bar{T}_s \geq T_r$ as might occur at high temperatures. M is never zero for a live subject. $\bar{C}$ cannot be 'infinite' or negative under any conditions.

The first step in the resolution of this difficulty is to seek the limiting values for $\bar{C}$. We obtain this in the following approximate way. The conductivity of tissue can range from 18 kcal-cm/m^2/hr/^oC when vasoconstricted (i.e., this is the conductivity of fat) to 50 kcal-cm/m^2/hr/^oC (i.e., the conductivity of water (or blood)). Thus tissue conductance is an <u>active</u> parameter. Taking an average tissue thickness (from the surface to the middle of the muscle layer) on the order of 2 cm ((3), p. 89) the conductance $\bar{C}$ can range from 9 to 25 kcal/m^2/hr/^oC.

In order to avoid the non-physical infinite or negative $\bar{C}$ we introduce the following completely new physiologically based hypothesis. The sweat glands are located beneath the surface of the skin. Thus we suggest that at least part, and under some conditions all, of the evaporative heat loss effectively takes place below the skin's surface. The evaporated water vapor passes out through the pores. Thus, in the definition of $\bar{C}$, M must be reduced by that fraction, g, of the evaporation which takes place beneath the surface. Until the water vapor pressure in the pores approaches the saturation pressure we would expect $g \approx 1$. As the vapor becomes saturated water seeps to the surface, evaporation takes place there, and g becomes less than 1.

We propose that the mean tissue conductance $\bar{C}$ should be redefined as

$$\bar{C} = \frac{M - gE}{T_r - \bar{T}_s}$$

Using the data in Figure 1.3 we obtain $\bar{C}$ vs. T_a for various values of g (Figure 1.9). The curve g = 0 corresponds to the previous definition of $\bar{C}$ and illustrates the former difficulty. For $g > 0$ we see that the values of $\bar{C}$ can be maintained within physiological limits, at least at high ambient temperatures. Here we see that, near $g \approx 1/3$, $\bar{C}$ levels off at about 18 kcal/m^2/hr/^oC. (Perhaps this suggests that 1/3 represents a limiting value of g attained at high ambient temperatures. Physically this would mean that 1/3 of the evaporation is from below the surface and 2/3 is evaporation directly from wetted surface areas.)

The value of $\bar{C}$ (Figure 1.9) at low ambient temperature leads to another problem. Here $\bar{C} \approx 3$ kcal/m^2/hr/^oC regardless of g (since E is considerably smaller than M in this region). How can we explain $\bar{C} \approx 3$ kcal/m^2/hr/^oC given that the physiological lower limit on C is apparently 9 kcal/m^2/hr/^oC? The traditional explanation has been to propose a "metabolic response" in cold enrironments. If such a mechanism existed it would serve to raise the value of M-E and thus the value of $\bar{C}$. But M-E (or really M since E is small) would have to increase by a factor of 3 to raise $\bar{C}$ from 3 to 9 kcal/m^2/hr/^oC. As Figure 1.3a shows, however, for a given activity level M does not change more than about 30% over the whole survivable temperature range. Thus we need a more realistic mechanism.

The following observation opens a potentially fruitful direction. In experiments in the cold it is noted that, after 2 or 3 hours, the extremities (arms halfway to the elbow, legs halfway to the knee) blanch and their temperatures drop to the ambient temperature. Clearly some central control in the body has redirected blood flows and abandoned those regions in favor of maintaining regulation over the remainder of the body. Over the 'unregulated' areas heat is not being transferred from the surface to the environment. If we say that a fraction f of the total area remains regulated then the two transfer equations become

$$M - E = fh(T_s - T_a)$$

$$M - gE = fC(T_r - T_s)$$

where T_s is the mean temperature over the regulated regions. The mean total surface temperature $\bar{T}_s$ is

$$\bar{T}_s = fT_s + (1 - f)T_a \ .$$

This set of three equations represents the physical and physical-physiological thermoregulation of the body. The coefficient h is a physical factor and, from above, has the value 7 kcal/m^2/hr/^oC. The coefficient C represents an active physical-physiological mechanism; it is the tissue conductance corresponding to the surface temperature T_s. The parameters f and g are physiological quantities which characterize mechanisms which we can state qualitatively but cannot yet explain physically in any definite way.

Our immediate aim is to determine empirically a course of f and g consistent with observations within the range $T_a \approx 5^oC$ to $T_a \approx 45^oC$. First we must model the physical-physiological behavior of C. The following modelling is rather rough, but in fact this makes little difference because the results for f and g are not strongly dependent on C.

We assume that (typically) the tissue layer (from surface to middle of muscle) has a thickness of 2 cm, that its conductivity can change from 18 to 50 kcal-cm/m^2/hr/^oC, and that this transition takes place (linearly) between local temperatures of 28^oC and 34^oC (cf. (3), p. 132). If we combine these assumptions with the observation that temperature increases approximately linearly from the surface (T_s) into the middle of the muscle layer (T_r) then we obtain C as given in Table 1.3.

Table 1.3

Local Tissue Conductance for Some Local Skin Temperatures

T_s	C
25	13
27	16
29	19
31	20
33	22
35	24

(This model of the tissue conductance also sheds light on how great an effect the skin temperature has on the microvasculature of the tissue. If we call the muscle temperature T_r, the muscle thickness t_m, and the skin thickness t_s, the average local bed temperature T is easily seen to be

$$T = T_s + \tfrac{1}{2} \frac{T_r - T_s}{t_s + \tfrac{1}{2} t_m} t_s$$

By this definition T is the average temperature over the skin thickness t_s. If we write $N = t_m/t_s$ this expression becomes

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

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

Given now the values of C and h we can determine the course of f and g. We combine the two transfer equations to eliminate T_s and obtain

$$f = \frac{(C+h)(M-E)}{hC(T_r-T_a)} + \frac{E(1-g)}{C(T_r-T_a)}$$

Using Table 1.3 and Figure 1.3, and iterating once or twice, we obtain f vs. g for values of T_a 5°C and 45°C (Figure 1.10). The heavy dotted line indicates the likely course of f and g. There is some uncertainty in the indicated course because the computation in the region $T_a \approx 30\text{-}35^\circ C$ involved the taking of small differences (M-E) between large quantities (M and E). Thus the likely points are indicated by rather large 'dots'. However Figure 1.10 shows vividly why it is not possible to construct a rational model with g = 0 over the entire range of ambient temperatures. With g = 0, above $T_a \approx 30\text{-}31^\circ C$ the body has no mechanism available to maintain regulation, i.e., f cannot exceed unity.

Picture of Steady-State Thermoregulation

At this point we feel we have placed the theory of steady-state thermoregulation on a firm physical and physical-physiological foundation. Introduction of the physiological parameters f and g has provided the mechanisms required to obtain consistency between the various measured parameters, M, E, $\bar{T}_s$, T_r. We can now put together the following picture of thermoregulation, and indicate problems which remain unsolved.

Under 'comfortable' conditions, generally considered to be $T_a \approx 30^\circ C$, $\bar{T}_s \approx 33\text{-}34^\circ C$, the surface is nearly completely regulated. That is, f = 0.85 (Figure 1.10) and even the "unregulated" portion is at a not uncomfortable 30°C. (We should point out that under conditions such as described here, where T_a is near $\bar{T}_s$, our idea of a separation into "regulated" and "unregulated" parts becomes vague.) Most of the evaporative loss takes place by

subsurface evaporation (i.e., $g \approx .95$) and the skin is not much wetted.

As the ambient temperature drops below 30°C vasoconstriction within peripheral tissues begins. The degree of vasoconstriction and its effect on the tissue conductance C at any point on the body's surface depend upon the ambient temperature, the duration of exposure, and the part of the surface considered. The usual proposal of a metabolic increase to provide for the added heat transfer away from the surface was seen to be inadequate. The only way out for the body is to adjust its transfer surface so as to maintain the required heat balance. This adjustment is performed by redistribution of the blood flow to the peripheral tissues. The central hypothalamic thermoregulatory mechanisms mediate this redistribution. The ultimate effect is that the temperatures of some regions drop to the ambient temperature. Perhaps as much as 60% of the surface area becomes thus 'unregulated' (at $T_a \approx 5°C$). There is considerable doubt whether, under the experimental conditions we have prescribed, a person can survive at this temperature. The observations of Scholander et al. (28) indicate that one can - at least an Australian aborigine can. (However, we would suspect that those subject were permitted to alter their posture so as to reduce their effective exposed areas and thus reduce the necessarily unregulated areas to a survivable limit.)

Thermoregulation in a warm environment ($T_a \gtrsim 30°C$) is maintained by a combination of vasodilatation (increasing tissue conductance, allowing greater heat exchange to the surface) and evaporative losses. The new concept of subsurface evaporation allows us to model the evaporative loss by two distinct mechanisms.

First, there is the subsurface 'pot-boiling' which depends on the internal bed temperature and state of vasoconstriction of the local tissue. It is thus a mechanism that we expect to be activated at some minimum local temperature and then to increase with temperature, perhaps leveling off as some maximum local sweat rate is reached. By the second mechanism evaporation takes place from any surface area which may have become wetted. (The transfer of liquid water from subsurface to surface contributes little to the heat loss mechanism - only if the water is vaporized is there an appreciable loss.) A region becomes wetted when its pores become saturated. We see from Figure 1.10 how the shift from subsurface evaporation to the surface takes place. Between $T_a = 30°C$ and $T_a = 40°C$, g (the fraction of subsurface evporation) decreases from near 1 to about 0.2. Nearly all the pores are saturated with water vapor, the subsurface evaporation is 'blocked', and the surface becomes nearly completely wetted.

The completely wetted surface represents a limiting condition. The maximum evaporative loss rate for the completely wetted body is determined now by strictly physical and geometrical factors. The physical description is rather straightforward. The argument is based on the similarity of the heat and mass transfer equations when the transfers take place in the same hydrodynamic field, that is, when the process is psychrometric. (Pertinent details are in our report (29).) The important result is that if the heat transfer coefficient (for convection) is h_c (i.e., heat transferred = h_c x temperature

difference) then the mass transfer coefficient h_m (i.e., mass transfer = h_m x water vapor partial pressure difference) is given (numerically) by

$$h_m \approx 2h_c$$

Reference to Figure 3.8 shows that (for small wind velocity V ≈ 15 ft/min) $h_c \approx 2$ kcal/m^2/hr/^{o}C and so we expect $h_m \approx 4$kcal/m^2/hr/mmH_g. (We can compare this with the experimental result of Kerslake and Waddell (20). Their velocity was 50 ft/min and so their h_c, and thus h_m, should be approximately $\sqrt{50/15}$ times ours. That is, they should measure $h_m \approx 1.83 \times 4 \approx 7.4$ kcal/m^2/hr/mmH_g. They actually measured 7.8 $\pm$ .2 kcal/m^2/hr/mmH_g. Thus, the experimental and theoretical results, even from this rough argument, agree to about 5%.) The maximum evaporative heat loss then depends on a combination of ambient temperature (which determines skin temperature) and relative humidity, which combined determine the water vapor partial pressure difference between skin and environment. Requirements for heat loss by the body in excess of this limit cannot be met, and the result is heat prostration.

This new view of a dual mechanism to achieve evaporative heat loss remains to be proved by the physiologists. We have shown that it provides a consistent basis for modelling human thermoregulation under high ambient temperature conditions. It seems worth mentioning that there are potentially useful clinical implications for the understanding and treatment of fever. The observation that a patient begins to sweat (often profusely) only when his fever "breaks" indicates that the fever itself is caused or maintained by an inhibition of the sweating mechanism. We suggest that the patient becomes febrile not because of a shift in any "set-point" temperature (e.g., (11), p. 1068) but because of some 'chemical' imbalance which inhibits the subsurface evaporation at the peripheral skin layers. We suspect that the effective action of the so-called "antipyretic" drugs is to restore this chemical balance in the blood supply to the peripheral tissue and thus to reactivate the sweat mechanism.

Recapitulation

We have shown that a consistent theory of steady-state thermoregulation is being developed by consideration of the physical and physical-physiological properties of heat transfer through and across peripheral tissues. We have proposed two new ideas with regard to the nature and behavior of the vasomotor response of the skin and the mechanisms of evaporative heat loss. The model we have constructed is essentially phenomenological; we have left in abeyance questions as to the mechanisms which control the responses we have modelled. We view our work as an indispensible semi-empirical first step toward understanding the physiological nature of thermoregulation.

We envision a hierarchical ordering of survival mechanisms. When exposed to hot or cold environments the body's central control, the hypothalamus, will act, via the blood, to initiate vasomotor responses. The time scale for this is about seven minutes. The effects of this is that, at one extreme, the body will gradually allow large areas to become unregulated and cold in order to

save the rest and, at the other extreme, will develop profuse sweating. A higher level of control, in the cortex, oversees these responses and continuously determines whether or not to permit the subject to remain in a stressful situation. Even this level of control can be overcome, that is, the subject may become comatose, if decisions to alleviate severe conditions are too long deferred.

In investigating the phenomenology of the first control level we found it necessary to introduce two quite new ideas in order to construct a model consistent with both physical requirements and physiological observations. First we proposed that the body will cut off, and allow to go unregulated, a significant portion of its area in order to maintain its deep body temperature. We suggest that (for a resting nude individual) this is the only available survival mechanism. Second, we have proposed, in order to clarify difficulties in determining tissue conductances, that a significant portion of the evaporative heat loss actually takes place below the surface. The effect of this is to reduce the 'effective' skin conductances to levels which correspond to physical-physiological values. We have combined these ideas into a consistent model of the thermoregulatory system and have deduced probable values for the various parameters for resting, nude individuals in the temperature range from $5^{o}C$ to $45^{o}C$.

Suggested Directions for Future Research

There still remains a number of fundamental issues that we have not dealt with. Perhaps they can be summarized by asking how the body maintains a nearly constant internal temperature of $37^{o}C$. The solution to this problem awaits a greater understanding of the relevant physiological processes which occur in the hypothalamus, the vascular system, the muscles, and the skin.

We hope that by this point the reader appreciates that, before a successful attack could be made on that basic question, there were serious elementary physical problems which had to be clarified. We have focused attention sharply on these physical problems and begun their clarification by reexamination of available data and by restricting the scope of this chapter to a semi-phenomenological steady-state study. Complete, pertinent data were hard to come by. In particular, more and better defined data, taken at ambient temperatures below $20^{o}C$, are required to determine whether the present simple formulation of the fundamental heat transfer, i.e., $M - E = h(\bar{T}_s - T_a)$, is adequate. No hypotheses are implicit in this equation (beyond the simple faith that the laws of physics should apply); its validity can be tested, and the physical theory for h tested, simply by obtaining the right kind of data. More metabolism data, more mean skin temperature data, careful definition of experimental conditions (e.g., duration 4-5 hours, physical set-up, subject position) are still needed to verify the theory.

Consistent modelling required two physiological assumptions which should be examined experimentally. The idea of an unregulated surface area in the

cold was originally inspired by observation of cold regions on the body surface. The extension of this idea into a useful hypothesis summarizing blood flow distribution to various body regions, and capable of accounting for thermoregulation at temperatures closer to 0°C, should be tested.

A challenging physiological experiment may be the testing of our second hypothesis, the idea of a subsurface evaporative heat loss required, to obtain a physically consistent modelling of mean tissue conductance. A first round approach might be to measure heat fluxes at incremental layers below the surface. Changes in heat flux with depth that could not be accounted for (even by incompletely understood mechanisms) by blood heat exchanges would be attributed to subsurface evaporation. Assuming that the results of these experiments indicated the existence of such evaporation, the final proof would rest on the actual observation and measurement of the passage of water vapor through the skin.

The present study has modelled (theoretically and hypothetically) an autoregulatory nature of peripheral tissues. There remain considerable difficulties in trying to model internal regulatory processes. For example, we do not know the answers to many simple physiological questions: How is the blood flow redistributed? by a central mechanism? by peripheral tissue autoregulation? by both? How is the sweating mechanism activated? What is its dependence on local tissue temperature? on blood flow and chemistry? on psychological factors? In proposing mechanisms for these phenomena we must insure that the modelling is sound both physically and physiologically. We have a certain freedom to hypothesize physiological mechanisms; there is no such freedom with physical facts.

A final remark: one may note that we have divided the thermoregulation problem into three categories: (a) "physiological" processes for which mechanisms are yet unknown, (b) "physical-physiological" processes for which mechanisms can be partly modelled, and (c) "physical" processes which are well-known and circumscribe modelling of (a) and (b). To the extent that a problem is classified as purely "physiological", it is not understood. In our opinion, the ultimate goal of the scientist is to render all problems "physical" and thus explainable in terms of well-known principles. We believe that this work represents a step in that direction for the thermoregulatory system.

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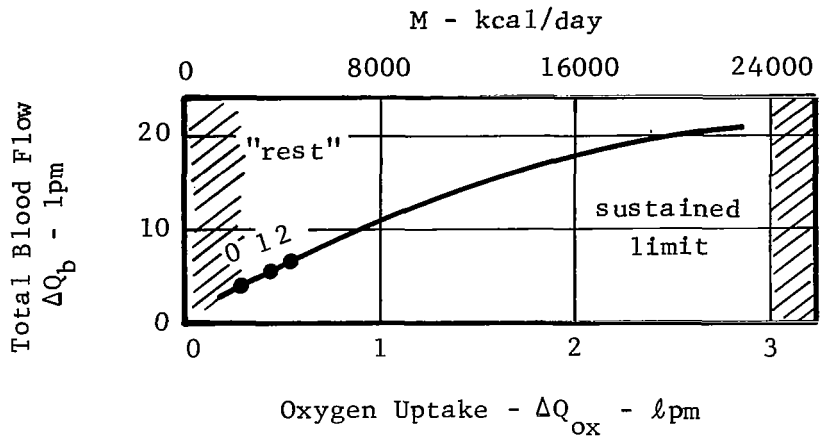

Figure 1.1 - Total blood flow vs. oxygen uptake. 0 - rest operating point; 1 - nominal average operating point; 2 - nominal maximal possible average operating point

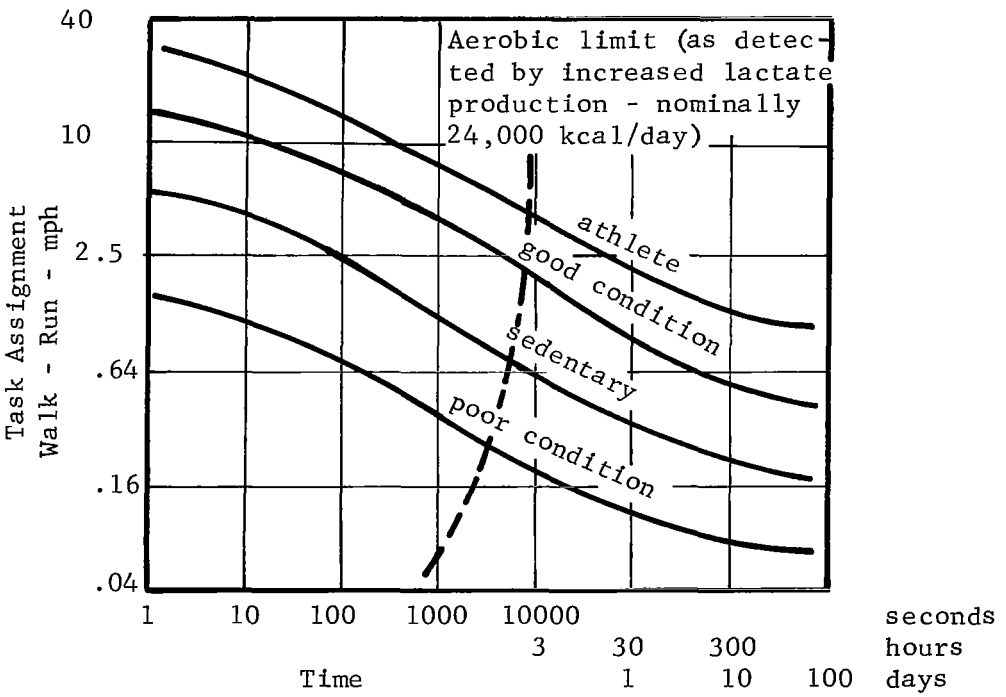

Figure 1.2 - Average peak human performance in a common metabolic task (walk-run), both steady state (in oxidative thermodynamic equilibrium) and transient.

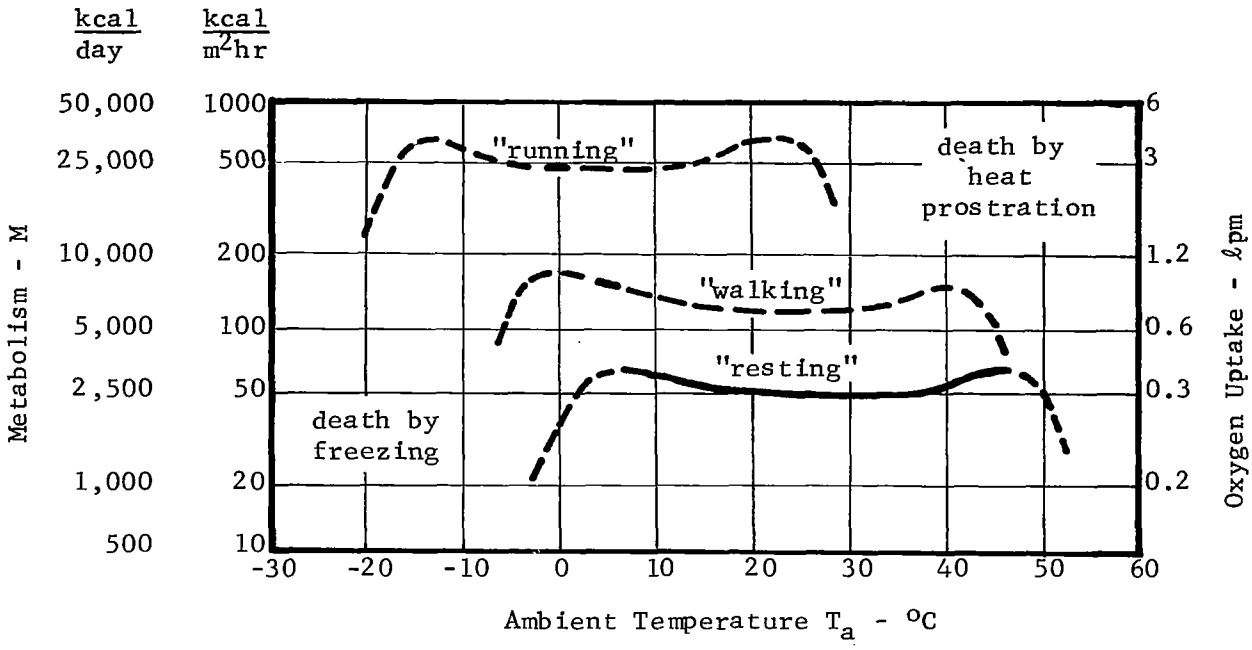

Figure 1.3a - Steady state (3-4 hours) metabolic regulation for various activity levels (nude subject). Dotted portion represents estimated extrapolations.

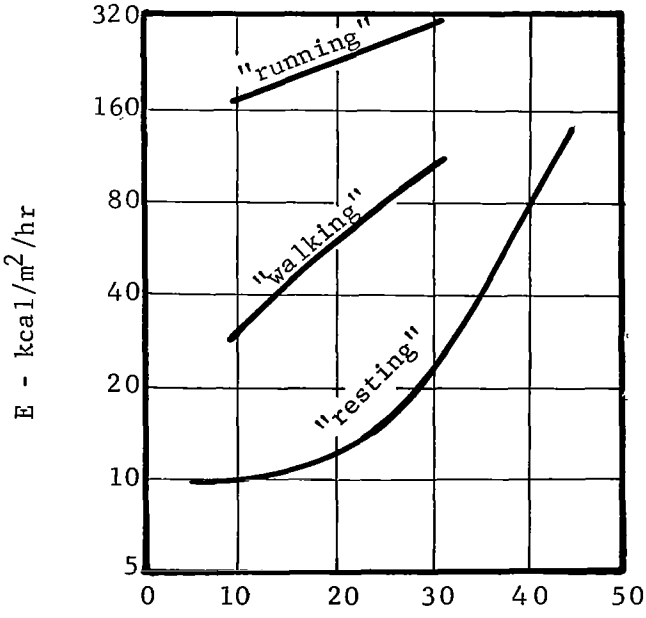

Figure 1.3b - Evaporative heat losses for various activities (nude subjects).

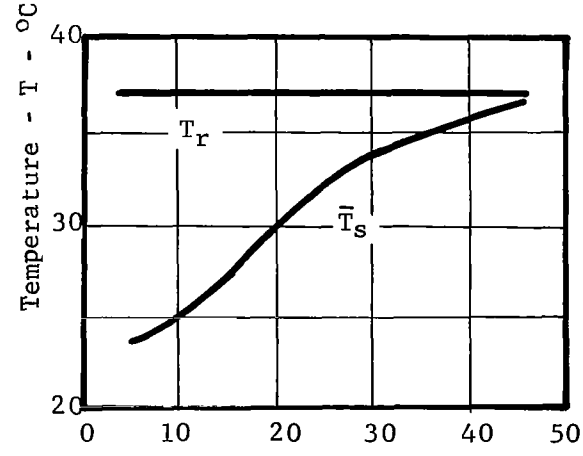

Figure 1.3c - Mean skin ($\bar{T}_s$) temperatures for resting, nude individual.

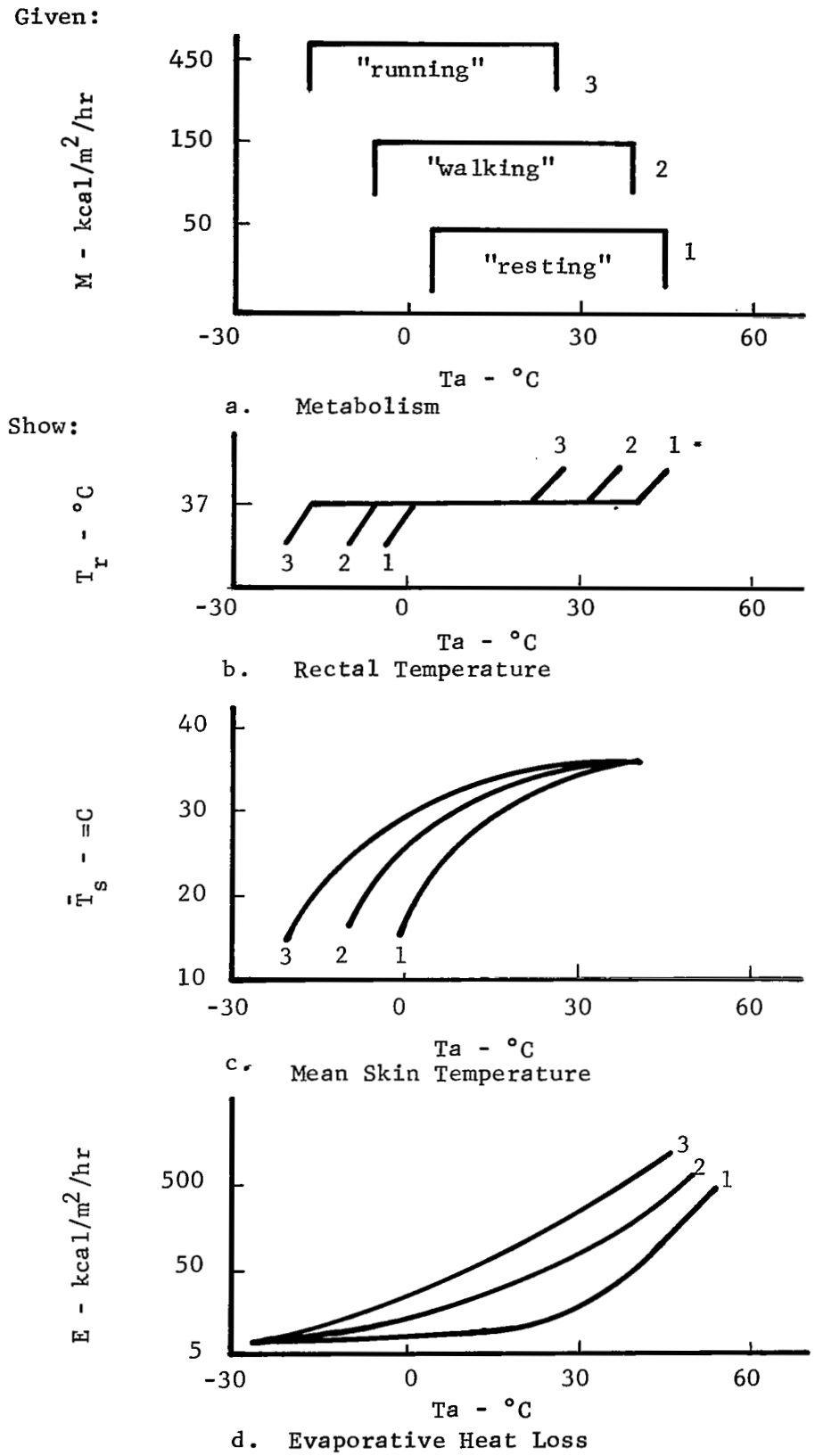

Figure 1.4 Schematic Representation of Thermoregulation Problem.

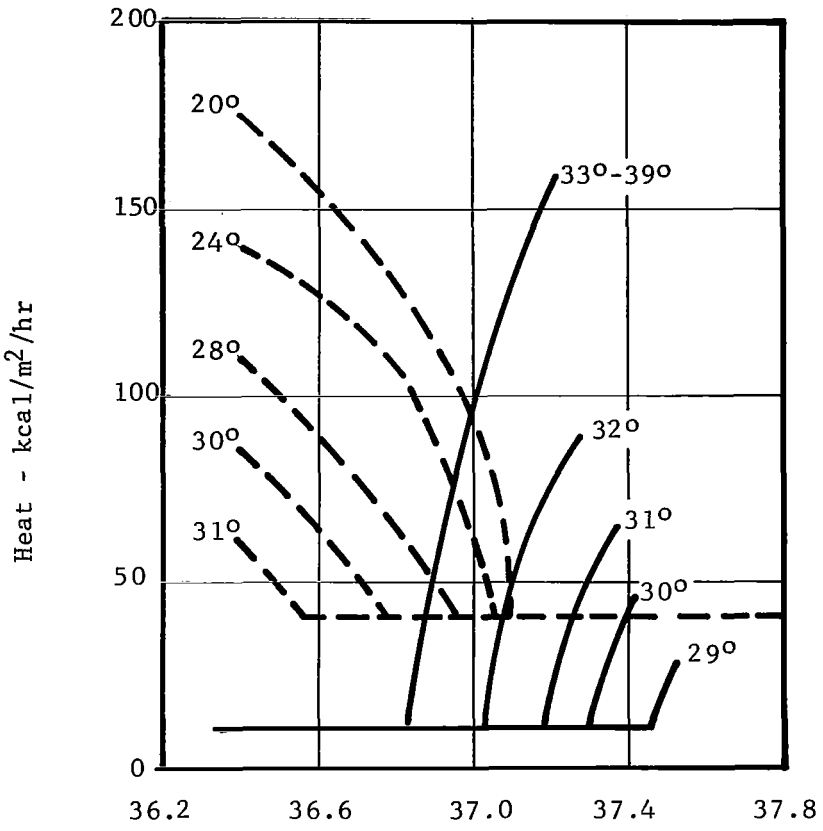

Figure 1.5 - Summary of Benzinger's Data (10).

Dashed lines (— — — —, Figure 9B) represent metabolic heat production. Solid lines (————, Figure 18) represent evaporative heat loss. This figure illustrates the dynamics of temperature regulation.

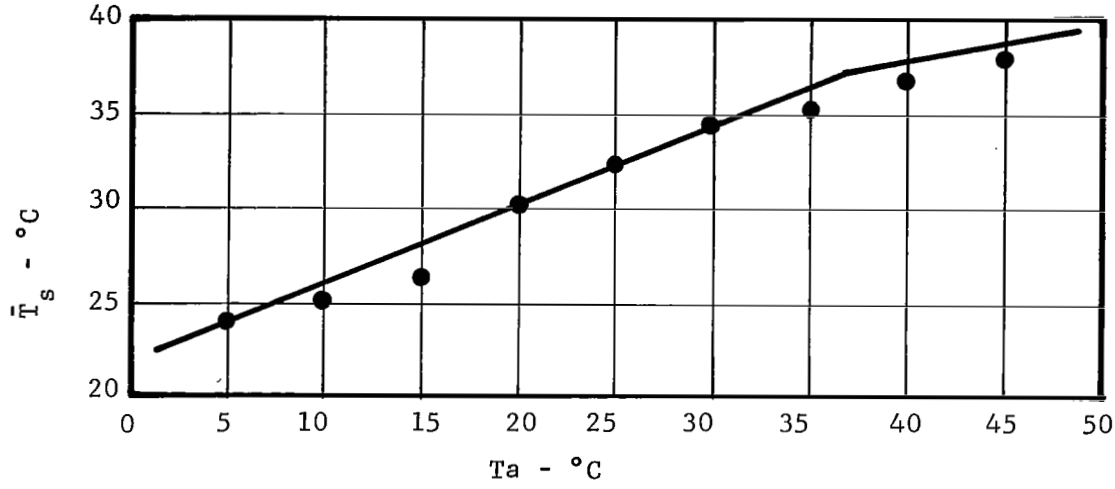

Figure 1.6 Calculated Values of $\bar{T}_s$ compared to experimental values (●).

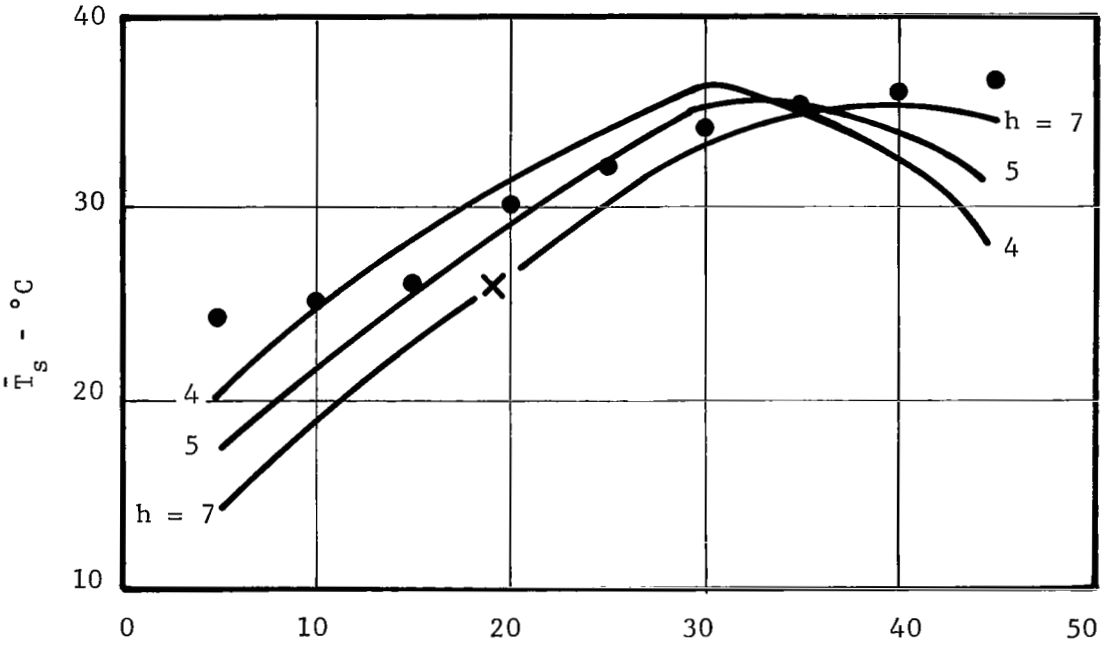

Figure 1.7 Mean skin temperature $\bar{T}_s$ vs. ambient temperature T_a for various values of h (h in kcal/m^2/hr/°C). The dots (●) are data from literature. The (✕) is from our experiment of November 11, 1970.

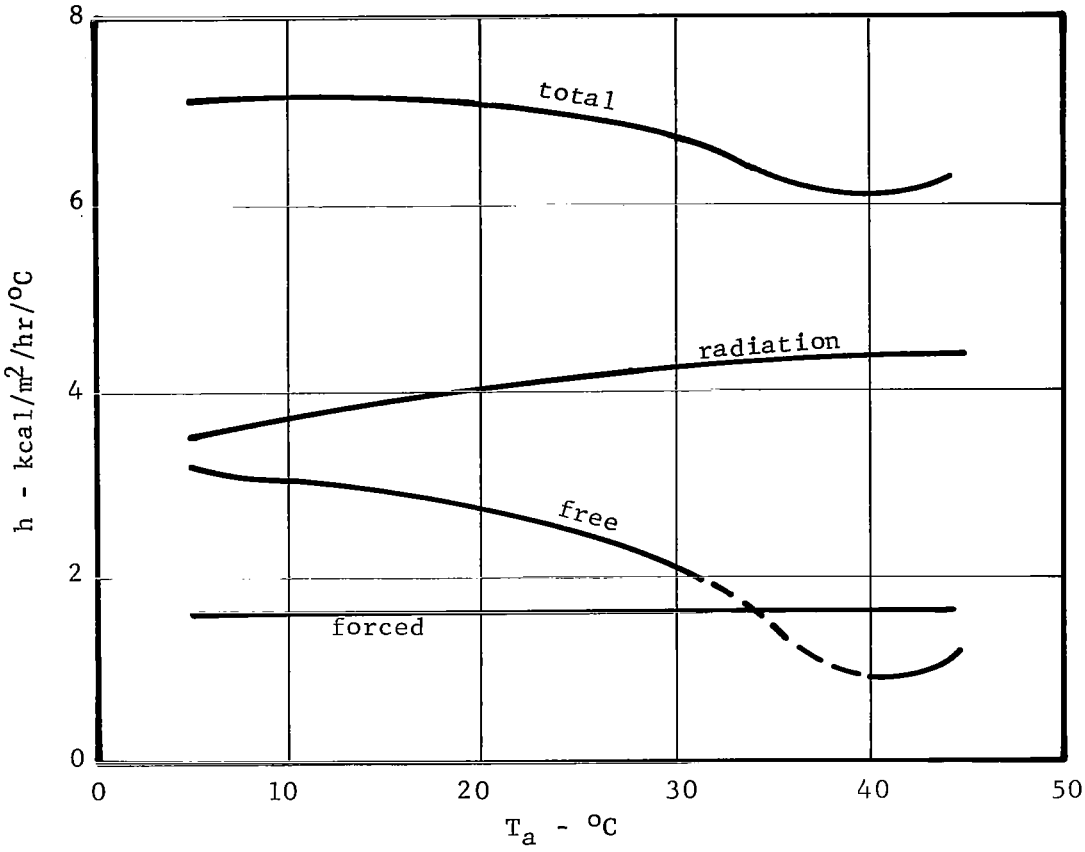

Figure 1.8 - Components of heat transfer coefficient vs. ambient temperature for resting, nude subject, low wind (less than 1 mph), uninhibited free convection.

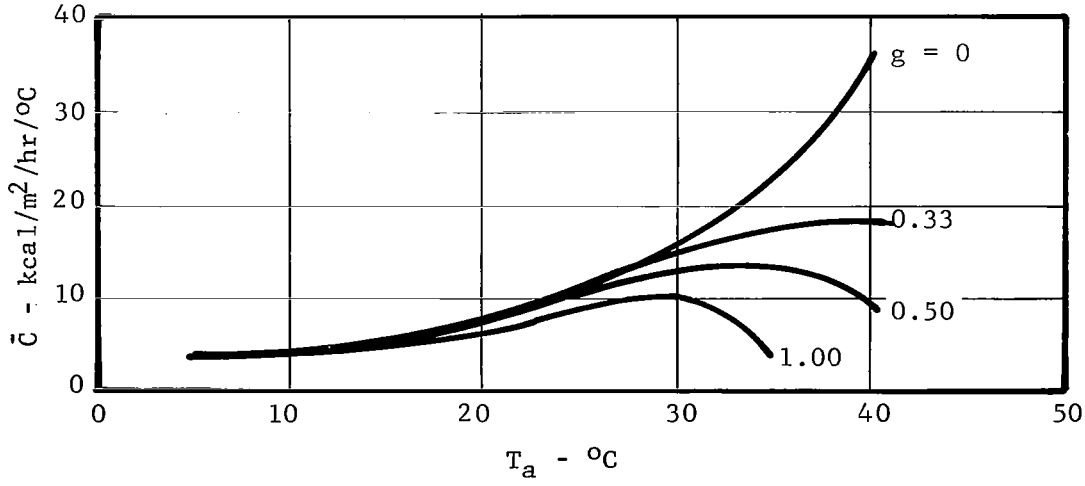

Figure 1.9 - Mean Skin Conductance $\bar{C}$ vs. T_a for different values of the subsurface evaporation parameter g.

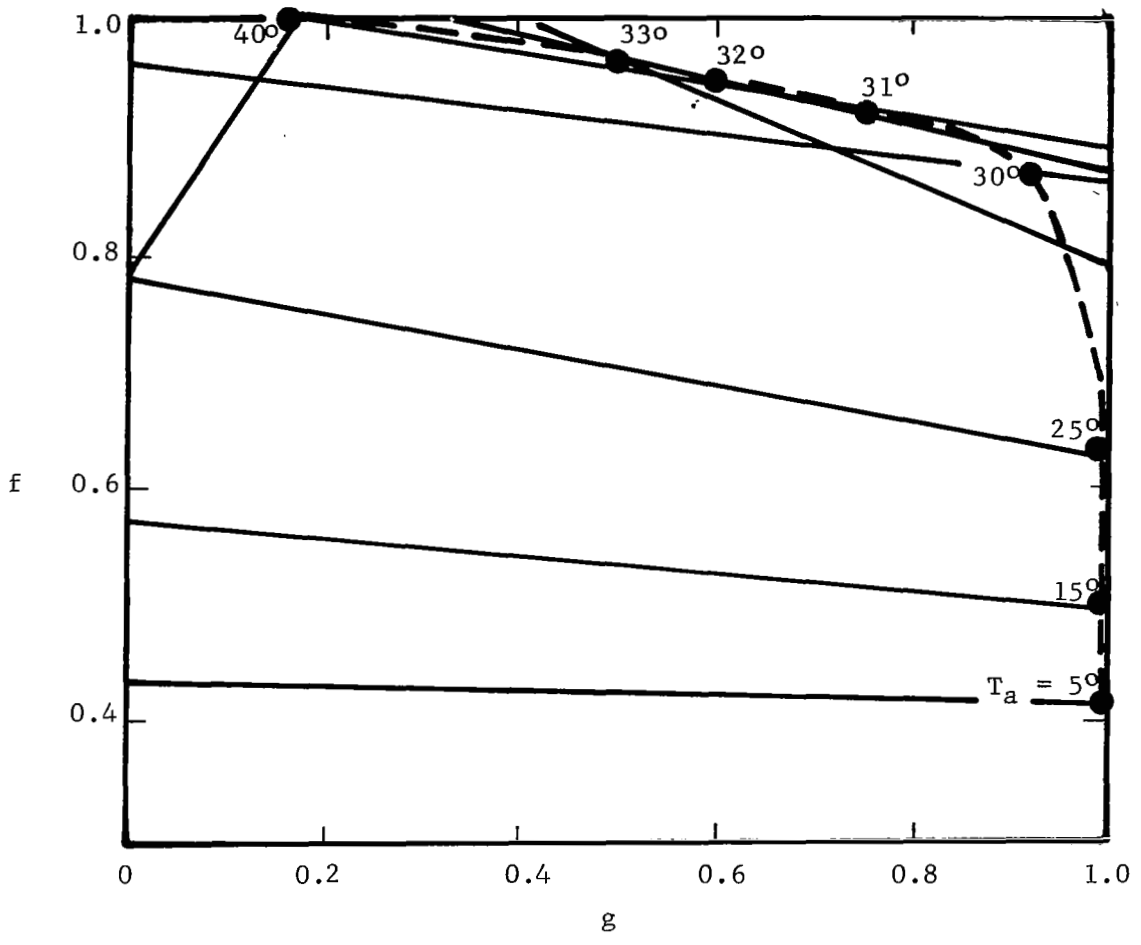

Figure 1.10 - Parameter f (fractional regulated area) vs. parameter g (fractional subsurface evaporation) over the range T_a = 5°C to 40°C. Solid dots (●) represent a consistent selection on lines of constant T_a so as to provide smooth monotonic relations among f, g and T_a.

II. COMMENTS ON THE PROBLEM OF THE BIOCHEMICAL OSCILLATOR

The following comments, part of an invited talk, were delivered during a Physiological Control Systems Symposium at a December 1970 AIChE meeting in Chicago.

The author's experience began in instrumentation, automatic regulation, and control. There is a little known background history in these fields of interest to those concerned with the subject of the chemical oscillator. In the 1930's, C. E. Mason was involved in how to regulate and control refineries and, of necessity, began to innovate. He went from those applications to directing research for the Foxboro Company where he developed the first line of pneumatic automatic controllers for process industry variables (pressure, temperature, flow). Besides an inventive genius, he was also seminal in training and developing a theoretical and practical background for many of the major creators in this field.

By the late 1940's, having started to bring the subject of automatic control into maturity (through the Gibson Island conferences, precursors of the present Gordon Research Conferences), Mason was also du Pont's consultant in automatic control. It was there and through the Instruments and Regulators Division of ASME that he spread the gospel of dynamic analysis and automatic control to the chemical process industries, and to their outstanding practitioners. (The author was fortunately touched by Mason's magic.)

Mason's control point of view was influenced by the predominant R-C character of chemical process systems. First order relaxational kinetics, hold-up times, fluid and thermal resistances and capacitances were the components and items that he saw. Control, in the main, was influenced by these characteristics. Difficulties were encountered with interacting rather than noninteracting systems, with high order systems, with the concept of controllability, and with the methods of relating the system's characteristics to setting the constants of three-mode controllers. In the 1950's, the author outlined a general distributed R-C analysis of the problem of controllability for Mason in an attempt to clarify the problem.

By then, the chemical engineers of the process industries were ready for automatic control of both batch and continuous processes, and in fact for computer control. Dynamics beyond the characteristics of R-C networks were gradually revealed, and the subject of chemical oscillations really appeared on the more immediate agenda of history, particularly with fast catalytic processes and batch polymerization.

For example, in the author's experience at about that time (1960), some collaborative consultation with chemical engineering educators in Cleveland (a ChE group at Case Tech. under Seymour Calvert) raised the question of R-C-L dynamics in various batch and continuous chemical processes.

In the author's group a peculiar dialogue took place. It appeared that the physicist took for granted that the chemist had the capability for providing chemical oscillators as part of his repertoire. Both were shocked when the physicist realized that the chemist did not have this - that 'all' of the

chemist's processes were degradative relaxations, and the chemist was shocked to find that the physicist didn't realize this. At that point in time the dialogue was resolved, after some thought, by suggesting that if a chemical reaction were coupled to another system, such as providing inertia with a mechanical system, this in fact would take care of the problem and 'chemical' oscillators could be provided. After all, the point was made, all the practical chemical 'thermodynamic' engines worked this way, and 'coupling' was the essential process by which basic first order processes (in a mathematical sense) were connected together. The detail of producing 180^{o} phase shift, leading for example to

$$m\ddot{x} + kx = o$$

in a mechanical system, instead of leading to a negative sign, as in a chemical system

$$\dot{x}_1 + k_1 x_2 = 0$$

$$\dot{x}_2 + k_2 x_1 = 0$$

so that

$$\ddot{x}_1 - \left(k_1 k_2\right) x_1 = 0$$

$$\ddot{x}_2 - \left(k_1 k_2\right) x_2 = 0$$

appeared to be only a minor issue contained in finding the right phenomena to couple with.

However when this group began its first serious venture into biology (see (1) for an extensive physical review), it was realized that the issue of chemical oscillators was a more fundamental question than the way it first may appear to chemical engineers in the chemical process industries. The chemical process industry issue is used as an analogue because both the practitioner of that field and the biochemist are dealing with a complex 'autonomous' chemical plant.

The issue of the chemical oscillator was clarified to us when a chemical engineering colleague called our attention to a chemo-thermal oscillator that he had come across (a description has been recently published - see Bush (12)). The problem, we realized, was the broad common problem of nonlinear stability that we had been pursuing in many fields. (See, for example, Iberall(3) or in (4), or see (12)).

At that point in our learning, we finally realized that a 'chemical' oscillator did not have to be a pure sequence of chemical steps (e.g. a group of chemicals oscillating in concentration in a beaker), but could arise by coupling of other than chemical steps to chemical steps. As we will discuss later, there was still a missing step in our understanding of what might be required for a biochemical oscillator.

Regardless of what the system was coupled to, the problem remained one of finding a coupling with a chemical process step that would make the overall process linearly unstable, but nonlinearly stable as a limit cycle oscillator (according to nonlinear mechanical concepts), or a thermodynamic 'engine' cycle (i.e. in thermodynamic concepts, a system that could enter into a cycle of performance by transforming some constant potential source of energy into energy in transit, namely a power supply involving periodic transformation).

With regard to the biochemical oscillator, one major line that has stimulated the question of the biochemical oscillator has been the nature and origin of life. For example, using him as a protagonist, Pattee (see (4)) has suggested that the central question requiring explanation for the nature of life is its 'hereditary' property. He asks what this means in the language of physics. He rejects the view that life "is just a certain collection of DNA, RNA, enzymes, and other molecules in the proper spatial configuration". The organization of molecules by physics is known to require for its organization only a few forces. As yet no combinations of such forces are known which can be uniquely associated with living organizations. Thus he points out that "molecular biologists tend to ...underestimate the exceptional physical requirements for persistent hereditary processes...". Stated again, he thinks that "the potential for hereditary evolution is the primary characteristic of life...".

We submit that Pattee's hereditary processes ("Hereditary processes require the existence of a set of relatively fixed objects or traits any one of which can be transferred in a recognizable form from parent to offspring in the course of time") represent a periodic process, i.e. there is essential need for biochemical oscillators. Detailed reading of his material, suggests that Pattee expects that problem to be solved at the molecular level. (For example: considering a simple hereditary tactic copolymerization "...in such a copolymer, hereditary propagation must depend on specific catalytic control of the rates of monomer addition...". Then later, in discussing whether classical non-holonomic machinery can exist reliable enough to assure persistent hereditary evolution in a noisy environment, his basic criterion for life, he concludes that they can't, because: "The elementary rate-controlling or logical machinery of living systems are not macroscopic organs but individual molecules - the enzymes." Classical machines would have high error rate. On the other hand, living cells execute their hereditary rules with reliability using single molecules. Thus he concludes, that the dynamic behavior of enzymes, as hereditary elements, can not be described by classical models.)

However not all investigators of a biophysical bent have been willing to wait for the development of biochemical oscillators, or at least chemical oscillators, at a purely chemical-molecular level. (i.e. of what might be referred to, even if catalytic 'molecules' are used, as chemo-chemo coupling).

The reader must note the logical picture that faced us after our first (1962) review paper in biology (1). It was clear that self-maintained oscillatory processes were intrinsic to biological systems. Actually the precursor to that review was work we had done on the human body as a thermal source, in

evaluating the effectiveness of clothing segments in providing insulation. The issue is that in order to evaluate the thermal fluxes, temperature potentials, and impedances by an ohmic relation, we had to recognize that the source is an active inconstant source; namely that the human is a thermodynamic engine, but that its internal combustion processes had not been dynamically evaluated. Experimentally we found a spectrum of large power oscillations within the body system - with periods of 2 minutes, 7 minutes, 30 minutes, and 3½ hours. Thus, in addition to well known oscillators, such as the heart beat (which had been analyzed as a nonlinear relaxation oscillator by van der Pol), the breathing oscillator, and unit electrical processes such as brain waves, we now added basic metabolic oscillators.

When we began our 1962 review of control in the biosystem, we quickly found the central principle in biology enunciated as homeostasis, or homeostatic regulation. This represented a regulation of the internal variables in the system - its fluxes and potentials - independent of conditions external to the complex organism. It seemed clear to us that to achieve such regulated states would require mechanisms involved in dynamic regulation or control. It was such description that we found lacking in the biological literature, except for a few isolated instances. (For example: the modelling of Danziger and Elmergreen of thyroid function and of Yates and Urquhart of adrenal function).

Having our own observations on the oscillating nature of metabolic processes to add to the known periodic nature of heart beat, breathing, EEG, the alternation of rest and wake, we began to trace out a broader spectrum of periodic phenomena involving autonomous oscillators in the complex biological spectrum. For example, we have found these in other metabolic constituents in blood - blood sugar, blood gases (oxygen and CO_2), lactate, free fatty acids, even in the file of red cells in capillaries.

Seeking function and structure beyond these oscillatory processes, we then expected to be confronted with the identification of the regulators and controllers. However, it finally dawned on us, as we uncovered the ubiquity of large amplitude oscillations, that in toto the network chains from which the oscillations emerged likely made up the biological system. Coupled with mechanisms embodying their control algorithms, functionally they represented a dynamic scheme of regulation within the body for which we have proposed the name homeokinesis.

Homeokinesis denotes the scheme of mediation of the operating conditions of a large but compact collection of autonomous coupled oscillators, mainly by inhibition or release from inhibition, so that their mean state provides the near constancy of the internal variables.

Thus, our biological theme came to rest within the identification of these dynamic causal chains that make up the many spectral lines to be found in the biological system. We view the approach as biospectroscopy, or dynamics systems analysis. We have discussed a number of these chains in various references.

At the same time, many molecular biologists and biophysicists became increasingly interested in conditions for the operation of a chemical oscillator. (See, for example, Higgins, (5).) Much of the impetus was directed toward foundations for the theory of life, the living process, and the origins of life.

When we enunciated the oscillatory nature of macroscopic processes in the biological organism, we viewed these as being one parallel track of dynamic systems analysis at various hierarchically ordered levels.

As physical scientists we, of course, had grown up with the spectroscopy of atoms. There was a missing link at the molecular level of chemical oscillators, on which we will comment in a few sentences. We were pleased when we discovered the work of Goodwin (6), who clearly enunciated the character of the cell as an oscillator system. We, of course, were happy with our own contribution to the macrodynamics of the entire organism, and then in extension to the macrodynamics of behavior ((7) and Iberall in (4)).

There remained the gap associated with the chemical oscillator. There were no theoretical grounds to exclude the possibility, only the question of under what conditions could one be formed. It was clear to us that it could be done on a macroscopic scale by coupling with other phenomena.

It finally occurred to us from the work of Britton Chance on metabolic oscillators in cells and ours on total body metabolism, that much of the problem was a matter of scale. Very much as in the fractionating column, it is a matter of field size of competing phenomena to get a particular dynamic reaction to come off and provide substantial yield, that is to entrain a process into sustained operation. We were pleased to find such views suggested by Scriven (in (4)). We stressed it as cooperative phenomena (8).

It remained for Katchalsky, as he discussed it at the 1969 International Biophysics Congress, to point out that the chemical engineers already had arrived at some of the theoretical pieces for simple catalysis. They are contained in two parameters associated with catalysis, the reaction length, and the coefficient of anisotropy.

Many of the issues came into focus at the 1969 International Biophysics Congress, notably in the reports of Katchalsky of Zhabotinsky's work toward a chemical oscillator and Katchalsky's work. This occurred in a session that he chaired on the origins of life.

The work of Zhabotinsky is finally becoming available. The first easily accessible report is in Nature ((9); the catalytic oxidation of malonic acid by potassium bromate using cerium trisulphate as catalyst). The remarks of Katchalsky were quite interesting. In discussing the problem of achieving a chemical oscillator, in work that he had done in achieving high polymeric peptides, he referenced the prophetic words of Bernal for the possible significance of clay as a primeval substrate for the origin of life. More important, he demonstrated a scale of about 1000 Å (using a swelling clay, montmorillonite

as a pH sensitive stratum for the polycondensation process).

Apparently Katchalsky's and Prigogine's remarks are available as talks they gave at the Second International Conference on Theoretical Physics and Biology (10).

Both Katchalsky and Prigogine start their discussions of the chemical oscillator (as a lead-in to the biochemical oscillator) from the hydrodynamic modelling of rapid flow, inhomogeneous dissipative processes. They regard the Bénard cells (see for example Scriven's discussions in (4)) as a prime example of such hydrodynamic instability producing dynamic form.

(Katchalsky: "...the 'central dogma' of molecular biophysics all information about...structure and function is coded in DNA and the phenomena of life is only the unfolding of the genetic script. Granting that the dogma may be accepted literally, the dynamics of biological structures still remain an open problem...". "Structuring and maintenance of flow patterns through the coupling of macroscopic flows is well known in classical hydrodynamics...".

"The recognition that the coupling between chemical reaction and diffusional flow may also lead to instabilities and the formation of dynamic patterns is due to A.M.Turing...".

"The classical hydrodynamic example of the maintenance of dynamic structures is the phenomenon Bénard discovered in 1900".)

At this point an argument begins. At this moment, the only sustained oscillator we know of is the Bush example. It is not clear yet whether oscillations will continue indefinitely in the Zhabotinsky examples. (Although it is said that many people are repeating and elaborating the work, our intent is not to challenge the possibility, only the scope of the interpretations.) Nor has B. Chance yet shown oscillations that will persist indefinitely.

In our opinion it is invalid to expect chemical oscillations out of simple rate kinetics and diffusion in chemical reactions. This was precisely the problem we tackled twenty years ago for C. E. Mason, and described most generally as equivalent to propagation in an inhomogeneous R-C line.

The question of whether a molecular catalyst can locally produce an inhomogeneity capable of producing a local oscillator (e.g. a local biochemical oscillator) brings us up to Pattee's question. We (and we would surmise that Pattee would agree) don't know the answer. The requirement for a high 'hereditary' determinacy is very difficult.

Now with regard to adding rapid flow processes to the prescription, as Katchalsky and Prigogine and Scriven (and we believe Morowitz) have done, we have some added comments.

Here the issue precedes Bénard, going back to Reynolds and the maintenance of a turbulent field. A selected list of references through the

classic literature of hydrodynamic stability (some of the seminal work from early origins, and more recent) may be found in (11). Some of the contributions of the author to the 'quantization' of the hydrodynamic field are listed in (12).

In our view, we add a different but very parallel criticism to Pattee's. Our experience with the hydrodynamic field suggests that wave propagation is a necessary ingredient to bring a hydrodynamic 'oscillator' into being. (It is useful to point out or remind the reader that the Reynolds number is the ratio of inertial to viscous forces, and it takes a critical ratio to bring 'turbulence' or any other flow structure - G. I. Taylor cells between rotating cylinders, Bénard cells, the Richardson instability - into being.)

It then appears to us that the combination of a degradative process of viscosity, the inertial forces (e.g. L-C, mass-spring, rotational inertia, buoyant density density gradients --- see the classic argument conducted by Rayleigh, seeking instability via inflection points, in the flow profile as compared to Reynolds' search via a viscous mechanism, and Lin's subsequent discussions), inhomogeneity in the field, and the nonlinearity (generally introduced by convection) can lead to hydrodynamic oscillators.

An alternate ingredient for instability that may lead to an oscillator is a 'mechanism' selected from another hierarchical level. The names of some typical devices that have been used are 'negative resistance' characteristics, hysteresis characteristics, Monod-Changeux conformation characteristics, snap-diaphragm action, tunnel diodes, clock escapement, or (as hoped by Pattee) suitable quantum mechanical non-holonomic constraints.

The idea, generally, is to work out a nonlinear chain which is clearly linearly unstable and which can feed from a potential energy source. Poincaré used the snap-diaphragm as a static illustration of instability. It is analogous in concept to the Monod-Changeux mechanism. However (as Pattee also implies), a snap-diaphragm will not create an oscillation by itself. As with all 'negative resistance' devices, they are commonly yoked with an inertial system, so that the overall nonlinear system will continue to oscillate. Whether we have simply deferred the question of the need for inertial forces as well as nonlinearity to another level is not clear.

We identify this as reference to another hierarchical level because (illustratively) a 'negative resistance' cannot be 'constructed' at the same hierarchical level as simple 'passive' positive resistances. There it violates the laws of thermodynamics. But by constructing ingredients for a thermodynamic engine from another level, they can be brought in without any overall contradiction. Loosely put, it is function at one level that can provide form or function of another level. If there is one level at which periodic function can be achieved, then it is possible for it to be achieved at all levels. In our cosmology we have the inter-conversion of mass and energy in the universe as a primary 'oscillator' source.

Thus, Pattee's uneasiness about biochemical oscillators is buried at the

level of finding a suitable nonholonomic constraint at the molecular level; ours of finding one at another hierarchical level which can be coupled to the basic level. We both are in favor of suitable substrates for sustaining the reactions.

In our opinion, Bush has found a suitable substrate - the coupling to a thermal boundary layer that provides the escapement. We are intrigued by Katchalsky's use of clay 'substrate' which by periodic swelling and relaxation can act as an escapement. Such or similar substrate paths ought to be able to lead finally to biochemical oscillators. But they must be found as specific dynamic 'escapements'. The static conditions - the double helix, and other details of molecular arrangements - may be necessary conditions, but they do not, of themselves, create the dynamic conditions for sustained oscillation.

The important contribution of Katchalsky's, repeated again, in our opinion is that he demonstrated a scale, at near solid state domain size (1000Å) rather than molecular or macroscopic size, which can be conducive to producing an oscillator. A concluding thought for chemical engineers interested in biological control might be that as the past 25 years have demonstrated in many ways, one may not be able to estimate in advance the size of the volume, the 'beaker', that one can use as a unit cell in some continuous flow relaxation process, in this case the 'beaker' or 'crucible' for life processes themselves. He must guide himself accordingly as he seeks the 'unit processes' in the biological system.

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III. DYNAMIC REGULATION OF THE BLOOD GLUCOSE LEVEL

Abstract

Harmonic fluctuations with periods centered in bands around 50 and 100-150 seconds were observed in the glucose level of rat arterial blood. The amplitude and frequency of these oscillations were found in both unanesthetized and anesthetized animals.

In a second phase, pharmacological agents were administered to anesthetized test animals and the dynamic glucose response noted. From the results some possible regulatory chains that may be responsible for each fluctuating band are screened.

Introduction

The concept of homeostasis pictures a biological system as having intrinsic autoregulatory properties. When the system is subjected to a transient disturbance, one or more of the regulated metabolic or behavioral variables will be displaced from the regulated state or level. After the disturbance ceases, these variables are expected to return to the regulated state. According to this hypothesis, the body maintains constant concentration levels of endogenous substances. An example of such a regulated variable is the blood glucose concentration.

Cahill (1) and Franckson et al.(2) suggest that the settling process to a regulated glucose level, after glucose intake, follows first order kinetics. That is, the course of glucose concentration is a simple exponential decay to a steady postabsorptive level.

Another possible regulatory response following a transient disturbance is one in which the return to the operating level is characterized by sequential overshoots and undercompensations. These generate an oscillatory pattern. The mean level may return to the original level, but high frequency oscillations around the mean level could persist, and may in fact, be characteristic of autoregulation (Hansen (16) and Iberall et al.(15)).

One might expect biologic regulation to be dependent upon dynamic processes, occuring within finite intervals of time. Changes of intermediate, by-product or end-product concentration within the chemical pathways could provide measures for each regulatory or control process. It might therefore be expected that the absolute level of these substances would not be static, but would fluctuate or oscillate at rates representative of the metabolic pathway of which they are part. One is therefore confronted by two extreme models - one a static model in which there is a transient return to a static steady state after disturbances, and the other a dynamic model in which the system is in a constant state of fluctuation.

Control of the state of the internal milieu by dynamic fluctuations has been described as homeokinesis (3). This concept is dependent upon the necessity of oscillations for furnishing the regulation of the biologic system premised by homeostasis.

The innate cyclicality associated with biological regulation was

postulated by Goodwin (4) for a single cell, and experimentally documented by Iberall (5) for an entire organism. Iberall demonstrated sustained metabolic oscillations (in minute volume, and in heat production) having periods in the range of 90-130 seconds, 340-500 seconds, 30-40 minutes and 3½-5 hours. Further investigation of the phenomenon by Iberall and Cardon (6) confirmed the presence of these oscillations occurring in the ranges 1-2 minutes, 5-10 minutes, near 20 minutes, 40-60 minutes and 2½-3½ hours. Goodman et al. (7) and Lenfant (8), using respiratory gases as the measured variables, further confirmed the presence of oscillations. The phase relations between minute volume, oxygen uptake and carbon dioxide elimination were also explicitly exhibited by Lenfant.

Additional intrinsic biological oscillations were further demonstrated by Iberall et al. (9). They demonstrated oscillations with similar time scales in a number of additional mammalian metabolic regulatory systems.

Other observations of free running periodic cycles in living organisms are being reported with increasing frequency. We cite some illustrations: hemoglobin synthesis by erythrocytes with a period of 50 seconds (10); a ninety minute cycle of oral activity (11); a 2 to 5 day cycle of urinary sodium excretion (12); a circadian rhythm of behavior induced in rats (13); or a 3 1/2 hour oscillatory pattern in the normal human blood cortisol level, which is shortened in individuals with Cushing's syndrome (14). These are examples of sustained oscillations with periods of seconds to days.

Wheras Iberall's first studies (5, 6, 15) could only identify a rather broad high frequency band (with periods in the range 30 to 200 seconds) in which a number of concomittant metabolic parameters might be oscillatory, it was clear from Goodman's studies that a number of non-stationary (e.g. varying) frequencies could exist.

Thus it is tempting to postulate that the generation of oscillations of particular periods may likely be an intrinsic characteristic of the regulatory processes of the biological system. This investigation attempts to probe more deeply at one such cyclic process in order to present more definitive evidence for its existence, and to test for possible sites of generation of the oscillatory components in the regulatory chain and plausible associated mechanisms: for example, whether glucose oscillations involve interactions between the liver, pancreas and adrenal medulla.

While spectral analysis is difficult, particularly in cases in which the presence of oscillations is in doubt, nevertheless such studies are essential to an understanding of the dynamics of interacting organ systems within the complex organism.

This particular subject is in controversy. Since Hansen's work (1923, see (16)), there have been reports of oscillations in blood glucose. The current tendency is to believe that oscillations do not exist. The challenge, by some highly reputable investigators in the field, of an earlier report (15), has made this second more careful study essential.

In 1923 Hansen (16) not only reported oscillations in human blood glucose levels, but even postulated that they were instrumental for control. Other, more recent investigations (17, 18)[1] have reported blood glucose oscillations in human, dog and guinea pig subjects.

Discrete oscillations have often been observed but not described. Burns' (19) graphs illustrate damped oscillations, and a plot of Himsworth's (20) 1939 data similarly reveals cyclic oscillations. The failure of many to observe the rhythmic oscillations of the blood glucose level may be due to sampling techniques in which the blood is pooled as it is withdrawn by downstream vessel occlusion, or, by mixing of the blood during active withdrawal with a syringe. Still another cause may be the use of automated laboratory procedures which also can mask any fluctuations between samples by mixing, and thus dampen the oscillation amplitudes.

In previous investigations glucose oscillations have been measured primarily in venous blood. Only the work of Anderson (18) and Iberall et al. (15) attempt to correlate the venous sample data with simultaneously drawn and analyzed samples from the arterial bed. For this study a procedure was developed in which free flowing arterial blood samples could be collected and analyzed.

In this report we cover two experimental investigations: the first to show whether anesthesia has any effect on the glucose fluctuations, and the second to test some possible hypotheses as to the source of the fluctuations. As indicated in the first test program the results obtained from unanesthetized, restrained animals were compared with identically prepared animals anesthetized with Pentobarbital Na.

A. Test Program 1 - The Effect of Anesthesia on Glucose Oscillations

Methods

Two groups of adult, male, Wistar rats were used. The animals in group one were anesthetized with Pentobarbital Na (30 mg/kg IP). Those in group two were anesthetized with diethyl ether, and regained consciousness prior to blood sampling.

The operative procedure was identical for both groups. After shaving the abdomen, a midline incision was made and the abdominal contents deflected to the left. From its origin at the aorta, the right iliac artery was separated from the surrounding tissue, for a distance of one centimeter. Two ligatures were loosely placed under the vessel and retracted. The vessel was cannulated in the direction of the aorta with a heparin filled shunt. After securing the proximal end, the tubing was looped back upon itself and inserted

[1] Also J. Sieracki, U. Pitts., personal communication.

into the same vessel just distal to its exit. With the tube ligated in place, all blood flow was shunted from the right iliac artery through the tube, and back into the artery at a distance approximately one centimeter from its point of emergence. The tube was externalized through the abdominal incision. The incision was sutured, and the free flow of blood through the tubing verified.

The shunt consisted of two 5 mm lengths of vinyl tube (.0.34" ID x .046" OD) inserted into the ends of a 20 centimeter length of silastic tubing (.040" ID x .085" OD). An 18 gauge stainless steel T, attached to a three way stopcock (#3139 Becton-Dickinson) was inserted into the silastic tube, such that free flow was maintained through the tubing and T connection. A teflon adapter inserted into the stopcock permitted sampling from the side arm of the connector into calibrated 100 Lambda capillary tubes, without leakage, sample blood mixing or need for active withdrawal (Fig. 1). The dead space within the sampling system was 0.05 cc. This volume was flushed with blood prior to first sample. Blood samples from group one were drawn with the animal anesthetized. The animals in group two were placed in restraints while anesthetized. The samples were collected from these individuals after complete recovery from anesthesia. Normal arousal was determined by the initiation of motor activity, manifested by attempts to escape the restraint.

At 15 second intervals the stopcock was opened and 0.1 ml samples of blood were collected in the Corning #7099 calibrated glass micropipets. Each blood sample was immediately placed in 0.5 ml of 0.5% $ZnSO_4 \cdot 5H_2O$. To this was added 0.5 ml of 0.3% $Ba(OH)_2$.

The contents of the tubes were mixed and allowed to stand for five minutes. They were then centrifuged to precipitate the cells, and 0.5 ml of supernatant pipetted off for analysis. In four animals (#10-13) an additional 0.1 ml aliquot of supernatant was removed from each sample, and pooled to form a volume of 2.4 ml. After mixing, a 0.5 ml sample was drawn from this pool and analyzed for glucose. The procedure followed was identical with that used for the other samples. The mean concentration of glucose for each animal was calculated from the fifteen second serial samples. This calculated mean was compared with the glucose concentration of the pooled sample. (Table 1).

Glucose was determined according to the micro method of Folin-Wu (21). An additional suction filtration of the final solution just prior to introduction into the spectrophotometer was added to remove any insoluble material suspended in the solution. The optical density was measured at 420 mμ using a Research Specialties Co. spectrophotometer Model 4000 coupled with a model 4400 Datascribe print output.

A total of twenty four, 0.1 ml samples taken at 15 second intervals were drawn from each animal. This represented a total of 2.4 ml drawn over a six minute period, plus an additional small volume for purging the system after completion of blood withdrawal. Each animal was place in a cage, and all, including those anesthetized, after recovery from anesthesia, appeared

normal. The data was analyzed according to a 'pencil filtering' method discussed by Halpern et al. (22). Basically the technique consists of plotting the concentration of glucose in milligrams percent (mg%) for each sample against time (Fig. 2a). From this graph, the cycle maxima (or minima) were counted and divided into the total elapsed sample time (seconds). The highest frequency observed with the 15 second rate had a period of about 50 seconds.

The slower cycle frequencies were obtained by successive filtering (Fig. 2b). This was accomplished by joining the midpoints of the lines between minima and maxima in the original data plot. The new maxima are again counted and divided by the time elapsed. For this, the time is the interval between the ends of the filtered line. Successive filtration of the data produces a sequence of increasing periods.

Results

All animals recovered from the operation and anesthesia, and did not appear to have any residual adverse reactions.

The blood glucose concentration was found to oscillate in all animals studied, with a maximum single amplitude of $\pm$ 15 mg%. Within the test period sampled, two distinct cycles were observed in the anesthetized animals (Fig. 3a, Table 2). The first period found was about 50 seconds and the second period was about 100 seconds.

The blood glucose levels of the unanesthetized, restrained animals also exhibited two periods of oscillations of about 50 and 100 seconds, similar to the anesthetized animals (Fig. 3b, Table 2).

Although great differences in concentrations are observed between many successive samples drawn from the same animal, the mean blood glucose concentration for all animals tested was 85 mg%. This same value, found by averaging all sample concentrations, could be observed by drawing one large sample of blood over a period of not less than 50 seconds.

From the data presented in Table 3 it appears that the fluctuations found using this sampling and analysis technique are not an artifact. In each case (animals 10-13) the pooled supernatant mean varied by no more than 4 mg% from the mean calculated from the absolute glucose concentrations at fifteen second intervals. On the other hand, this value is only a small fraction of the variance exhibited by the individual samples.

To test the significance of the fluctuating amplitudes further, additional analysis was performed in a second phase of this study.

B. Test Program 2 - Further Refinement of Statistics and Some Tests of Mechanisms for the Source of Oscillations

Critical review of these data suggested a disbelief as to their reliability and the request for further refinement of methods for assuring the reliability of the statistical sampling. Since the issue raised was not whether glucose oscillates in those test animals under anesthetic as compared to no anesthetic (i.e. one result was disbelieved as much as the other), we chose to use an experimental protocol under which our animals were anesthetized for further study. However, we proposed to show a calibration background for our time sequenced data. The calibration background is interleafed at random with the test samples.

At the same time, to avoid the infinitely sterile exercise of endless repetition of studies to probe at the reality of oscillations, we proposed to examine a hypothesis discussed earlier (9), whether the glucose oscillations and other metabolic concomitants (heat, oxygen uptake, CO_2 production, lactate production) might be related to a possible fluctuating centrally elaborated catecholamine signal.

Abstract

From four groups of rats, one being a control and the others pretreated with either 2-deoxy-d-glucose, glucagon, or surgical adrenalectomy, 24 serial samples of free flowing arterial blood were collected at fifteen second intervals and analyzed for glucose, using the Folin-Wn micro method.

Analysis of the data showed that the blood glucose level varies with a regular periodic pattern. Frequency analysis by both a pencil-filtering of data and a computerized Fourier analysis, displayed frequency characteristics which were distinct for each group tested. The control group and glucagon treated group exhibited oscillations with periods in the range 40-60 sec., 120-180 sec, and perhaps 75-90 sec. The 2-DG treated group exhibited oscillations in the range 40-60 sec and perhaps 75-90 sec. The adrenalectomized group exhibited oscillations with periods in the range 40-60 sec and 120-180 sec.

From the results of harmonic analysis for the data of each group and the known character of the three treatments - 2-DG to inhibit peripheral uptake of glucose and to stimulate the adrenal medulla to liberate epinephrine; glucagon to stimulate glucose release from the liver and to stimulate the adrenal medulla to librate epinephrine; and adrenalectomy principally to eliminate epinephrine liberation from the adrenals - physiologic processes most likely linked with the observed cyclic processes are postulated.

The observed oscillatory processes are indicative of the more complex nature of glucose regulation within the liver than is commonly suspected.

Methods

Twelve male Wistar rats, each weighing 300 to 400 grams, were randomly segregated into four groups. The animals were fasted for twelve hours (water ad lib) prior to blood glucose analysis. Group A was untreated. Group B was pretreated with 2-deoxy-d-glucose (750 mg/kg S.C.), and Group C with glucagon (400 mg/kg I.A.) both obtained from Calbiochem, Los Angeles, California. The rats in Group D were adrenalectomized 10 to 14 days prior to testing.

Following anesthesia with Pentobarbital Na (35 mg/kg), the same surgical procedure was used as described earlier.

The collection technique was also as described earlier. Before collecting the initial sample, the dead space (0.05ml) within the stopcock and side arm of the stainless steel "T" was purged with a drop of blood from the animal. Twenty-four serial blood samples were then collected at fifteen second intervals from each animal through the side arm. Serial sample blood withdrawal from groups A and D were made immediately following surgery.

In a preliminary study of two supplementary groups, the time of peak 2-DG and glucagon activity had been determined (Fig. 4). In these groups duplicate samples of blood were drawn at fixed intervals (15 minutes apart for those with 2-DG and 10 minutes apart for those treated with glucagon) before and after drug administration (Fig. 4a,b). Each sample was analyzed in duplicate and the means at each sample time (four values for each animal at each time) compiled and graphed. From the response curves drawn the optimal time for sampling was determined.

Serial sampling from the animals in group B was performed 90 minutes post drug administration. In group C serial sampling was performed 40 minutes post drug administration.

Each sample was immediately placed into an individual preweighed, cold, centrifuge tube, containing 0.5ml H_2O and 0.5ml 0.5% $ZnSO_4 \cdot 7H_2O$. The tubes and their contents were reweighed and the absolute weight of blood added to each tube was determined.

One half ml of 0.3% Ba $(OH)_2$ was added to each tube. This mixture effectively inhibits cellular glucose utilization and the subsequent depletion of the extracellular glucose concentration.

The animals were then exsanguinated. For each animal the pool of collected blood was well mixed and divided into three smaller pools to serve as background references for the reliability of the time dependent measurements. The three pools were chosen so that they would span the range of the serial samples. The first pool was maintained unchanged. One ml of a solution of glucose dissolved in 0.9% sodium chloride was added to 2 ml of the second pool. The concentration of glucose in this solution was sufficient to bring the final 3 ml volume glucose concentration up 50 mg% above the original

pool concentration. The third pool was diluted with an equal volume of 0.9% sodium chloride to halve the original glucose concentration. From each of these three well mixed pools, six 100 Lamba samples were drawn. Each sample was added to the tubes (which had been pre-weighed) containing zinc sulfate solution and weighed to evaluate any pipeting error. Barium hydroxide was added. These tubes were then randomly spaced among the serial samples, and all were centrifuged. All samples were maintained on ice until centrifugation.

The twenty-four serial samples and the six samples drawn from each of the three separate pools were analyzed for each animal. Two 0.5 ml aliquots of supernatant liquid from each centrifuge tube were pipetted off for duplicate glucose analysis. In the data analysis the average of the results from the two aliquots was considered to represent the individual estimates of glucose concentration. Internal reliability was judged on the basis that the two individual determinations agreed within expected variability limits. A great deal of care was taken to assure that the two determinations agreed within expected limits. In the few cases where greater uncertainty was encountered, the individual point that seemed to be more in accordance with its temporally neighboring points were selected. However the uncertainty assigned to this singular point was the standard deviation of the entire variable sample (i.e. 16 mg%) rather than the reliability of a single standard sample (i.e. 4 mg%).

The glucose content was determined according to the micromethod of Folin-Wu (23). Just prior to colorimeter analysis, each final sample was passed through a Gelman Metricel filter with 5.0 micron pores, to remove insoluble suspended material.

Glucose concentration was determined as a function of optical density, using a Dana model 5400 digital voltmeter coupled to a Bausch and Lomb Spectronic 20 colorimeter with regulated power compensation. Each sample concentration was read at a wavelength of 420 mμ. The voltmeter output increased the resolution of the colorimeter readings ten times. Differences of less than 1 transmittance unit could be detected. These units were converted to density units, from which the glucose concentration was calculated.

The eighteen reference samples were analyzed and used as a background to establish the magnitude of the experimental error of any particular glucose sample within the range of interest. Their known constancy permits their use to test the null hypothesis of how much apparent 'dynamic' variation could be ascribed to measurement error.[1]

[1]If we concede that the control pool is only known in the sense of its calibration by a particular technique, the other two pools, however, are known, relative to the central pool, by absolute offsets. Thus our relative levels are known reliably. By treating pooled samples as random members of a test sequence, from the relative constancy of their expected statistical variation, i.e. they do not drift in time nor do they show larger than expected fluctuations, we can note the characteristics of the temporally sampled data to see if they show comparable or greater variation than the reference pooled data. Greater variation now must be ascribed to 'systematic' fluctuations.

Though the concentration of the original base pool is unknown and determined experimentally by the test technique used, the relative concentrations of the other two pools are known. Thus, the 'prediction' of their mean value is an independent check on the reliability of estimates from the pools. The mean and standard deviation for each pool were determined and plotted as in Fig. 5a., which illustrates a typical case. The two calculated pool means are presented and shown lying within one standard deviation of the experimentally determined means. The analysis error, as determined by the variation within each homogeneous pool, was used as a guide for estimating the significance of the glucose oscillations found in the serially collected data.

The serial sample data of a typical animal is plotted in Fig. 5b with the means and standard deviations of the three reference pools from the same animal.

Each point of serial data cannot be considered to be more certain than an amount of the order of one standard deviation of the reference pool data, in the vicinity of that sample data point. The unit standard deviation of the pool is thus used as a measure of the uncertainty. The uncertainty is indicated by a band around the serial data in Fig. 5b. Within this range a curve of least fluctuation may be drawn (as shown by the dashed line). What remains cannot be explained as experimental error. This technique filters out unwanted high frequency components with periods of the order of the sampling interval but still takes into account errors and uncertainties in the chemical analysis. Thus, the reality of oscillations may be noted in the residual excursions.

This 'pencil-filtering' technique is quite useful, and has several advantages over more complex kinds of data analysis, for example, Fourier analysis. It is very simple to use in practice, requiring only a little intuition and experience. It brings forth clearly and unambiguously the most certain information contained in the data. Further, and most important for analysis of the data contained in this report, it can be applied with confidence to short segments of data. That is, data covering many cycles are not required in order to determine unequivocally the existence of fluctuating pattern (as would be required by correlation techniques), and yet it permits making reasonable estimates of the most predominant frequencies in the spectrum. Instead it makes use of the ergodic hypothesis that determinations from individual members of an ensemble will exhibit, in brief observations, characteristics similar to individuals in long observations. (Short segments of data, however, cannot guarantee stationarity; only many repeated segments of data can.)

Data for each test animal are shown in Fig. 6. The frequencies found by Fourier analysis are indicated in Fig. 7.

The frequency spectrum for each group of animals as determined by both the pencil filtering and Fourier analysis are compared. The differences and similarities between the groups are presented in Table 3. Making use of characteristic responses exhibited in these data and the known effects of the test agents and of adrenalectomy, a basis for explaining the oscillations in terms of physiological mechanisms is suggested.

Results

The mean blood glucose responses of the animals in the two supplementary groups, used to determine the optimal time for serial sampling after drug administration, are plotted in Figures 7a and 7b.

First, with regard to the animals pretreated with 2-DG (Fig. 4), they developed hyperglycemia with the same time-course as that reported by Smith and Epstein (23). The onset of hyperglycemia began within fifteen minutes and peaked between 90 and 120 minutes post 2-DG administration.

Also, with regard to the response to glucagon, the hyperglycemic response to the intrarterial administration of glucagon was similar to that found by Sarcione et al. (24), who injected glucagon into the tail vein of rats. The glucagon induced hyperglycemic response began within ten minutes, reached a peak at thirty minutes, and persisted for longer than eighty minutes.

Fig. 6 shows the raw serial sample data for each animal of all four groups. The bands in the background show means and standard deviations of the reference pools associated with each animal. In every case the amplitudes of the oscillations are greater than the experimental uncertainties indicated by the reference pools. The pencil-filtering technique was applied to each set of data and the dominant frequencies extracted.

The data was also analyzed with the Fourier analysis mentioned in the previous section. The calculated Fourier coefficients for each period are shown in Fig. 7. In each group the plotted coefficients for each period are the median of the coefficients for the three animals of that group. The twelve periods evaluated are equal fractions of one cycle per minute, from one-sixth cpm to two cpm. The results are tabulated in Table 3 where the oscillations are classified as highly certain (+++), as discriminated from the noise, or moderately certain (++). Zero (0) indicates no oscillations, and (-) indicates undecidability. The 'highly certain' determinations, loosely, represent a discrimination of about 4 to 1 in signal to noise ratio. Table 3 also shows the frequencies obtained by pencil filtering. Since this technique permits the discrimination only of the most significant frequencies, these oscillations have been classified as highly certain.

Comparison of the computer analysis with pencil filtering discloses the similarity of highly certain periods discovered by both techniques (40-60 seconds, 120-180 seconds). Additional weaker oscillations are found by the Fourier analysis, notably with periods near 30 seconds, which is twice the sample time, near 360 seconds which is the total sampling time, and in the mid-range of 75 to 90 seconds. Technical sampling reasons (see Goodman (7), for example, for discussion) require dismissing the 360 second cycle, and the 30 second cycle as possibly artifacts. It is also difficult to separate the frequencies into discrete stationary spectral lines. With such uncertainties in mind, we can consider the results for each sample group, considering only those oscillations of which we can be certain.

The control group (A) glucose oscillations contained highly certain harmonics with periods of 40-60 seconds and 120-180 seconds. An additional harmonic with a period of 75-90 seconds was also seen with the Fourier analysis.

Group B, pretreated with 2-DG, showed a highly certain harmonic with a period of 40-60 seconds and a more questionable harmonic with a period of 75-90 seconds.

Group C, pretreated with glucagon, had a highly certain glucose oscillatory periods of 40-60 seconds and 120-190 seconds with a more questionable (computer analysis only) harmonic at 75-90 seconds.

The adrenalectomized animals, group D, had highly certain oscillatory periods of 40-60 seconds and 120-180 seconds.

C. Discussion

When we examine all of the metabolic data available to us (taken from the references listed), and including data on red cell fluctuations in small capillaries; blood glucose, blood O_2 and CO_2, blood lactate and free fatty acids; local and overall organism temperature and heat production; oxygen uptake, minute volume, and CO_2 determined in the respiration; piece-meal data taken in man, guinea pig, dog, rat, mouse) we seem to find about three major bands of harmonic fluctuations in the range 20 to 500 seconds. One band is centered at approximately 50 seconds (it may include an independent band at 30 seconds); a second is centered at about 100 seconds; and a third is centered at about 400 seconds. In this study, we have glucose fluctuations in rats near 50 seconds and 150 seconds (we view the 100 second and 150 second periods as being indistinguishable). We propose to use pharmacological evidence to distinguish or at least screen regulatory mechanisms which may generate these cycles. We, of course, are assuming that these metabolic oscillations are coupled (e.g. glucose/oxygen) in some way. We will attempt to interpret the nature of these regulatory chains in terms of our glucose findings.

The compound 2-DG, a chemical analog of glucose, is said to have a two-fold action. Brown (25) has shown that it acts as a competitive inhibitor of glucose utilization by metabolizing cells, and subsequently it causes an increase in the deposition of liver glycogen. This inhibition of glucose uptake and metabolic action by the tissues is not enough to induce hyperglycemia because increased liver glycogen deposition compensates for the decreased tissue uptake. 2-DG simultaneously increases the release of epinephrine, due to its action on the brain and the subsequent nervous stimulation of the adrenal medulla. The release of epinephrine is necessary for the development of hyperglycemia, since Brown has shown that in adrenalectomized rats, 2-DG administration does not induce hyperglycemia, but only a compensatory increase in liver glycogen.

Glucagon, similarly, has a dual function. It causes increased glycogenolysis in the liver, accompanied by the release of epinephrine from the

adrenal medulla. Alpha blockade or demedullation of the adrenal glands blocks the hyperglycermic response although glycogenolysis is maintained (24) In addition glucagon increases the peripheral utilization of glucose, by initiating a secondary release of insulin from the pancreas in response to the elevated blood glucose level.

Comparison of the glucose oscillation frequencies of groups B and C with those of the control group permits differentiation between oscillations generated by peripheral tissue glucose uptake and release and liver glycogenolysis. Information as to the nature of adrenal interaction in this regulatory network is obtained by comparison of adrenalectomized and control animals.

A correlation of the observed oscillatory frequencies with biochemical events by comparison of the harmonics generated by each of the four groups with each other and with the agent or surgical procedure used, is shown in Table 3. Such a correlation suggests the events to which these time scales may be coupled.

A strong fluctuation of 40-60 seconds was found in all groups, independent of the treatment. These rapid fluctuations imply the existence of a surprisingly fast acting regulatory chain. Linking this frequency with insulin activity in the pancreatic-hepatic regulatory pathway was first proposed by Anderson et al.(18). Our data support the idea of insulin-liver coupling.

A possible 75-90 second period is found in the control, the 2-DG treated and glucagon treated groups. It is absent from the group of adrenalectomized animals. In the group pretreated with 2-DG the fluctuation at this frequency is of less certain magnitude. Even though the evidence is weak or perhaps masked in these observations, the possibility of adrenal medulla secretion as a link in glucose regulation at this time scale is suggested. Without the adrenals no oscillations exist. On the other hand, when 2-DG is administered to otherwise normal animals the pronounced hyperglycemia (dependent upon epinephrine release) could distort or mask the harmonic characteristics at this time scale.

Thus, action of epinephrine, liberated from the adrenal medulla, on a liver glucose function with this period is not ruled out.

The strong slower harmonic with a period of 120-180 seconds is found in all groups except those pretreated with 2-DG. Since the primary action of 2-DG is as a competitive inhibition of peripheral glucose uptake and utilization, and a harmonic with this period is not observed when this agent is used, the peripheral removal of glucose from the blood stream appears to be the source of this harmonic.

Iberall and Cardon (1965, see (6)) have suggested that oscillations in oxygen uptake, in minute volume ventilation, in thermally detected heat production, and fluctuations in red cells in small capillaries with this approximate period are the concomitants of a thermodynamic engine cycle. They have suggested that the cycle is monitered by an oxygen choke. This mechanistic

view attempts to account for the exchange of energy within the system at this time scale on the local microvascular level. This proposal receives further support from the glucose oscillations observed in this series of tests. It appears likely that all tissue may exhibit a local near 100 second engine cycle metered by an oxygen choke, and that in a very active engine source like muscle, the glucose uptake is tied to the oxygen uptake. It will take direct phase measurements between oxygen and glucose to consider this hypothesis in greater detail.

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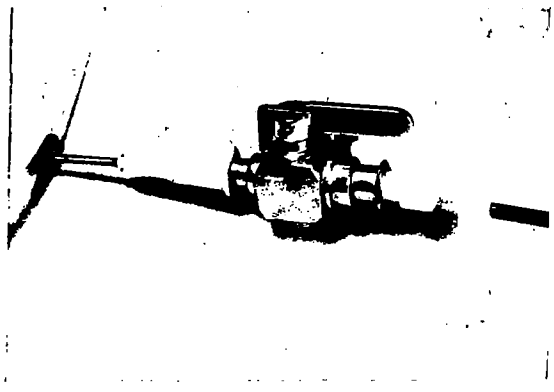


Fig. 1: Shunt Sampling Device. A stainless steel "T" is constructed out of 18 gauge tubing. Two ends of the "T" are connected silastic tubing, which forms the bulk of the shunt. A continuous blood flow is maintained through these tubes and "T" connection.

The side arm of the "T" is connected to a B-D three way stopcock, into the end of which is inserted a teflon adapter. This adapter is constructed so that an unbroken path for blood sampling can be maintained between the shunt and a capillary tube, pressed against it.

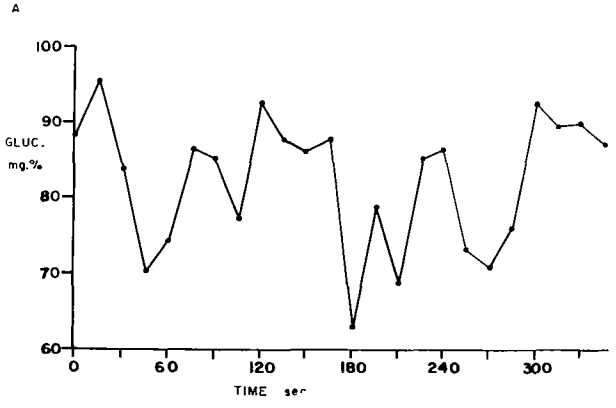


Fig. 2a: Graphic representation of the blood glucose concentration (mg%) plotted against sampling time (sec). The number of cycles, counted from the graph, is divided into the total elapsed time. The period thus obtained (345/8 = 45) is the highest frequency oscillation.

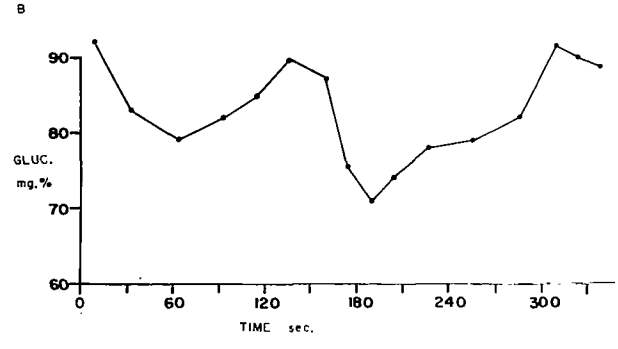


Fig. 2b: The lines connecting the midpoints of the oscillatory undulations in Fig. 2a are counted and the division process repeated. This yields a period of about 95 sec. Subsequent filtering of this data completely smooths the curve toward the mean blood glucose concentration.

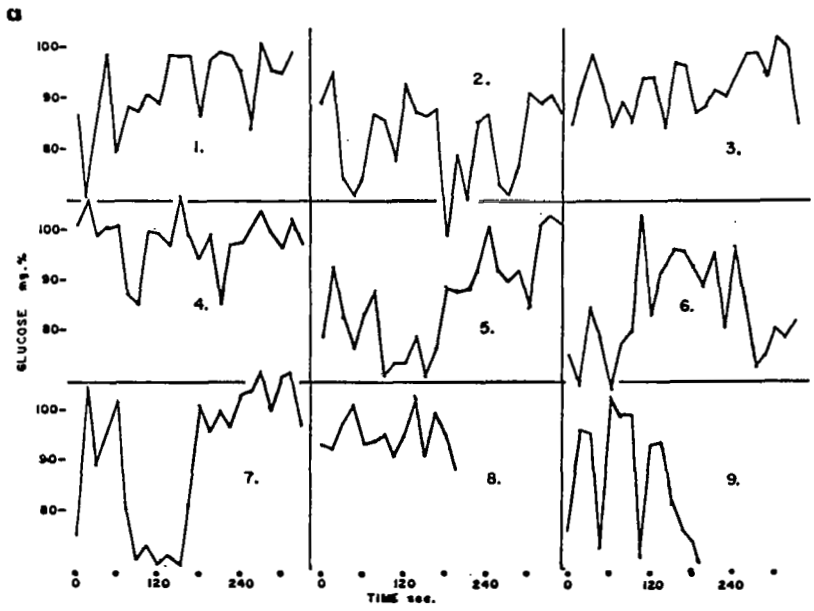


Fig. 3a: Blood Glucose Oscillations in Anesthetized Rats. The arterial blood glucose concentration in nine rats are plotted against sample time. The fluctuations have not been smoothed. Note the rapid marked fluctuations in all animals.

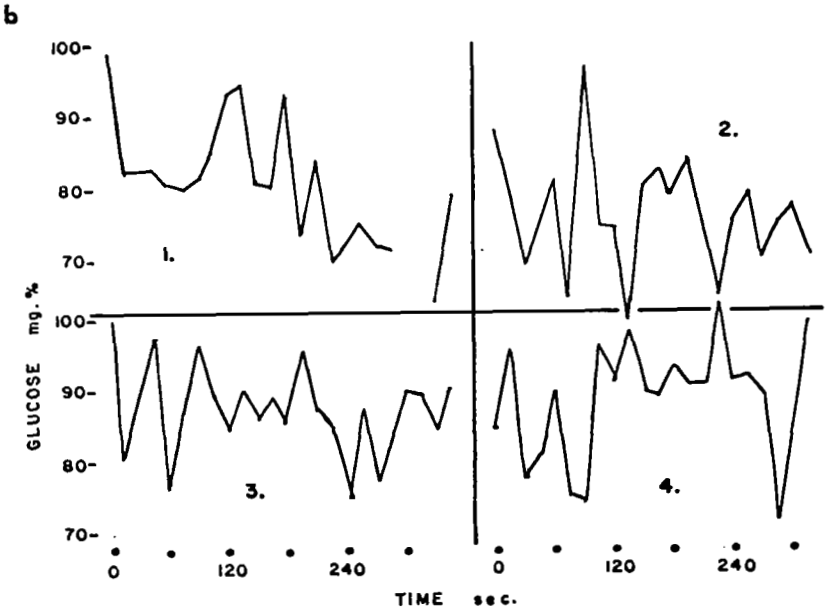


Fig. 3b: Blood Glucose Oscillations, Unanesthetized Rats. Similar graphic representation of the data for four unanesthetized rats. No statistically significant difference can be noted between these and the anesthetized animals.

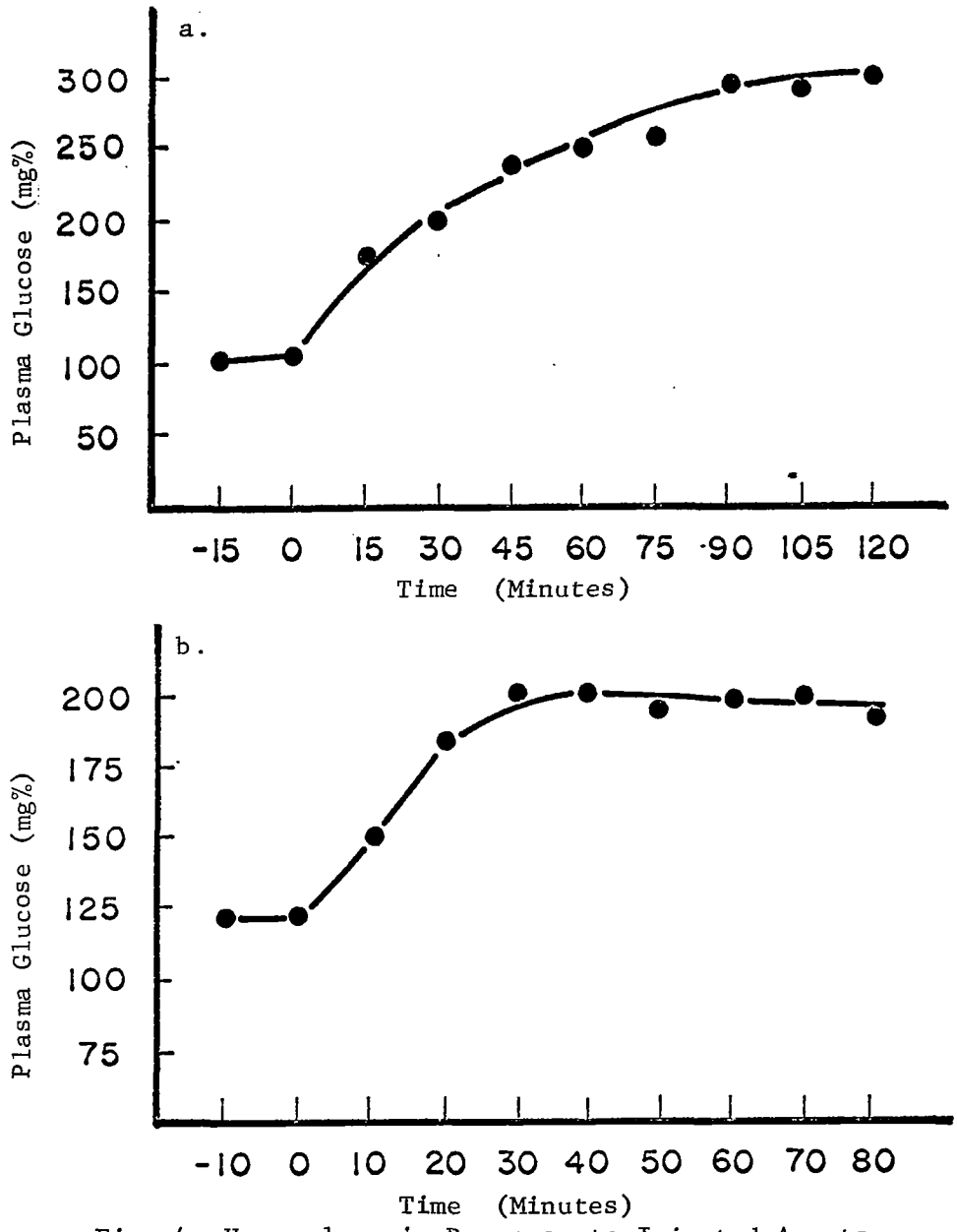


Fig. 4: Hyperglycemic Response to Injected Agents

Figs. 4a: 2 deoxy-d-glucose (750 mg/kg S.C.)
4b: glucagon (0.4 mg/kg I.A.)

Each point is the mean value of two samples drawn and analysed in duplicate from a minimum of five animals. From these graphs the optimal time for withdrawal of the serial blood samples was determined for test groups B and C in Fig. 7.
The test agent was injected at time zero, just after withdrawal of the second (zero time) sample.

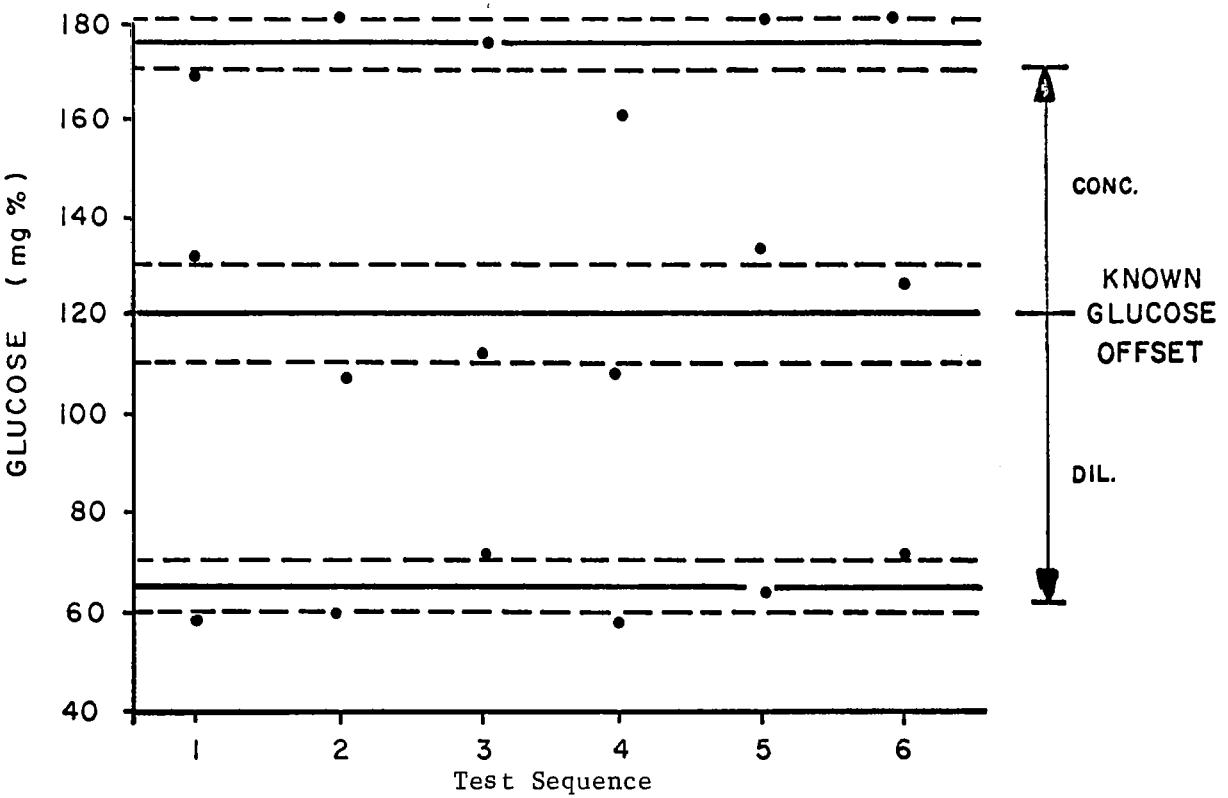


Fig. 5a: Error Analysis of Data From A Single Animal

The values determined by chemical analysis for each pool are sequentially plotted in 5a. The calculated means and standard deviations for each pool are plotted in the same graph. Note that the calculated increase in concentration, 50 mg% above the initial pool, is within one standard deviation of the actual concentration found. The volume, diluted in half, similarly, has an experimentally determined concentration within one standard deviation of that calculated.

These deviations are used as a guide for the determination of the error in the analysis of the serial sample data shown in 5b.

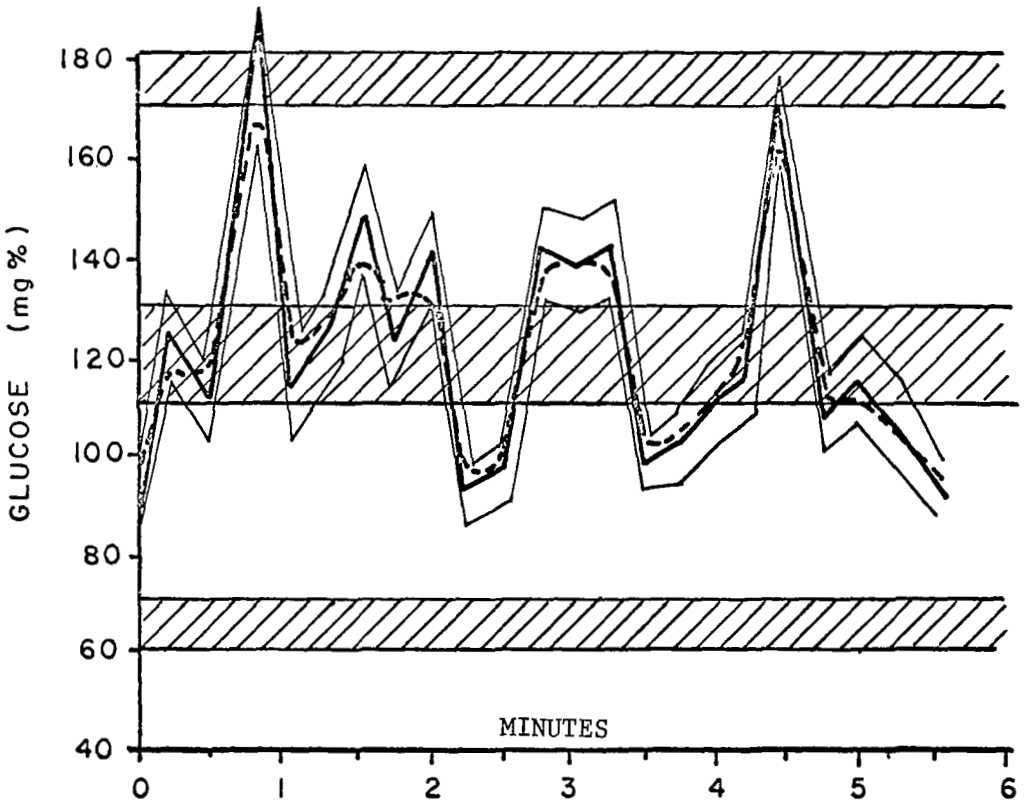
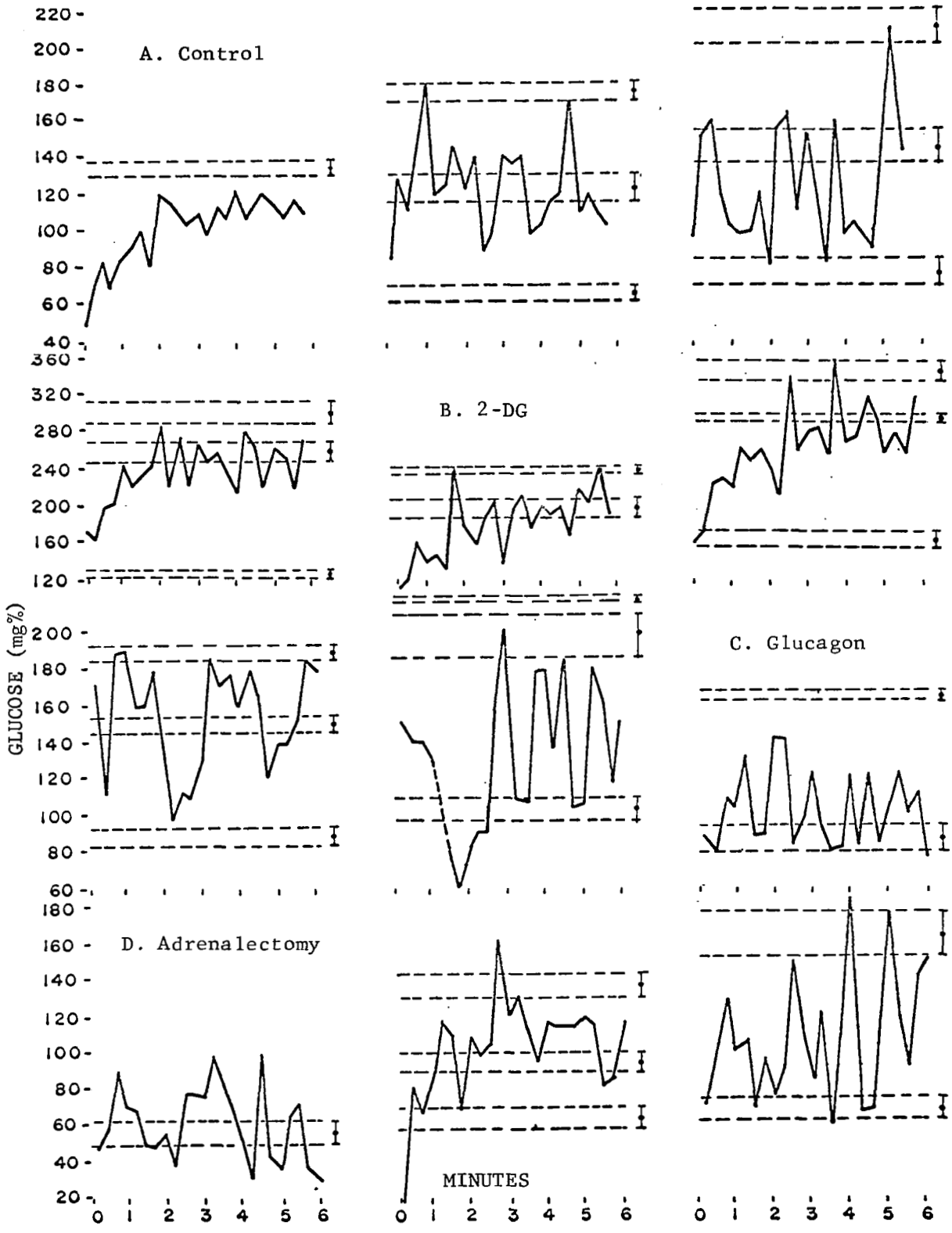


Fig. 5b: Error Analysis of Data From A Single Animal

The serial sample data are plotted along with the standard deviation estimated for each value. The three calibration pools, plus their uncertainties, are shown in the background.

The dashed line is a smoothed curve of the smallest temporal fluctuation in glucose concentration that the error analysis permits.



Legend for Fig. 6 on following page.

Fig. 6: Fifteen Second Sampling Glucose Concentration
Each graph represents the serial concentrations determined for each animal from pairs of blood samples. In addition, the means and standard deviations of calibration pools are shown in the background.

In all cases the oscillatory amplitudes exhibited by serial sampling are significantly greater than the deviations shown in the background pools

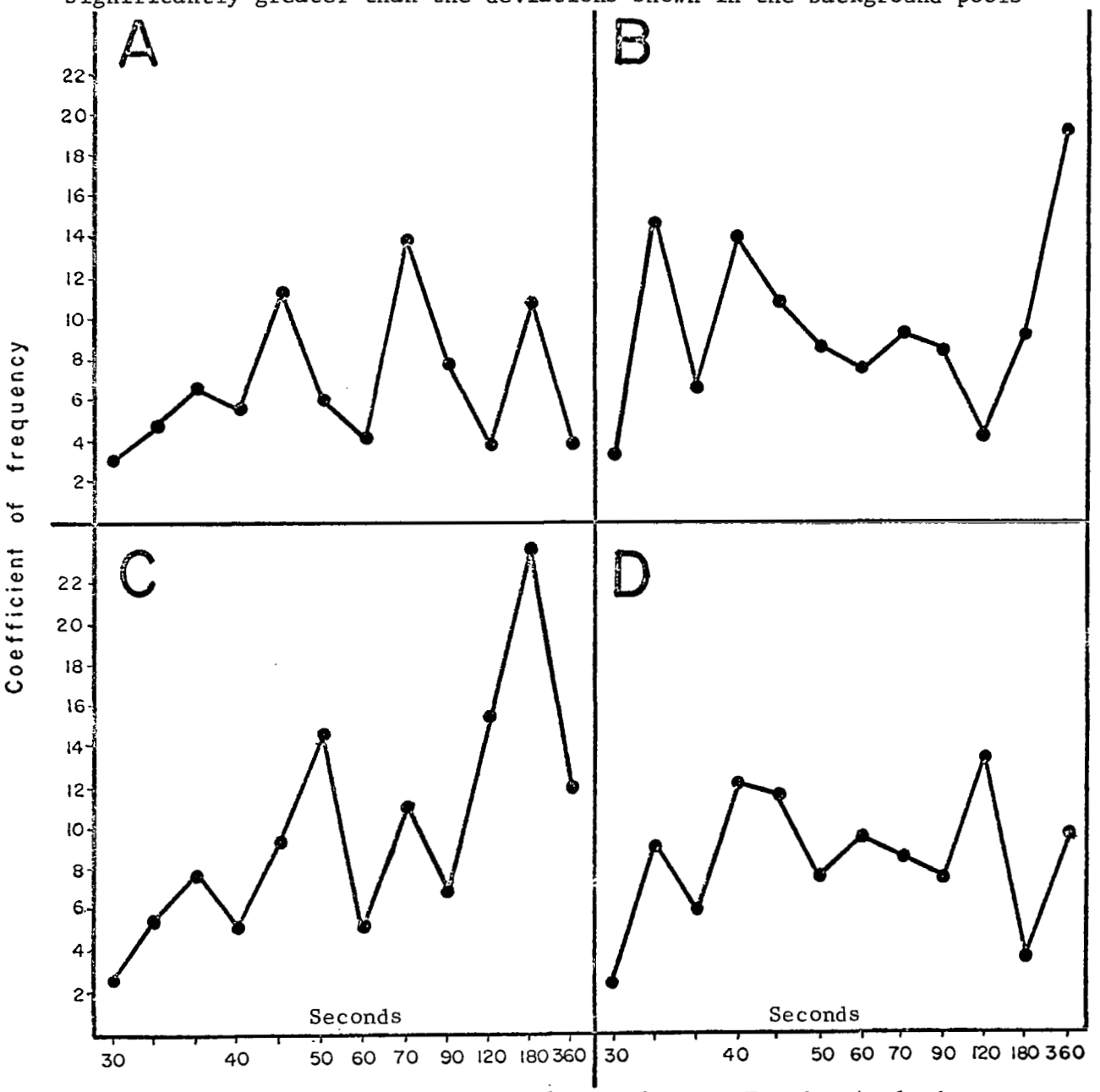


Fig. 7: Relative Amplitudes of Fluctuations By Fourier Analysis

Each graph represents the compiled amplitude coefficients for each group of animals in Fig. 6 as determined by a computerized Fourier analysis. The abscissa is divided into equal fractional parts of a sixty second cycle.

The plot does not represent the actual glucose concentration at any given time. Instead, the amplitudes are an indication of the probability that oscillations are occurring at each of the plotted frequencies. Anything but prominent peaks must be regarded as noise.

Table 1: Comparison of Serial and Pooled Samples

mg% Glucose

	- Animal No. -			
seconds	10	11	12	13
0	87.7	79.9	46.0	64.7
15	80.8	110.9	84.9	82.5
30	82.5	135.4	39.4	87.4
45	76.5	105.3	56.5	77.6
60	63.6	133.5	37.5	42.1
75	67.0	103.5	64.0	59.9
90	54.4	81.8	66.9	79.3
105	68.8	76.2	95.3	71.2
120	58.4	71.4	83.0	93.8
135	57.6	104.4	67.8	63.1
150	63.6	96.8	66.0	80.9
165	64.4	101.5	59.3	92.2
180	66.2	109.1	98.2	145.0
195	79.1	134.4	83.0	94.8
210	56.7	119.4	82.1	102.9
225	98.0	158.0	71.6	81.9
240	108.3	189.9	85.8	86.8
255	134.9	149.5	92.5	138.5
270	62.7	113.8	69.7	98.1
285	75.6	95.0	89.7	70.6
300	89.4	79.9	75.4	130.4
315	58.4	104.4	93.4	112.6
330	72.2	80.8	60.3	127.2
345	74.8	72.4	76.4	107.8
Mean	75.1	108.6	72.7	91.3
S.D.	18.3	29.6	17.1	25.7
Pooled Mean	79.2	105.3	75.3	93.3
Δ Mean	4.1	3.3	2.6	2.0

Table 2: Rat Arterial Blood Glucose Oscillations

Anesthetized	Mean Oscillations		Unanesthetized		
Animal	Periods	Seconds	Animal	Periods	Seconds
1	51	95	1	50	--
2	45	95	2	45	90
3	45	90	3	51	90
4	51	135	4	51	114
5	51	--	Mean	49.	98.
6	51	90	S.D.	3.	14.
7	45	110			
8	48	97			
9	52	85			
Mean	49.	100.			
S.D.	3.	15.			

Table 3
Observed Oscillations and Possible Functional Correlates

Oscillatory Period -sec.	Control Group A		2-DG Group B		Glucagon Group C		Adrenalectomy Group D		Physiologic Correlate
	Fourier	Pencil Filter	Fourier	Pencil Filter	Fourier	Pencil Filter	Fourier	Pencil Filter	
30-36	—	—	+++	—	—	—	++	—	artifact of computer analysis
40-60	+++	+++	+++	+++	+++	+++	+++	+++	pancreas - liver interaction
75-90	+++	—	++	0	+++	—	0	0	adreno.-medullary liver inter-action
120-180	+++	+++	0	0	+++	+++	+++	+++	peripheral uptake
360	0	—	+++	—	0	—	—	—	artifact of computer analysis

Legend

0	no fluctuation found
+++	strong fluctuation
++	weaker fluctuation
—	not decidable