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SIXTH REPORT

GENERAL DYNAMICS OF THE PHYSICAL-CHEMICAL SYSTEMS IN MAMMALS

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ABSTRACT

This report is the third technical report under the present contract, and the sixth in a series. The aim of the program is to develop models adequate to account for the dynamic characteristics of selected systems in mammals from a physical-chemical point of view. It is quite clear that a highly coordinated central thesis of dynamic regulation - 'homeokinesis' - has emerged as the physical basis for the physiological view of homeostasis, both for physiological and psychological phenomena. Its foundation is a large class of oscillators, forming a rather extensive biological spectrum, whose dynamic shifting represents the paths toward regulation. Most characteristic of the biological system is the 'moment' to 'moment' locking of the oscillator systems into orbital synchronous paths, whose stability margins are determined by cues furnished by external and internal inputs to the brain. The nervous system images a patterned memory for guide algorithms upon which to act. In this report, the modelling of these dynamic regulator chains is pursued.

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I. INTRODUCTION

This is the sixth report in two series (1), (2). In these reports one may note the development of the following ideas. Homeostatic control in the biological system originates from dynamic regulation (of which so-called on-off control is a common example) in which the stability of non-linear circuits of near-relaxation oscillatory type is mediated near the boundary between aperiodic and periodic instability. The biological system thus shows, most characteristically, sustained or intermittent operation of a great variety of oscillators. It is perhaps best to regard the system as an intrinsically non-linearly unstable system, which is monitored by chemical and electrical mechanisms, into marginal stability. The dynamics of the system has been pursued in some detail for explanation of the temperature regulation system at the level of the microcirculation control and hypothalamus control; in the cardiovascular system first for explanation of the passive transmission characteristics of the arterial tree, and second for a sketchy overview of control in the cardiovascular system; in the hormonal system for segregation into a temporal spectrum of effects; and in the behavioral system for consistency of some orienting physical views of the dynamics of a complex computer control network with psychological and physiological views.

Our current position is that these studies have exhausted their original scientific-philosophic impetus, data in the literature, preliminary experimental work and a continuing more detailed theoretical study. They have created a theoretical characterization of the biological system. It is now timely to consider a correlating primary but relevant experimental program. In this report, content and reasons for the particular experimental program will be reviewed.

In particular, it is postulated that this will be directed toward the thermal, mechanical and chemical flow of information. For this, the great communications network is the blood carrier. The electrical system has been intentionally omitted.

Our position is that although the field of bio-electric phenomena is currently under intensive exploration, no coherent, summarizing view has yet emerged. If much of the electrical system is a signalling complex, it is desirable to decode the operations from its slower more fundamental characteristics. Thus our contribution is directed toward a chemical process or biological systems engineering view, with attention concentrated on the hydraulic system, particularly the blood carrier.

Our current efforts are directed toward an attempt to complete the internal power balance, dynamics of the metabolic cycle, associated dynamics of hormonal cycles, major ancillary constituents of the metabolic cycle and the dynamics associated with the systemic circulations. This will, we believe, provide a view of what the blood carrier system sees as a communication network, in essence, a spectrum of the circulating information content of the vascular system.

Modelling of the organ systems and constituent parameters will come later.

II. THE TEMPERATURE REGULATING SYSTEM

A. DISCUSSION

<u>Summary</u>

A basic round of new information that is needed are the answers to the following questions:

1. Can we show the regulation of temperature at the hypothalamus in dividing the systemic circulations?

   a. What is the anatomy of the venous return circulation from the systems?

   b. What is the structure and function associated with the mixing systemic streams and their heat transfer in providing temperature signal, or in providing electrical signal to the hypothalamus to determine its response?

2. Can we clarify the regulating relation of division of flow between the deep and the peripheral circulations?

   a. What is the regulation or control logic in the peripheral circulation?

3. What are the salient endocrine linkages in the temperature regulating system?

4. Can we show the dynamics of the fundamental oxygen utilization in active tissue such as muscles?

5. Can we clarify the relation between the follower type of gas exchange of oxygen and carbon dioxide at the interface between the system and ambient, and the oxygen consumption and carbon dioxide production inside?

6. Is there a primitive level at which acclimatization type of adjustments take place?

7. What can we infer regarding the function of the nervous system, in an experimentally defensible sense, from the degree to which we can sketch out the temperature regulating system?

The answers to these questions would not exhaust the temperature regulating system, but they would provide a foundational but primitive sketch of pertinent block diagrams for the system.

Discussion

1. Can we show the regulation of temperature at the hypothalamus in dividing the systemic circulations?

A 1960 textbook summary, Ruch and Fulton (3) states, essentially

1. A thermoregulating function from the hypothalamus is clearly indicated in both warmth and cold (p. 237-239);

2. this is demonstrated by lesions, by electrical stimulation, and by thermal stimulation;

3. lesions do not abolish hypothalamic response but apparently affect any frequency response faster than hours; control temperature drifts off with a time constant in the hours domain, and is only restored in the domain of days to weeks (p. 238-240);

4. thermal stimulation indicates that rather large changes are necessary locally to elicit crude responses (p. 240);

5. heat production is characteristically affected by muscular exercise, but much more uncertainly by mechanisms that do not involve the contraction of skeletal muscles (p. 995);

6. all reactions identified with maintaining thermal equilibrium are under the control of the central nervous system, through both somatic and visceral motor nerves, and possibly via the anterior pituitary and some other endocrines (p. 999);

7. integration of temperature equilibrium reactions takes place at the hypothalamus which can change the rate of heat production and dissipation by its effect on motor neurons of the brain stem and spinal cord (p. 999-1000);

8. through these motor neurons, the hypothalamus normally modulates the rate of heat formation and dissipation in such a way that central body temperature of a normal resting individual is almost constant (p. 1000);

9. hypothalamic heating (Fusco, 1959) "demonstrates the sensitivity of the hypothalamic mechanism to local heating and show that the nature of ... dog's responses depend upon environment temperature. For example, at 29°C the local heating leads to an increase in tissue conductance and evaporative heat loss that were not seen at 14°C." (p. 1002);

A more complete review in 1961, Hardy (4) states essentially

1. it is a natural feeling on the part of those studying temperature regulation that there is a location in the body in which temperature is relatively regulated even during exposure to severe thermal loads (p. 559);

2. however surface temperature changes leads to the concept of dividing the body into a thermal region of core and shell with steep thermal gradient in the shell with an average 2-3 cm depth in humans (p. 559); one may not overlook steep local gradients between artery and vein;

3. exercise results in a mild increase in internal temperature (however, "data on hypothalamic temperature during exercise do not exist") (p. 561);

4. whereas early efforts (Ott and Richet, 1884) attempted to identify heat centers in the brain, this concept was not universally accepted. However the work on lesions generally led to the conclusion finally proposed by Bazett (1933) that centers of temperature regulation were to be found in the region of the hypothalamus;

5. the work of Thauer and Keller demonstrated that with destroyed structure in the hypothalamus, temperature regulation recovers within a few weeks, indicating somewhat diffuse temperature regulation structures other than the localized hypothalamus are available (p. 564);

6. the long time response of the hypothalamus to extensive lesions (p. 565), short time response of large electrical stimulation (p. 567-569), or short time response to large thermal signals (p. 569-572) does not show extensive, but does show unsymmetrical, deep body temperature response to what are essentially large non-physiological disturbances. Barbour's (1912) results were considered classic in demonstrating thermostatic action. Hot (50°C) water or cold (10°C) water circulated in the skull showed body temperature falling upon heating, and rising upon cooling (p. 569);

7. some observations that are not explained are means for artificially driving the hypothalamus to make an animal pant and shiver simultaneously (p. 571); dependence of vasomotor and shivering reaction on ambient temperature; and the inability to obtain the same effects in the same animal at different times under apparently identical conditions (p. 572). As an example, heating or cooling the hypothalamus might not give an expected response;

8. explanation of the temperature regulator extend from heat centers, to dual heat centers in the hypothalamus, to regulation by shifting body water, to regulation of metabolism. The author believes that it is body temperature which is regulated, involving participation of dual receptors in the hypothalamus, skin, respiratory tract, and other tissues. A 'setpoint' for hypothalamic action is established by the difference in firing rate of hypothalamic cold and warm receptors (p. 582).

It is quite obvious to us that these observations do not establish a chain for the regulation of deep body temperature. Consider the following structure of empirically derived observations that can be made.

1. The effect of disturbance at the hypothalamus, by any means and in any quantity, clearly demolishes deep body temperature control in the vicinity of the hypothalamus as far as short term (i.e., hours or less), or close temperature regulation is concerned. The drifting of temperature with lesions shows changes for hours before it begins to stabilize, and weeks before it begins to return toward normal temperature.

2. Therefore, the hypothalamus, if involved in temperature regulation, is really involved in the shorter-than-hours regulation. (Its presence shows shorter-than-hours regulation; its absence or interference shows hours or longer response).

3. Perhaps it is fortuitous, but the data with hypothalamic lesions that have been inspected show transient changes with a time constant in the hours domain. This agrees in order of magnitude with the body thermal time constant. Does this not represent a mixing-plus-conductive equalization toward control by some other mechanism or mechanisms? Possibly the hypothalamic pathways, or others, regain the function so that thermal control recurs.

4. What is the nature of thermal, metabolic, and ventilatory response of the mammal in the less-than-hours domain? Here we differ with most biological investigators. We say that there is a rich harmonic spectrum of effects in the minutes to hours range and count almost a two to one metabolic change at the level of one-two minutes; a 30-50% change at the seven minutes level; and a 20-30% change at the 20-40 minutes level. Goodman has verified our results in ventilation. The classic studies in thermal, metabolic, and ventilatory response have not shown or discussed these dynamics.

5. This experimental discrepancy creates a very serious difference of opinion regarding the ability to account for the hypothalamic role in thermoregulation.

For example it is quite clear (see chapter by Brobeck in (3), or (4)), that Fusco's 1959 thesis is considered quite salient in interpretations of modern experimental hypothalamic heating. Examine the data (p. 1004 (3)). Responses of a dog are shown over a 5 hour period to hypothalamic heating at a variety of ambient temperatures - measurements are shown approximately every half hour.

The first basic results are that rectal temperature is not affected, and mean skin temperature is not affected, and that both are fairly constant in time. If true, then the first result one might derive is that heat production is constant, and tissue conductance is constant; for

$$M = C\,(T_r - T_s) = K\,(T_s - T_o)$$

M = metabolism
C = tissue conductance
K = air boundary layer conductance
T_r = deep body (rectal) temperature
T_s = mean skin temperature
T_o = ambient temperature

If K and T_o are physically constant, and T_s is found constant then M is constant; if T_r is constant then C is constant. Thus one would infer that hypothalamic heating affected neither metabolism, temperature or tissue conductance.

If on the other hand, it is said that these inferences are drawn without attention to the experimental sensitivity, then it must be pointed out that the experiment does not show any real sensitivity. Moderate 'transients' are shown in which heat production twines around heat loss. Cyclicalities, if any, are of the order of 50 minutes (that is, all of these data shows a grand total of perhaps 24 'cycles' for 5 hours x 6 records); in power amplitude they are of the order of $\pm$ 30%. The lack of data in a null experiment, compared with heating data, both taken at high repetition rate for test periods of the order of 5 hours make it impossible to distinguish 'normal' metabolic response from hypothalamic heated response. One is still left with the very casual result that in the main there do not seem to be any significant changes in mean metabolism. The main resultant seems to be possibly 'transients', but even these are not certain if our presumption of a considerable high frequency spectrum of effects is true. Thus the only observation that remains is considerable variability in tissue conductance. However the same argument exists here.

In conclusion after studying this experiment, as well as others, it is clear that the investigators have simply not measured a sufficiently high frequency domain of effects covering the minutes to hours range, against a background of various desired steady states - such as hypothalamus heating, or none, etc., - to have noted anything but very individualistic passing transients.

6. The most preponderant effect likely reported from heating or cooling the hypothalamus is not an effect on the mean skin temperature, mean metabolism, or heat loss, but an effect of changing the tissue conductance (vasomotor activity), and possibly secondarily a change of deep body temperature.

7. Mean metabolism is tied to activity level.

8. Thus skin temperature is normally more tied to metabolism and ambient temperature through whatever is the body boundary characteristic (free or forced convective, or clothing conductive insulation, etc.).

9. Benzinger has shown quasi-static but non-equilibrium metabolism (i.e., 7 minutes metabolism) tied to hypothalamus temperature for constant surface temperatures. His method of driving (baths) makes skin temperature

independent of metabolism. Thus the question arises of interpreting the connection of metabolism and hypothalamus temperature. Benzinger assumes T_H is causal for M. We now propose the opposite. M is causal for T_H.

There is essentially no doubt that mean metabolism depends almost solely on activity level. Now Benzinger also shows, as well as we did, that the instantaneous metabolism is not equal to the mean metabolism. Thus it must cycle and twine around the mean.

There can be little doubt in our minds that cycling in the domain 1-60 minutes must take place. (In addition to our observations one can refer to the data of Lewis which shows a variety of thermal effects in this domain). Thus at most there can only be uncertainty as to the cyclic amplitude of the metabolic variation. Lumping all data known, including our own, it is not surprising to find a running factor of 2 to 1 or so to be characteristic of 'instantaneous' metabolic change, and likely fairly independent of temperature or mean activity level. Thus the amplitude tends to be escapement governed by the detailed metabolic process.

The detailed metabolic process is taking place near capillaries which supply the oxygen, <u>with intrinsically only very short time oxygen storage</u>. It is their composite physiological reaction which must determine the metabolic excursion amplitude. Activity must determine their mean state settings. The hypothalamus temperature most likely must be governed by the head blood supply. Thus it must be a response element in this time domain. Whether the precise time domain is the value we have suggested is moot, although it may be suspected as being correct from Benzinger's data.

10. What does there remain for hypothalamus temperature to govern? The answer again focuses on the tissue conductance, the vasomotor activity.

Thus we come close to most sympathy for Barbour's 1912 view that body temperature is regulated by shifting body water.

11. We are thus driven to an inquiry into whether the hypothalamus temperature drives the tissue conductance, and to make this more meaningful, whether the hypothalamus temperature determines the tissue conductance, taking into account the ambient temperature, by operating to control the relative division between peripheral and deep systems circulations?

$$M = K (T_s - T_o)$$

Note, this makes T_s determinate since M, K, and T_o are fixed.

$$M = C (T_r - T_s)$$

If T_r is to remain constant, C must adjust

$$C = \frac{M}{T_r - \frac{M}{K} - T_o}$$

How this may be accomplished is far from clear, and we know of no data to base a model on. The most rudimentary answer is to say that the hypothalamus acts as a thermostatic dynamic regulator, and simply modulates the peripheral circulation on and off in what becomes about a near 7 minute duty cycle. However, the peripheral circulation is made up of parts of the systemic circulations. Thus the subdivision has to be made within these systems rather than centrally. Thus, somehow it is a more coordinated view of the system which is regulated dynamically. This requires greater exploration.

On an even more primitive level we are unable to reconcile what should appear to be some rudimentary physical balances with regard to the human body. We wonder whether anyone could offer some contradictory or confirming data, or some explanations for the apparent discrepancies.

The issue is the application of two laws of heat transfer to the body. We will assume these are for the human in ultimate physical equilibrium (that is, a description of data taken after a few hours and subsequently observed and averaged over the period of a number of hours), and to simplify matters for a nude human at rest in a low humidity, low wind environment. Then, more precisely than stated before

$$\frac{M}{A} = \frac{E}{A} + K\ (T_s - T_o) + \frac{fM}{A} + \frac{W}{A}$$

$$\frac{M}{A} = C\ (T_r - T_s)$$

M = metabolism (as measured by average oxygen consumption)
A = effective surface area of the body
f = fraction of the metabolism that is lost through the breath
E = evaporative heat loss, from the skin
W = external work done (average)
T_s = average skin temperature
T_o = ambient temperature (standard operative)
K = composite correction and radiation heat transfer coefficient
T_r = deep body temperature
C = tissue conductance, skin to deep body (its justification would be such depth measurements as Bazett and McGlone that establish gross linear temperature gradients for depths of ½ to 1 inch in regions like the thigh and forearm).

Consider for simplicity the case in which the work W = 0. Since there is an active physiological control in which the body changes how much 'effective wetted' area that is available for evaporation, we may further exclude this regulating region, which appears to occur at ambient temperatures above 30°C at normal low humidities. On the other hand, there have been data taken at physical equilibrium into the range 0-5°C. Thus the pertinent data in the range 5-30°C appears to be the following:

TABLE I. HUMAN DATA - NUDE QUIESCENT SUBJECT IN LOW WIND, LOW HUMIDITY ENVIRONMENT

Ambient temp. T_o-°C	Ave. skin temp. T_s - °C	Deep body temp. T_r - °C	Metabolism per area $\frac{M}{A}$ - $\frac{Kcal}{m^2\ hr}$	Evaporative Loss: Total loss $(E + fM)/A$	Evaporative Loss: From mouth fM/A	Evaporative Loss: From skin E/A	Heat transf. from skin $[M(1-f)-E]/A$	Temp. diff. T_s-T_o	Boundary layer cond. K-Kcal/m^2hr.°C
5	23	36-37	67	11	7	4	56	18	3.1
10	25	36-37	65	11	7	4	54	15	3.6
15	27.5	36-37	61	12	7	5	49	12.5	3.9
20	30	36-37	57	14	7	7	43	10	4.3
25	32	36-37	55	16	6	10	39	7	5.6
30	34	36-37	55	25	6	19	30	4	7.5
Errors	$\pm$ 1°	$\pm$ ½°	$\pm$ 10%	$\pm$ 20%					

Temp. Diff. T_r-T_s (T_r = 36.5)	Tissue Cond. C
13.5	5.0
11.5	5.6
9	6.8
6	9.5
4.5	12
2.5	22

The discrepancies are contained in the inconstancy of the boundary layer conductance. There are many semi-theoretical estimates of this conductance. Typical experimental and theoretical values quoted are

a) 1 Kcal/m^2 hr. °C.
b) 2
c) 4-6

For low wind velocity

d) $$7.0 \left[.48 + .52 \sqrt{\frac{V \frac{cm}{sec}}{7.6}} \right] = 3.5$$

e) $$5 + 2 \times \frac{V \frac{cm}{sec}}{7.6} = 5$$

f) $$7 + 0.5 \times \frac{V \frac{cm}{sec}}{7.6} = 7$$

g) $$5.4 + 1.9 (T_s - T_o)^{1/3} + .3 \times \frac{V \frac{cm}{sec}}{7.6} = 9$$

The unsatisfactory state is that values ranging from 3 - 7 are quoted, which appear to fit the tabulated estimate, but unfortunately are variable. If anything, as the last expression indicates, the operating Prandtl-Grashof product range would suggest an <u>increasing</u> transfer coefficient with increasing temperature difference of skin to ambient. Yet what appears to be found is a <u>decreasing</u> transfer coefficient. The temperature difference of 18°C., at 5°C. ambient as compared to 4°C. at 30°C. ambient should represent a considerable change in heat transfer coefficient. Yet the conductance of the larger temperature difference is less than half that at the lower difference.

On the other hand, the tissue conductance range proposed in (5) is about 9-10 Kcal/m^2 hr. °C. for maximum constricted tissue, to about 78 at the limit of high activity at high temperature. As discussed in NASA CR-141 (1), there is a discrepancy between these data, Benzinger's data, and the tabulated data. Thus it is even the conductance range which is in doubt. (Essentially, it is the temperature distribution in the tissue which is dubious).

Thus there is some approximate factor-of-two determinacy of the overall heat balance from the body, and some approximate factor-of-two or three determinacy of the vasomotor conductance model of the outer tissue-humoral heat exchange system. It is therefore timely to change the point of view.

B. RUDIMENTS FOR AN INTERNAL BALANCE

Since it is clear that the overall balance is physically validated, but only in a crude way, one may begin to suspect that the problem is the spread out distributed nature of the system - the chemical factory that makes up the human. We can attempt to tighten the focus of comprehension by considering the possibility of an internal balance. We may start from the premise that the main distributing system for the components (in the short physical balance time of hours, not in physiological balance time of days and longer) is the blood system.

Thus if we could compartmentalize the chemical factory, then we might be able to tighten up our mass and energy balances to a point where most of the redundancy and vagueness is leached out. In this report, we will illustrate the beginnings of a zonal balance, and subsequently consider how the sum-over-the system is arrived at and coordinated.

For this purpose, we can consider the system segments served by the blood exchanges -

- base of neck to head
- left and right arms
- the thoracic cage (region is the base of neck to diaphragm and to the scapular arches; it includes heart as a source, lungs and intercostals as loads)
- the abdominal cavity (liver, kidneys, stomach, intestines, rectum, adrenals)
- left and right lower limbs.

It is clear that to establish the balances for head, arms, lower limbs are relatively easy, the abdominal cavity considerably more difficult, and the thoracic cage extremely difficult. Thus one of the easy systems, the remote hind limb of an animal, was considered a first experimental choice. Its advantage is its geometric isolation, yet it presents the full problem of regulation and control of a major motor system. Its fluxes in and out must carry a fair amount of the communications and power regulation and control used by the chemical factory that makes up the complex (mammalian) biological system.

Accordingly, we proposed a first examination of the metabolic heat and mass balance. This involves the problems of temperature distribution, heat production, fuel sugar consumption, O_2 consumption, and CO_2 production. All this is a precursor to showing hormonal chain and then nervous system involvement. Our first problem is to determine the mean balances and dynamics of the components involved in the metabolic cycle.

Our proposal is to study the dynamics for a normally operative animal, but for a first start it was simplest to use available instrumentation that best suited a quiescent animal.

C. TEMPERATURE CHARACTERISTICS IN A MOTOR SYSTEM (HIND LEG).

Descriptive

The aorta ends by bifurcating into a left and right common iliac artery which provide the circulation to each of the hind limbs. The common iliac bifurcates into an internal and external iliac artery. The internal iliac (or hypogastric artery) supplies the upper posterior portion of thigh and buttock (nominally 5% or so of the total iliac circulation). The external iliac continues as the femoral artery, which supplies the remainder of the hind limb plus the abdominal wall and superficial genitalia (the latter two both comprise only about 5% of the femoral flow). Thus, through the inguinal ring, it is already the femoral artery which is passing to the limb, with these two small (5%) losses having taken place above and below the ring.

Within a short distance (one cm. in guinea pig, one inch in human) from the ring (or the base of the inverted femoral triangle) the first and major superficial branch occurs, the saphenous, which then supplies (takes approximately half of the femoral flow) the skin and subcutaneous areas of the hind limb down to and around the surface of the foot (dorsum). Continuing along the femoral, the next major branch (about 1 cm above the apex of the inverted femoral triangle, or 2 cm. below the saphenous, in guinea pig) is the profunda femoris artery, which supplies the muscles of the thigh and knee capsule (approximately 15% of femoral flow). The continuing femoral (carrying perhaps 35% of the femoral flow) becomes the popliteal at the level of the knee, then branches into the tibial arteries, which in turn branch into the plantar vessels.

Of present concern is the fact that the superficial supply for the entire limb is primarily furnished by the saphenous, as a distinct branch of the femoral artery, and that the deep tissues and musculature of the thigh are supplied by the profunda femoris, as a second distinct branch. Thus in the main, one can isolate the fluid exchanges for the heat and power supply to this extended motor system.

As a first round, it was proposed to consider the heat balance in the leg as indicated by temperature. The choice was made to measure femoral artery and vein temperature as an overall indicator of the heat balance; the saphenous artery and vein temperature as an indicator of the peripheral exchange; and the profunda artery and vein temperature as an indicator of the musculature exchange. Means were not available for flow measurement or for enough channels to make more extensive temperature surveys. The data thus are only a beginning of balance problems.

Method

Guinea pigs of either sex were anesthetized with 33 mg/kg, sodium pentobarbital, (Nembutal) intraperitoneally and prepared for thermocouple implantation by exposure of the femoral triangle from the dorsal aspect. The femoral vessels were denuded for a length of approximately 6 mm in preparation for attachment. The long saphenous vein was cleared at a point after it pierced the cribriform fascia and femoral sheath and prior to its ending in the femoral vein at the upper quadrant. The profunda femoris vessels were cleared behind the adductor longus muscle directly at the apex of the femoral triangle. Its position made this step difficult to manipulate and practice was required to develop a technique.

Copper constantan thermocouples were used. Initially 0.002 inch wire was utilized, but these proved to be too fragile and difficult to manipulate. A 0.005 inch thermocouple was then substituted which consisted of side by side wires with an approximate two diameter bead at the tip. They were coated with several consecutive layers of medical grade silicone rubber and tested for resistance. The overall thickness increase due to insulation was in the nominal micron range. The average insulation was checked in air and salt solution and only those couples whose resistance was greater than 250,000 ohms were used.

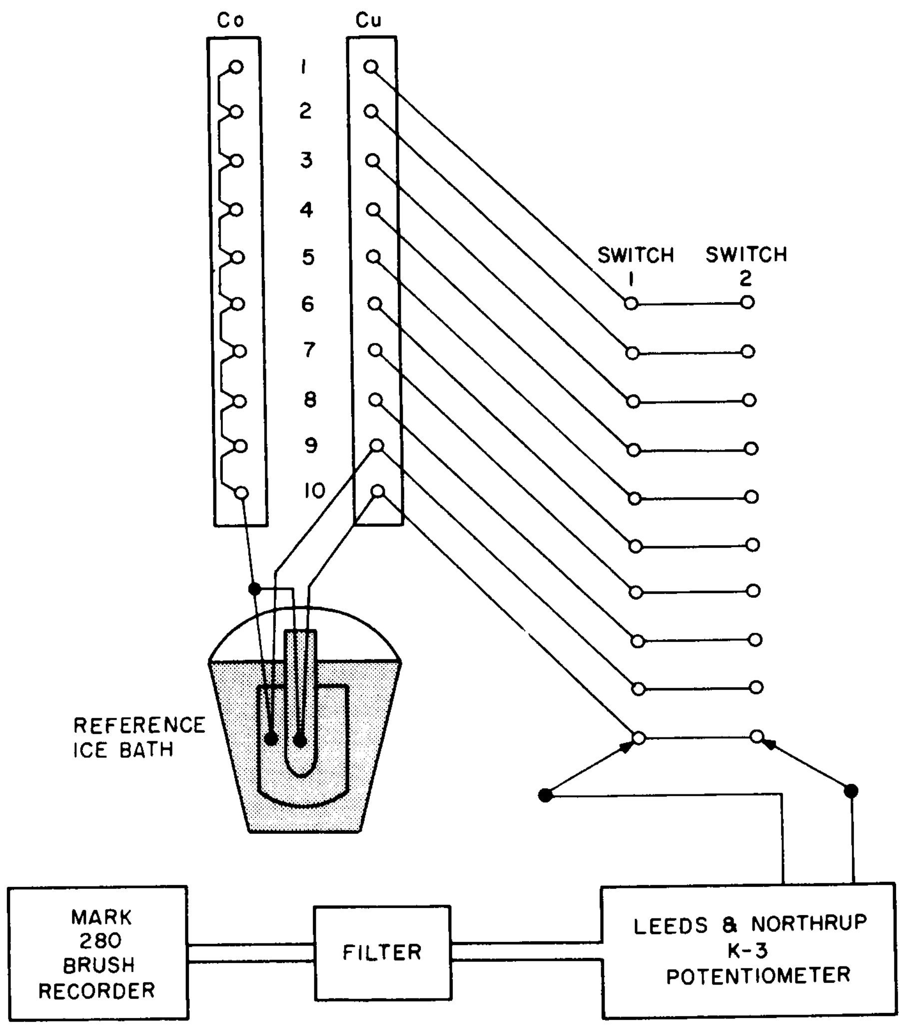
The initial technique was to place the thermocouple on the blood vessel, with the leads wrapped around the vessel twice. This was held in place by medical grade silicone gauze with sutured ends wrapped around the vessel and assembly. This constrained the bead and windings but permitted some degree of motion and erosive action along the axis of the blood vessel. The current technique which has been found to work best, is to wind sterile, surgical adhesive tape (3M Co.), around the bead and the vessel. Approximately 2 mm by 5 mm pieces of tape are required to maintain the assembly in place.

These preparations, with careful handling and coapting of the wound edges at the point of exit of the undulating leads from the body have remained viable and useful for temperature measurements for up to six weeks. The animals have remained alive and apparently well. When failure occurred, it was primarily electrical, probably due to breakdown of the insulation.

After placement of the thermocouples the leads were coiled flat and led subcutaneously to the animals back. This permitted easy movement in one direction and minimized the dangers of vessel kinking or rupture and tissue friction along its entire path, when the animals moved about. The leads were externalized through a teflon button consisting of a threaded bolt with numbered pores passing through centrally. This button is locked in place subcutaneously by means of a flange and lock nut. The leads traverse the assembly and are held in place in the well of the teflon bolt with silicone potting compound. The entire assembly may be capped to permanently protect the externalized leads.

Experimental data was recorded 2-3 days after the implantation procedure using unanesthetized, unrestrained and grossly normal appearing guinea pigs. The animals were either kept in a large flat cardboard carton or allowed to remain on the laboratory table top with food and water ad lib. The circuitry is shown in Figure 1.

Both visual readout and recordings were obtained using a Leeds & Northrup K-3 potentiometer and a Brush Mark 280 recorder. The time constants of the thermocouples was less than ½ second.



Thermocouple leads implanted in animal are connected to Cu terminals in numbered sequence. The Co is a common lead.

Figure 1. Electrical Circuitry for Temperature Measurements

TABLE II. GUINEA PIG FEMORAL SYSTEM, TEMPERATURES, °F

	Average	Cyclic Range
Femoral Artery	102.7 $\pm$ 1.4 °F	0.6 $\pm$ 0.2°F
Femoral Vein	102.8 $\pm$ 1.2 °F	0.4 $\pm$ 0.1°F
Profunda Femoris Artery	102.7 $\pm$ 1.3 °F	0.4 $\pm$ 0.1°F
Profunda Femoris Vein	102.85 $\pm$ 1.8 °F	0.7 $\pm$ 0.1°F
Saphenous Vein	100.0 $\pm$ 0.4 °F	1.4 $\pm$ 0.7°F
*Femoral (A-V)	0.7 $\pm$ 0.4 °F	0.5 $\pm$ 0.2°F

NOTE: No. of animals - 6.

Data from normal animals with some mobility, food and water ad lib.

*These data taken directly as differences from two animals.

Results

Results are illustrated in Figure 2 and summarized in Table II. Comonly in the experiments the mixed femoral venous blood showed a slightly higher temperature than the arterial blood. The arteriovenous difference mean range was 0.1 to 0.7, averaging about $0.4 \pm 0.4^{o}F$.

The subcutaneous and cutaneous mixed venous blood as measured in the saphenous vein was lower than the femoral vein temperature in all experiments. When compared with the deep musculature mixed venous return as measured in the profunda femoris vein, the latter was generally higher by approximately $3^{o}F$.

Correlation of the main hind limb system mixed venous return in the femoral vein with the profunda mixed blood temperature showed that the deep muscle venous return of the latter functions as a heat contributor to the main system flow. The femoral-profunda arterial differential was approximately $0.1^{o}F$, or less, indicating little or no heat loss during the blood traverse time from the base of the femoral triangle to the apex just beyond the point of origin of the profunda vessel.

Frequency analysis indicated the cycle and amplitudes shown in Table III.

TABLE III. GUINEA PIG, TEMPERATURE ANALYSIS

Cycles (sec.)	Cycle Amplitude (^{o}F)
Approx. 3-5	Approx. 0.2
Approx. 30	Approx. 0.25
Approx. 60	Approx. 0.3
Approx. 100-200	Approx. 0.35
Approx. 325-400	Approx. 0.35

Discussion

The data indicates that, in general, the hind limb motor system does not serve as a heat contributor to the overall system.

The cutaneous flow primarily functions as a heat dissipator, since the cutaneous venous return was invariably lower in temperature than the hind limb main mixed venous return as well as the deep musculature mixed venous return.

In all experiments the deep muscle mixed venous return was significantly higher in temperature than either the cutaneous mixed venous return and only

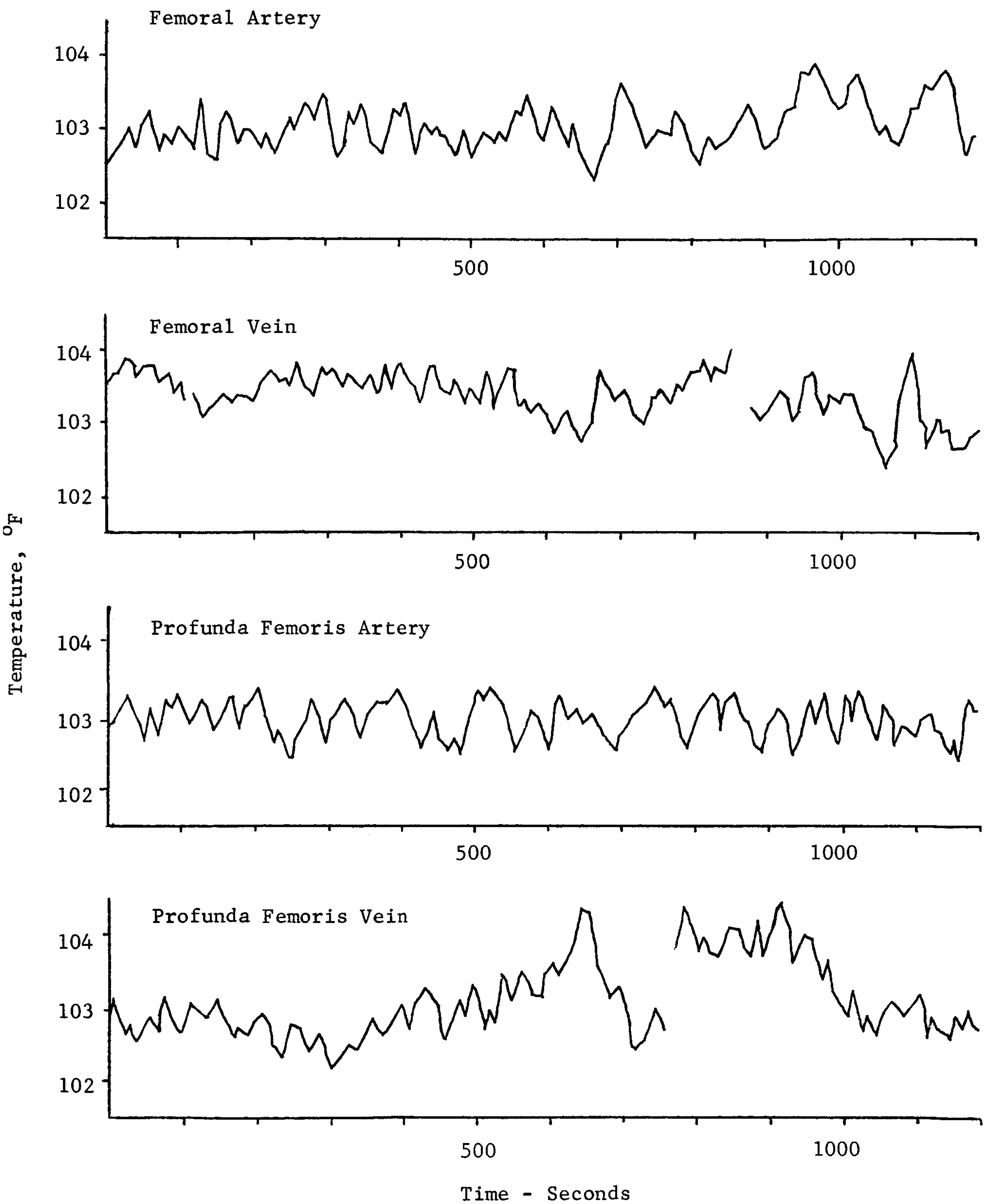


Figure 2. Temperature Fluctuations in Hind Limb Vessels of Guinea Pig (Composite of Several Experiments in Different Animals - Each Record is from an Individual Experiment)

slightly higher than the main hind limb mixed venous return, thus indicating that the muscles likely function as a heat supplier locally.

Correlation between the main arterial supply close to its entrance point into the hind limb and the first major muscle supply branch indicated essentially no loss in temperature during traverse time across the femoral triangle.

The temperature records showed cycle frequencies at 3-5, 30, 60, 100-200 and 325-400 seconds with cycle amplitudes of a few tenths of a degree F, respectively.

Heat Balance

The heat balance has been attempted for the hind limb using the temperature difference found here between the femoral artery and vein, mean sugar level differences, mean oxygen and CO_2 level difference, described in subsequent sections of this report, and estimates of loss of heat through the skin. The experiments are obviously crude beginnings in all categories but they may serve to indicate the problems inherent in heat balance attempts in animals. The most important factor is that small differences in large values must always be used. The measurements are subject to the usual difficulties of measurements in biological systems; a major problem is the effect on the animal of the procedure itself.

There is further possibility that local anaerobic metabolism takes place in one part of the body and products are carried to another part where the heat production is completed with total oxidation. Then local heat production in the first part may be more than that calculated from oxygen consumption or CO_2 produced. This possibility cannot be accepted without considerable further experimental verification.

The temperature of the femoral artery in the quiescent animal varied from a mean value of 101.0° to 104.4°F in six animals. In one animal, the temperature was 97.0°F consistently during an experimental period of several hours. This animal was not included because the low temperature was considered possible indication of some physiological disturbance. In any one animal, the cyclic maximum to minimum variation was 0.5° to 0.65°F. One animal was exercised on a treadmill. The temperature varied from a minimum of 104.4°F to a maximum of 107°F.

The temperature in the femoral vein varied from 100.3° to 105.0° F for quiescent animals and in the exercising animal was 104.5° to 107.7°F.

The means of arterial-venous differences were 0.1 to 0.7°F in quiescent animals and over 1.0°F in the exercizing animal.

An estimate can be made of the heat balance for the hind leg. The mean femoral arterial venous temperature difference for six guinea pigs was found to be $0.4 \pm 0.4^{o}F$. A rough estimate of the cardiac output in the guinea pig is 2/150 x 4200 (flow in human) = 60 cc/min and that in the femoral about 1/20 of the total or 3 cc/min. Then the heat flow difference between the artery and vein would be $(0.2^{o}C)$ (3 gm/min) (1 cal/gm^{o}C) = 0.6 ± 0.6 cal/min. (The apparent arterial velocity suggested that 3 cc/min was reasonable.)

The heat loss from the hind limb can be estimated by taking the total loss from the entire animal and multiplying by the fraction of the total surface area represented by the hind limb. Herrington (in 6) gives a formula of $9.0 \times W^{2/3}$ for the surface area of guinea pigs and rats. Thus, for a 1000 gm animal the surface area would be 900 cm^2. Using for the dimensions of the hind limb a conical section of 4 cm and 1 cm diameters of the bases by 3 cm long for the thigh, a cylinder 1 cm in diameter and 3 cm long for the leg, and a 1 cm long cylinder 1 cm in diameter for the paw, the estimate of the area is about 33 cm^2. Thus, the surface area of the thigh is 33/900 ths of the total surface area, and the heat loss from the hind limb would then be the total body heat loss multiplied by this fraction of the total surface area. The total body heat loss is equal to the total metabolism which can be estimated from the total oxygen consumption which is given by Altman (7) as 820 mm^3 per gm per hour. This converts to 13 cc/min for a 1000 gm animal. The calories produced per cc of O_2 can be estimated from the human. Assuming an average total caloric intake of approximately 2400 kcal per day or about 2 kcal/min, and a total oxygen consumption of about 300 cc/min, the calories produced by one cc of O_2 is thus about 7 cal. The total metabolism for the guinea pig would then be 7 x 13 = 91 cal/min. Peterson (8) gives the oxygen consumption for the guinea pig of 52.0 cc per 100 gm per hour, or 9 cc/min. The total metabolism would then be 63 cal/min. For our crude purposes, the two values may be averaged, thus the guinea pig total metabolism will be considered 77 cal/min.

The heat loss from the hind limb would then be 77 x 33/900 or approximately 2.8 cal/min.

Then the heat produced is equal to the heat lost through the skin plus heat returned to the body through the blood or $2.8 + 0.6 = 3.4 \pm 0.6$ cal/min.

The saphenous vein mean temperature is $100.0^{o}F$. Assuming all this flow is returned from the hind limb periphery, one might expect a lower temperature than the return from the deep tissue and a lower temperature than the return from the total femoral vein return. This was the case. Thus, the measurements apparently are accurate enough, despite the fact that there is surely some degree of mixed return from skin and deep tissue even in the saphenous.

The heat production in the hind limb may be estimated by several additional methods. One method would be to take the total metabolism and multiply by the fraction of the total volume of the animal contained in the hind limb. For the animal described above, the volume is approximately 16 cc or 16/900 ths of the total volume or 1.8%. Then, the heat production in the hind limb is 77 x .018 or 1.4 cal/min.

One can further estimate hind limb metabolism from the blood flow of approximately 3 cc per min or 1/20 of the total flow. Then 1/20 x 77 = 3.9 cal/min.

Another estimate of hind limb metabolism can be made from the oxygen concentrations in the femoral artery and vein. The A-V difference has been found to be approximately 70 mm of Hg (115-45). This corresponds to a change of about 4 volumes percent. Thus for a flow of 3 cc per min, one would have .04 x 3 cc/min or .12 cc/min of oxygen. At 7 cal per cc O_2, one gets 0.8 cal/min.

Sugar utilization in the hind limb has been determined as another estimate of heat production. The A-V difference in the femoral system was 2-8 mg% or an average of 5 mg% (in total values of approximately 70-110 mg%). At 3 cc/min this is equal to 0.15 mg per min. At 4 cal/mg, the heat production is 0.60 cal/min. Subsequent studies in other guinea pigs with an extended sampling schedule gave repeated means of 7 mg percent. Using that figure the heat production would be 0.8 cal/min. The estimates involve small differences in the means of large values with oscillations larger than the differences. However, they may serve to indicate the nature of the heat balance and to point up the need for more sophisticated data.

Roughly, the sugar utilization checks the oxygen utilization.

Similarly, the carbon dioxide production was used to estimate heat production. The A-V difference was found to be an average of 9 volumes percent or 0.27 cc per min. The heat produced per cc of CO_2 is approximately 7 calories. Thus, the heat produced would be estimated at 1.9 cal/min.

In summation we have the following heat production estimates:

1. Heat loss through skin + heat transport in blood
   $= 2.8 + 0.6 \pm 0.6 = 3.4 \pm 0.6$ cal/min.

2. Total metabolism x percent of body volume
   = 77 x .018 = 1.4 cal/min

3. Total metabolism x percent of blood flow
   = 77 x 1/20 = 3.9 cal/min

4. A-V difference in oxygen concentration (oxygen utilized) x blood flow (estimated 3 cc/min)
   = 0.8 cal/min

5. A-V difference in sugar concentration (sugar utilized)
   = 0.6 cal/min to 0.8 cal/min

6. A-V difference in carbon dioxide (carbon dioxide produced)
   9 mg/100 cc x 3 cc/min x 7 cal/cc
   = 1.9 cal/min

One correction should be made in method 2, total metabolism times percent of total body volume. The value would be expected to be high considering that low volume organs like the brain, heart and liver utilize almost half the oxygen. Thus the total body metabolism exclusive of these organs would only be 40 to 50 calories and total metabolism x percent of body volume would be of the order of 50 x .018 or 0.9 cal/min.

Thus, heat production estimated from determined concentrations of oxygen and sugar is only a fraction of that estimated from the sum of heat loss through the skin and heat transport back into the body through the blood. The latter estimate may be high for the following reasons. The heat loss through the skin is not uniform over the surface of the animal but depends on the local skin temperature. Our earlier work has demonstrated that surface temperatures over the extremities are generally lower than those on the head and trunk. Thus, the loss over the extremities would be expected to be less than average for the entire animal. The blood flow may be less than the 3 cc/min estimated for the femoral system. This could result in lowering the overall heat production estimate by 1/3 to 1/2 or to 2 to 3 cal per min.

However, the sugar and oxygen utilization is still too low to account for this heat production. One could discount the sugar since investigators have claimed that the muscles use other fuels like fats or their derivatives. It is far more difficult to explain the low oxygen utilization though here too, reference is made to anaerobic metabolism. The accuracy of the figures for sugar and oxygen utilization is questionable, depending as it does on small differences in the means of large values and oscillating values, at that. However, to get to sugar and oxygen utilization values that would be in the range requires A-V differences 5 to 10 times larger than our data exhibits. Thus for total sugar values of 100 mg%, the A-V difference would have to be 25 to 50 mg%, and similarly, for the oxygen. It is not likely that these are the differences, i.e., that our values are that much in error. Thus, we still have the problems to determine heat losses accurately from an area, determine blood flow accurately, and determine mean oxygen and sugar blood levels more accurately. Some historical review is likely in order.

The higher CO_2 utilization is suggestive that other heat producing reactions may be taking place, though it is difficult to conceive of carbon dioxide production without oxygen. Still, at this stage one may speculate that the muscle heat production may be from reactions of partial oxidation leading to products which are transported to other high oxygen utilizing organs like the brain, heart, and liver where the oxidation is completed to carbon dioxide and water.

There is data in the literature on oxygen and sugar utilization in the femoral system of the human. For example, a review article by Quastel (9) cites Lennox, 1936, that oxygen saturation drops from 19.2 to 13.3 volume percent from the femoral artery to the vein. (Comparison is made to flow in the brain, face and arm, where the corresponding drops are 19.4 to 12.0; 20.3 to 13.0; and 20.5 to 17.8). The sugar utilization is given as 5 mg percent for the arm and 4 mg percent for the leg. This checks the value we obtained for the leg, 5 mg percent.

From the oxygen utilization in the human leg (5.9 cc O_2/100 cc blood), and using an estimate of 210 cc/min for flow in the femoral artery, one gets 12 cc per min and 87 cal/min. From the sugar utilization data of 4 mg percent one would get about 30-35 cal/min. Thus, it appears that metabolism in the leg uses other fuel in addition to carbohydrate. This was also discussed and pointed out further that the brain on the other hand does appear to use carbohydrate exclusively.

If we estimate the surface area of the human leg as approximately 1/9 of the total body area and use 240 cc/min for the total O_2 consumption, we have 1680 cal/min for total metabolism (thus total heat loss rate is 1680 cal/min,) then 1680/8 or 185 cal/min is an approximate figure for heat loss from the leg. Yet the heat produced, based on oxygen utilization, is only 87 cal/min. Thus for a heat balance, the blood would have to carry 100 cal/min into the leg.

We can obtain another estimate of the heat loss through the skin from a previous report in this series, Jan. 1965. Temperatures are given for several points on the leg at different ambient temperature. At 29.0°C ambient the mean body temperatures were 34.5 (33.5-35.2). Temperatures on the thigh, leg, heel, and toe averaged 34.1. Thus the heat loss from the leg would not be expected to be much different than from comparable areas of other parts of the body. In the table on page 9 of that report, data are shown for heat loss calculations. If one uses the data for 30° ambient, the average skin temperature is given as 34°, deep body temperature 36-37, and heat transfer from the skin plus evaporative loss is given as 49 kcal/m^2 hr. Then heat loss (exclusive of mouth evaporation) is 810 cal/m^2 min. Using an estimate for the leg area of 0.2 m^2, we get a heat loss of 162 cal/min, thus checking the estimate made above. However, if the boundary layer conductivity would be the lower values (given in the table, for lower ambient temperatures) then the heat loss from the skin would drop down closer to the heat production estimates from oxygen utilization. However, even so, the blood would be expected to carry heat into the leg rather than out of it.

Thus, we still have the problem that in our guinea pig temperature data, the venous temperature is essentially equal to arterial, little or no heat is being transported back into the core from the leg and there is insufficient heat production from oxygen utilization to account for total heat.

For the whole body, it now appears that most of the heat must be produced in the internal organs. This will be clear from consideration of the oxygen consumption for various organs as given by Rushmer (see ref. 2, CR-129). His values reduce to 52 cc/min for the brain (364 cal/min), 31 cc/min for the heart (217 cal/min), 58 cc/min for intestines (410 cal/min), 14 cc/min for the kidney (98 cal/min), and 60 cc/min for the skin, muscles, and other (420 cal/mm). Thus, of a total heat production of 1505 cal/min, corresponding to 215 cc/min O_2, less than 25% is produced in the arms, legs, skin, etc. Yet the extremities have a much larger proportion of the total surface area and would, accordingly, be responsible for a correspondingly larger proportion of the heat loss.

The model of the temperature regulation must also be modified now in recognition of the fact that the muscles are no longer the major heat source though they likely produce substantially more heat than the skin. This is also indicated in the Quastel article which cites data for oxygen levels in return blood from the skin much higher than return blood from the total leg, arm, or brain. Thus, oxygen consumption is likely also much less if blood flows are comparable. Our model of heat production in the muscle sheath is likely most valid for the extremities, but may play a much lesser role in the head and core where large heat producers are contained further inside the core.

A somewhat tangential question may be posed here - namely, what does the brain use all the power for? It certainly doesn't look like that much electrical or mechanical action is taking place. Perhaps those concerned with modelling the activity of the brain should consider this more.

We may return to consideration of the two minute cycle and its relation to overall heat production. It would appear now that this cycle is not restricted to heat production in muscles but to heat production generally throughout the body. This is evident from its prominence in ventilation rate at the mouth which sums all metabolism from the entire animal, and it is to be noted, most of the metabolism occurs elsewhere than in the muscles (in the quiescent state). However, our current model is that the two minute cycle is a blood flow or red cell flow in the microcirculation, thus an oxygen supply cycle,and it should therefore reflect all oxidative metabolism, whether mechanical in muscles, electrical in the nervous system, or chemical in the digestive system. Now, when the statement is made that metabolism is dependent on activity level, activity may be seen to mean not only muscular activity but electrical and chemical activity as well.

It has been shown that the temperatures of the internal organs respond somewhat more promptly to heating and cooling than the peripheral systems which are primarily dependent on vascular supply. Temperature measurements of blood in the aorta, portal and hepatic veins showed the lowest temperature to be in the aorta with the highest in the hepatic vein. This would indicate that the viscera are heat contributors. The nominal contributions from resting muscle in man was pointed out by Milhorat, who compared results between normal and muscular diseased individuals. In adults, muscle wasting caused slight reductions in heat production. (Source, Machle and Hatch (10).)

The metabolic pathways themselves require discussion. The cells of the body are able to oxidize various foodstuffs concurrently, and can convert one material to another. There is further complication by the fact that partial or complete aerobic or anaerobic metabolism may be possible. Some past history, while perhaps confusing, is indicative of the present physiological view.

Fick and Wislicenus (11) first observed that the total amount of energy liberated during work is more than that available from the oxidation of protein.

Von Liebig (12) showed an increase in urinary nitrogen after muscular work. He concluded that protein catabolism supplied the energy for skeletal contraction.

Benedict & Higgins (13) fed various amounts of sugar to fasting subjects. After the ingestion of 600 grams of glucose per day, the highest respiratory quotient observed was 0.87. Theoretically, the ingestion of glucose should have raised the quotient to 1.00 if glucose alone was oxidized.

On the basis of their extensive study of the metabolism during muscular work, Benedict and Cathcart (14) concluded that the more severe the muscular effort, the more carbohydrate is oxidized, but that exercise is not carried out exclusively at the expense of carbohydrate combustion.

By calculation of the respiratory quotient before and after the ingestion of alcohol, Higgins (15) noted that the lowest figure was 0.78, although the theoretical oxidation figure should have been 0.67.

Krogh & Lindhard (16) studied the effects of high carbohydrate and high fat diets. They observed that the respiratory quotient rose on the carbohydrate diet and fell on the fat diet but it never reached the theoretical levels of 1.00 and 0.71 respectively. The authors suggested that the energy is obtained from the oxidation of both fat and carbohydrate. The change in the respiratory quotient and the increase in metabolism following the ingestion of various sugars was studied by Cathcart and Markowitz (17). Glucose and maltose raised the metabolism but the quotient did not reach unity. Conversely, cane sugar raised the R.Q. to 1.00, but did not alter the metabolism.

Edwards, Margaria and Dill (18) observed that the respiratory quotient decreased with successive periods of work. They concluded that more fat was utilized as the carbohydrate supply diminished, and that the latter was no more essential for the metabolism of work than it was for energy exchange under basal conditions.

These data illustrate the point that even when the subject was on a diet consisting of a single chemically pure substance,oxidation of that material to the exclusion of all others never occurred. This is observable from our data in the gross balance. Apparently, the same holds true for muscle metabolism, per se.

During a study of tissue metabolism, Barcroft & Kato (19) stressed the fact that for the determination of the oxygen consumption of the tissues it was necessary to know the difference in concentration of red blood cells, as the oxygen carrier, in arterial and venous blood. They showed that only a slight decrease occurred in concentration of blood oxygen passing through resting muscle.

The investigations of Hill (20) have shown that the time-course and magnitude of the initial heat were essentially the same whether the muscle was exposed to aerobic or anaerobic conditions. Apparently the chemical changes which gave rise to the initial muscle heat production were non-oxidative. The greater part of the delayed muscle heat production was aerobic.

The report of Johnson, McClosky and Voegtlin (21) on muscle metabolism concluded that the energy necessary for muscle activity was not dependent upon the supply of molecular oxygen.

Muscle is believed to play a significant part in the production of the basal metabolism. However, the comprehensive study of Himwich & Castle (22) showed that the oxygen consumption per gm muscle was less than the oxygen consumption per gm of the entire animal. Based on muscle arteriovenous oxygen differences of 6.7 volumes percent, and arteriovenous carbon dioxide difference of 5.0 volumes percent, the average O_2 intake per gm muscle per hr. was 0.36 cc, or two thirds of the average per gm per hr. for the entire body, 0.51 cc. Assuming that the muscles weighed 8.8 kgm. or 0.4 of the average weight of the entire dog, 22 kgm., they utilized 3100 cc of oxygen per hour. This was less than 0.3 of the mean oxygen consumption of the whole body, 11,000 cc per hour.

Apparently, tissues other than resting muscles are larger consumers of the oxygen in the body under resting conditions. This would be in agreement with the work of Hunt & Bright (23) whose results showed a caloric production of 0.5-1.0 cal/kgm/hr for muscle, in contrast with an average visceral figure of 2-3 cal/kgm/hr and the liver result of 10-20 cal/kgm/hr.

The comprehensive review by Stadie (24) on fatty acid metabolism, pointed out the importance of their partial oxidation in the liver. It has become increasingly evident that the formation of ketone bodies in the liver is an initiating step in the metabolism of fatty acids for the energy requirements of the peripheral tissues.

The liver was unable to form ketones quickly enough to meet peripheral muscle demand. This reaction, unlike the rapid mobilization of hepatic carbohydrate, was significantly more time consuming. During this lag period much of the necessary fat calories were furnished by direct oxidation of fats in the peripheral tissues. Carbohydrate, per se, cannot be considered as the sole fuel of muscle during aerobic or anaerobic activity.

The occurrence of metabolism in the heart muscle is similar to those described for skeletal muscle in many respects (25). It is interesting to note that if complete oxidation is assumed, the total aerobic metabolism of carbohydrates in man and dog accounts for only approximately 35% of the total myocardial oxygen consumption. This indicated both the utilization of non-carbohydrate material as fuel as well as the existence of anaerobic glycolysis wherein completion of degradation to $CO_2 + H_2O$ never occurs.

Possibly one may have to consider the thermal equilibrium of the body as a series of constantly shifting regional equilibria or exchanges with differing levels subject to the operating variable from moment to moment. Considerably more data is necessary for the understanding of the pattern and magnitude of the tissue and vascular thermal shifts. This present section is unsatisfactory to the authors, and should be so to the reader. It is the penalty for very preliminary reporting of study in a complex recalcitrant problem.

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III. DYNAMIC REGULATION IN MAMMALIAN PHYSIOLOGIC SYSTEMS

M. H. Ehrenberg and S. Z. Cardon

A. OSCILLATIONS IN THE BLOOD SUGAR LEVELS

This report concerns itself with an experimental study of the time dependancy of the circulating blood sugar concentrations.

It has been theoretically suggested (1-5) that blood constituent concentration would oscillate, and that the mean concentrations are likely maintained by stability shifts of oscillatory processes for introducing the constituent into, or for their removal from the blood, or both. A study of the literature disclosed earlier experimental verification of the fluctuations in blood sugar levels (6,7). It has been hypothesized (2) that a fast cycle would be determined centrally, by interaction of insulin from the pancreas and glucose from the liver, and that blood glucose would be peripherally affected in the lower frequency blood flow cycles.

If the cyclic processes are experimentally corroborated it is then also conceivable that the other blood constituents maintained at regulated levels also exhibit oscillating concentrations, and that the homeostatic mechanisms generally are similarly operated.

Methods

Experiments were performed on unanesthetized, unrestrained guinea pigs that had been prepared in advance with femoral vessel shunts.

The animals were anesthetized with Nembutal, 33 mgm/kgm, I.P., and the shunts implanted. Aseptic techniques were observed. Siliconized catheters were sutured to the subcutaneous tissue and anchored to the skin. Nylon or stainless steel sutures, 0.003" were used. Approximately one quarter or less of the lumenal area was used to avoid vessel occlusion and permit free flow. Venous catheterization was somewhat more difficult and time consuming because of the thinner vessel walls. Antibiotics were administered prophylactically and therapeutically for several days post-operatively; 9000 units penicillin and 25 mgm streptomycin I.M., per kgm. Sterilized Gutapercha canal fillings were used as lumen plugs. Free flow was established and maintained quite readily.

The technique permitted blood sampling at any planned time schedule without apparent discomfort or excessive handling of the test animals. A twenty second interval was used throughout the tests. Physiological disturbances were observed in some animals at the end of the experiments. These mimicked the effects of slow hemorrhage with an apparent hemodilution, cardiac acceleration and pallor. All animals survived and were still apparently normal for several weeks post-experimentally.

Both arterial and venous samples were not drawn from the same animal at the same time, preventing any direct correlation between these two. Tests were performed on 8 animals, using a modified Folin-Wu technique with 0.1 ml samples (8). The blood was collected in individual, fluorided heparinized capillary tubes. The analyses were made immediately after sample withdrawal, except in 1 animal when the collected blood was quick frozen for several hours prior to analysis. No significant differences were noted in results. After preparation, direct readings were made with a Lumetron Colorimeter.

To verify results, the entire series was repeated using the glucose oxidase test, 0.02 ml samples, several weeks later (9). The enzyme tests were analyzed with the Beckman Spectrophotometer.

Results

The results of the wet chemistry analyses are illustrated in Figures 3 and 4. The oscillations of the blood sugar in both femoral artery and vein is apparent. Gross examination of the results indicated a frequency spectrum of approximately 1-2 minutes (50-140 seconds), 6-7 minutes (360-400 seconds), 20-40 minutes and 80 minutes. The tests were repeated and results confirmed by the glucose enzyme test. See Figure 5.

This procedure provides a measurement of glucose in protein free filtrates of whole blood, serum or plasma, utilizing a coupled glucose-oxidase-catalase enzyme system. The glucose is oxidized to gluconic acid and hydrogen peroxide by the action of the glucose oxidase, while H_2O_2 induces oxidation of methanol to formaldehyde by action of catalase. The formaldehyde produced by the coupled enzyme system is measured by the chromotropic acid color reaction. The advantages of this test are increased specificity and sensitivity so that very small samples can be used (.02 cc). This obviates the problem of humoral depletion over prolonged sample schedules. These data are noted in Figure 5.

Blood sugar oscillations have been experimentally demonstrated using the enzyme test at time domains of approximately 1-2, 7, 20-40 minutes with a possible cycle at 80 minutes. The amplitudes of the oscillations varied inversely with the frequency, so that the high frequency had the smallest and low frequency cycles exhibited the largest amplitudes.

Cyclicalities, heretofore considered as casual phenomena or artifacts by many investigators probably contain the key to glucose regulation and control, wherein high frequency cycles are intrinsic or local mechanisms and low frequencies are superimposed central regulatory mechanisms.

The range of arteriovenous differences, data obtained from different animals at different times, varied somewhat widely, with a mean of 5 mgm percent. Subsequent experiments on extended mixed samples showed a mean A-V difference of 7 mg percent.

The sugar utilization data was used for calculation of the heat balance in section II C above.

Discussion

A review of the literature has indicated oscillations in, and their possible significance in regulation and control of, blood sugar levels.

The first evidence for regulation was that of a relationship between the central nervous system and the blood sugar level as reported by Bernard (10). He observed that puncture of the floor of the fourth ventricle caused a transitory outpouring of sugar in the urine which was recognized as a consequence of a marked rise in blood sugar. He concluded that a center in the region of the pons was concerned with the blood sugar level and that the glucose mobilization was due to stimulation of this center. Variations in blood sugars on the same day in the same person were reported by Liefmann and Stern (11). Blood sugar tests taken on the same day at intervals of approximately one hour, from a resting patient, exhibited variations and were discussed by Baudouin (12). He believed that with sufficiently long time intervals after eating, the blood sugar would be comparatively constant. Bang (13) reported observations which showed that the blood sugar levels varied from day to day in the same patient. This was confirmed by Purjesz (14). Jacobsen (15) also confirmed oscillations in the blood sugar curves of patients, 3-5 hour test durations, on the same day. This early work is reviewed in Hansen (7).

It was noted during a review of this early as well as more recent literature, that many irregularities or variations in blood sugar were reported, but the respective authors did not discuss the occurrence or significance or possible mechanisms.

The fact that considerable removal of sugar actually occurred in the peripheral tissues was demonstrated by Hagedorn (16). He reported that the power of accelerating sugar utilization was apparently unlimited in normal persons, but the level of blood sugar was apparently limited.

The excellent study by Hansen (7) reported oscillations in blood sugar levels at the 7 minute, 40 minute and 70-80 minute frequencies. It was suggested that frequent sampling was important so that the peaks and troughs of the oscillations would be observed. These could easily have been missed by longer interval samples. The report proved that the oscillatory blood sugar levels occur everywhere in the blood and could be demonstrated in two different places of the same individual simultaneously, in fasting normal persons. The waves were observed on fasting patients as well as after eating and could not be regarded

Blood Sugar Concentration - mgm. percent

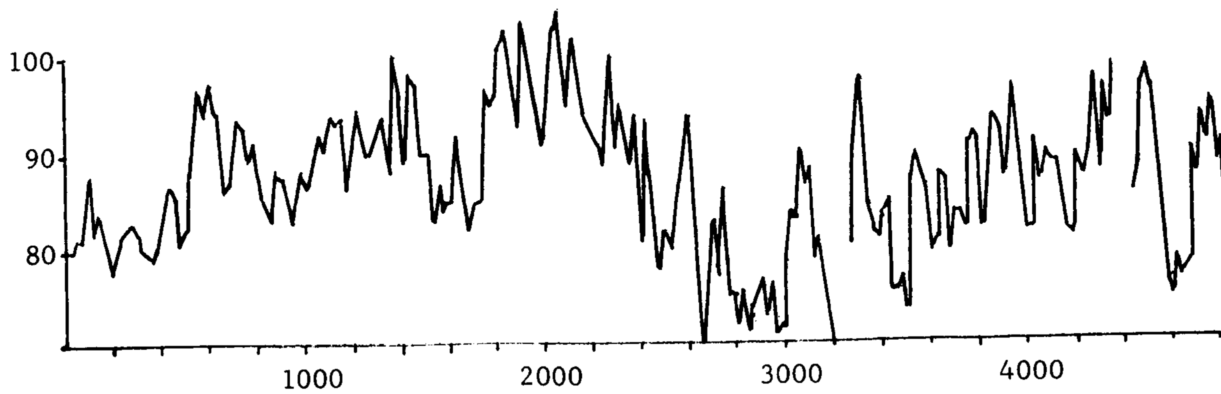

Figure 3. Guinea Pig 11, 0.98 Kg., Femoral Artery, Folin-Wu Analysis

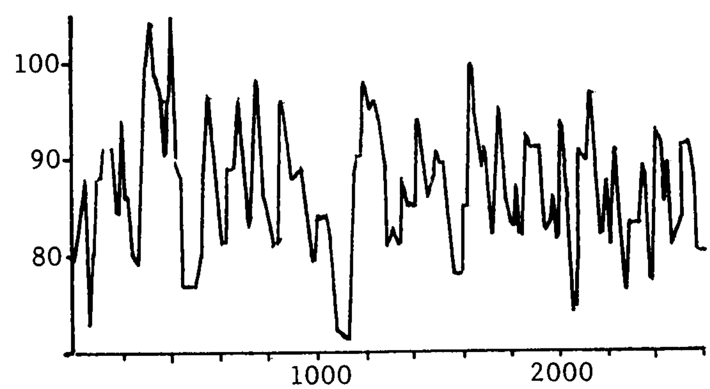

Figure 4. Guinea Pig 13, 1.09 Kg., Femoral Vein, Folin-Wu Analysis

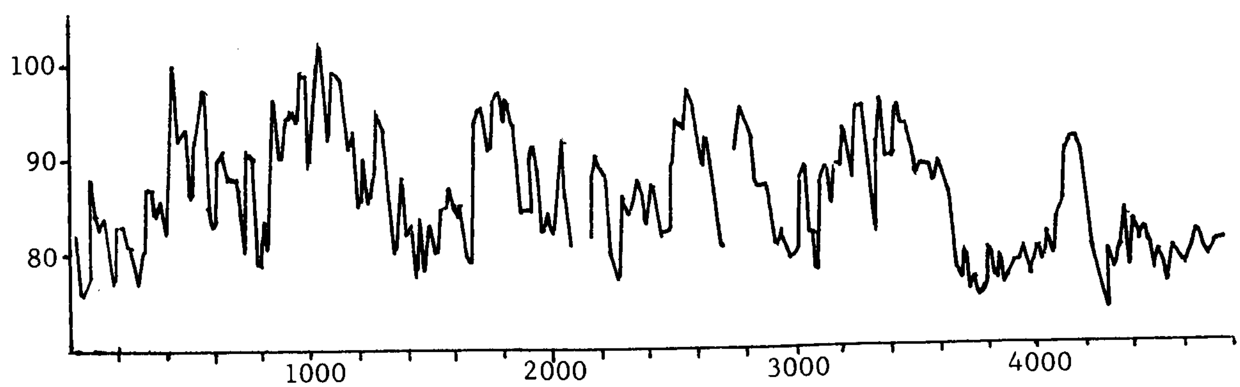

Figure 5. Guinea Pig 16, 1.12 Kg., Femoral Artery, Glucose Oxidase Analysis

Time - Seconds

as solely an absorption phenomenon. The data exhibited arterial blood sugar variations from 80-100 mgm%, and venous ranges from 75-110 mgm%, at the frequencies noted above. During the same year a study was published by Mann (17), on blood sugar levels in the dog. No mention of cyclicality occurred in the text, although the data exhibited an approximate 80 minute cycle in blood sugar levels. Due to extended sample periods higher frequency cycles would not be detected. Donhofer & Macleod (18) studied the effects of lesions and transections in various parts of the brain stem, in an extension and elaboration of earlier work. The brain was divided into four regions, I was rostral to the aqueduct of Sylvius, II between I and the pons, II and IV were respectively, the pontile and distal parts of the medulla oblongata. In 39 animals utilized in these studies, a steady rise in blood sugar reaching a maximum in 3-4 hours, was noted. It was most pronounced in transection of region III with a rise in blood sugar from 110 mg% in approximately 3½ hours. Confirmatory results were reported with decerebrated rats, which had been on high carbohydrate diets, by Bell, Horne & Magee (19).

A further step was provided by Macleod (20), who noted that the effects of region III excitation were abolished by splanchnic nerve section. It may be presumed that the nerve impulses passed either through the splanchnics directly or proceeded over the preganglionic sympathetics which innervated the adrenal medulla and evoked liberation of adrenalin into the blood stream. It had been well established that adrenalin produced a rise in blood sugar. It was further observed that bilateral adrenalectomy without interruption of the splanchnics pathway abolished the blood sugar rise response produced by decerebration.

A report was presented by Cohn, Levinson & McCarthy (21) which confirmed the blood sugar oscillations. These investigators showed a significant normal physiologic variation in the blood glucose content. Wavelike changes were observed in a series of determinations on dogs, both unanesthetized and during Nembutal anesthesia. Variations at near 30 minutes of 15-20 mgm%, which were beyond experimental error in their sugar determinations, were found. Wavelike variations in the glucose content of the blood in fasting dogs were also noted with approximate 80-90 minute cycles. Soskin, Priest & Schutz (22) published studies which indicated that "the passage of the blood sugar into the muscles appeared to be a reversible and cyclic phenomenon".

Without discussing periodicity or rhythmicity, Eveleth & Eveleth (23), stated that "the erratic sugar curves (non-constancy) frequently encountered in apparently normal swine during glucose tolerance tests indicated that pathologic conditions of the pancreas might be present. Autopsy findings however were negative". Presumably, these investigators believed that the variations in blood sugar curves resulted from impaired insulin production by a pathologic pancreas. Since autopsy findings were negative, this conclusion remains open to question.

The earlier studies of Cannon & Cattell (24), and Stewart & Rogoff (25) on the relationship between nervous system agents and adrenalin production were also observed and elaborated by Hrubetz (26) by direct studies on the circulating blood sugar levels. It was shown that atropine caused a decrease in blood sugar level, while physostigmine elicited a rise. The administration of physostigmine after atropine exhibited no effect on blood sugar levels. Also, pilocarpine caused a rise in blood sugar which could be prevented by administration of atropine. Acetylcholine was noted as a blood sugar level depressant.

In a continuation of earlier work, Soskin et al (27), using the dog femoral vessels presented a comprehensive report with new evidence that adrenalin decreases utilization of sugar by the muscles. Adrenalin in hyperglycemia, therefore, could result from this decreased utilization of sugar by the muscles. In their study of A-V differential, i.e., muscle sugar retention measured as venous output and arterial input, it was observed that sugar retention due to IV adrenalin administration was approximately five times greater than that due to IV sugar administration. At no time was sugar retention due to adrenalin less than that which occurred when sugar was administered. The authors summarized their results by stating that sugar utilization by muscles studied during similar levels of hyperglycemia caused by glucose or adrenalin indicated no evidence that any significant differences existed.

With continuous IV infusion of adrenalin over 7½ hours, the increased blood flow (25 cc/min to 110 cc/min) lasted approximately 100 minutes and then leveled off and remained at the same level for approximately 6 hours. The blood flow exhibited an oscillation of 30-40 minutes duration throughout the 7 hour experimental period. Neither the text nor the figure legends commented on this.

The arterial blood sugar rose from near 85 mg% to 220 mg% and peaked in about 60 minutes. It then gradually declined to approximately 125 mg%, increased to about 150 mg% and gradually fell to the starting level at about 7 hours. Adrenalin which was infused throughout the experiment tended to indicate a biphasic blood sugar effect. Oscillations in the blood sugar curve were notable at 30-40 minute and near 90 minute cycles. Sugar retention, venous output and arterial input, initially declined with adrenalin administration, from 0 mg/min to -20 mg/min, recovered in 30-40 minutes to the original base line of 0 mg/min, and thereafter showed a positive sugar retention for the remainder of the procedure. The blood showed a definite cyclical nature, with 30-40 minute cycles and approximate 70 minute cycles for the entire 7½ hour experiment.

The earlier work of Macleod (20) was extended by Nolte (28) who observed that the marked rise in blood sugar level following midbrain or pontile transection, which persisted for 3-4 hours, was obliterated by excision of the adrenals prior to the decerebration. There is evidence, Flock, Ingle & Bollman (29), that the major changes in glycogen, phosphocreatine, adenylphosphate, hexosephosphate, lactate and inorganic phosphate have occurred during the first half-minute to one minute of muscle activity. It was suggested that these substances were used at the onset of muscle activity prior to steady state, and that glucose, per se, from the blood stream is the chief source of energy under these conditions.

Himsworth (30) administered glucose to normal individuals and determined the blood sugar responses. He concluded that ingested glucose led to an increased functional capacity of insulin, an increased sensitivity to insulin and increased effectiveness of the hormone. By graphing his raw data, we found a tendency toward a 30-40 minute cycle in blood sugar levels, with an A-V difference of 2-8 mg%.

The thorough experimental study of Andersen et al (6), indicated that an increase in arterial glucose level was accompanied by a decrease in venous glucose level of the same extremity, in dogs. He noted that the amplitude of crest to trough undulations varied from 7 to 20 mg%, that they were long undulations with wavelengths from 2 to 7 minutes, with shorter 30 second cycles superimposed. Following each arterial surge of hyperglycemia, it was noted in both dogs and man, that there occurred a decided fall in venous glucose level. There appeared to be a temporal correlation between the arterial rise and the venous fall in the respective blood sugar oscillations. It was also observed that insulin function was a fluctuating phenomenon, with a pulsatile characteristic oscillation. The arterial oscillations were claimed to be essentially the same throughout the entire arterial tree and were identified with pulsatile glucose oscillations found in hepatic venous blood from the liver. These same undulations were noted in the arteries of all extremities. The peripheral arterial glucose levels were lower than the hepatic venous glucose output. In contrast to the similarity of peripheral arterial fluctuations, the peripheral venous oscillations were dissimilar in the extremities.

This study showed a high frequency cycle at 30 seconds and slower frequencies at 2 minutes and 7 minutes, with an adrenal medullary effect, apparently insulin mediated, in the time domain of approximately 70 minutes.

More recent studies by Burns, Bregant Van Peeran & Hood (31), presented data and charts which tended to indicate cyclicality. Although no mention of periodicity appeared in the text, our analysis of the data exhibited "damped" oscillations in the blood sugar.

It has been shown that the human heart uses glucose, pyruvate and lactate, and their utilization appears to be a function of their arterial concentrations, Bing (32). At normal concentrations glucose and lactate are used in approximately equal amounts. He suggests that blood sugar level may exert a moderating effect on myocardial activity and contractile force. The dog heart also utilizes carbohydrates in proportion to their arterial concentrations (33).

During an investigation (34) of the effect of exercise on plasma human growth hormone, plasma non-esterified fatty acids, blood sugar and R.Q., the subjects walked 20 + miles at 4 m.p.h., in the fasting state. The resultant blood sugar data clearly indicated near 45 minute and near 90 minute cycles. Higher frequency cycles were impossible to detect because of the prolonged sample interval of 15 minutes. It would have been most instructive and informative if 30 second samples had been taken.

Table IV represents data from the literature comparing results on oscillations in the blood sugar level. Many investigators have reported irregularities or presented data or graphs without citing or discussing the occurrence of cycles. We have reviewed the data and marked it accordingly. It must be remembered that in many reports, an extended sampling schedule eliminated the possibility of detecting high frequency activity. Only those analyses permitted by the data have been listed.

Some points merit further discussion.

Consideration of the large wave in blood sugar during intestinal absorption, (low frequency oscillation) as in the glucose tolerance tests, the rhythmical oscillations in the post absorption period, (higher frequency oscillation) in the fasting state, the maintainance of an "average" blood sugar level that does not occur except accompanied by short spurts, spikes and pits, (highest frequency oscillations) reinforces the conclusion that blood sugar is regulated dynamically. Post-absorptive glucose apparently activates insulin production and function as does ingested glucose during absorption. Since it has been established that insulin activity occurs during both the absorption and post absorption periods, some explanation is required for the mediation of insulin function during the post-absorptive period when the portal circulation is presumably free of ingested glucose. However, the stimulation of insulin production by circulating blood sugar level changes are possible, as suggested in (2). The interaction with adrenal medullary response must also be considered in the definition of the basic dynamic mechanisms.

The interaction of insulin with the liver is well known. All the insulin elaborated by the pancreas initially enters the liver, and exogenously administered insulin predominates in the liver, i.e., thirty minutes after administration of isotope-labeled insulin, the greatest concentration per mg tissue is observed in the liver, 0.52 μg, 0.17 μg in bones, 0.11 μg in intestine, 0.004 μg in skeletal muscle and virtually none in brain (35).

The data of Bonckoert and de Duve (36), indicates the liver to be the chief site of action of insulin and that it effects two thirds of insulin and that its uptake of glucose makes the most important quantitative contribution to insulin induced hypoglycemia.

The report of Genes (37), showed that in normal and pancreatectomized dogs, insulin significantly reduced the release of sugar by the liver in response to reduced inflow of sugar to the liver. Apparently insulin depressed but did not abolish the homeostatic function of the liver. The author did not discuss whether this represented retention per se or a reservoir effect. Their observations noted the significant variations constantly (continuously) taking place in the pulsatile manner of sugar release into the blood by the liver in the same dog.

The author concluded that insulin has two separate and opposite effects, direct action of suppressing the hepatic output of sugar leading to reduced blood sugar concentrations and an indirect effect of lowering the amount of sugar delivered to the liver which stimulates the hepatic sugar output.

TABLE IV. BLOOD SUGAR DATA IN THE SCIENTIFIC LITERATURE

Investigator	Year	Blood Sugar Cycles (minutes)				
Hansen	1923			7	40	70-80
+Mann et al	1923					80
Cohn et al	1933				30	80-90
+Soskin et al	1937				30-40	90
+Himsworth	1939				30-40	
Andersen et al	1956	30 sec.	2	7		70
+Hunter et al	1965				45	90
This report	1965-1966		1-2	7	30-40	80

+ Our analysis of author's data.

Our graphing of the Genes' results (37) clearly indicates the cyclical nature of the blood sugar output from the liver both before and after insulin administration, in contrast to non-cyclical nature of the blood sugar entering the liver prior to insulin administration. After insulin IV, either portal or femoral, the blood sugar entering the liver demonstrated a tendency toward cyclicality, Figure 6.

This may be considered as presumptive evidence that regulatory oscillations may arise in liver due to pulsatile insulin production or release, or to a feedback interaction of insulin from the pancreas with glucose in the liver.

Summary

Experimental evidence shows a 1-2, 7, 20-40 and 80 minute oscillatory cycles in blood sugar levels in animals.

A 30 second cycle found by Andersen (6) is hypothesized to be the local regulatory mechanism for sugar input; the 2 and 7 minute cycles represent local and peripheral regulation of removal of blood sugar. The 80 minute cycle may be a reflection of a blood flow cycle not necessarily connected to sugar regulation. This is likely true of the 3½ hour cycle which has been discussed elsewhere (5).

It is likely insulin is elaborated in a fluctuating, pulsatile manner, with frequencies similar to those of blood sugar.

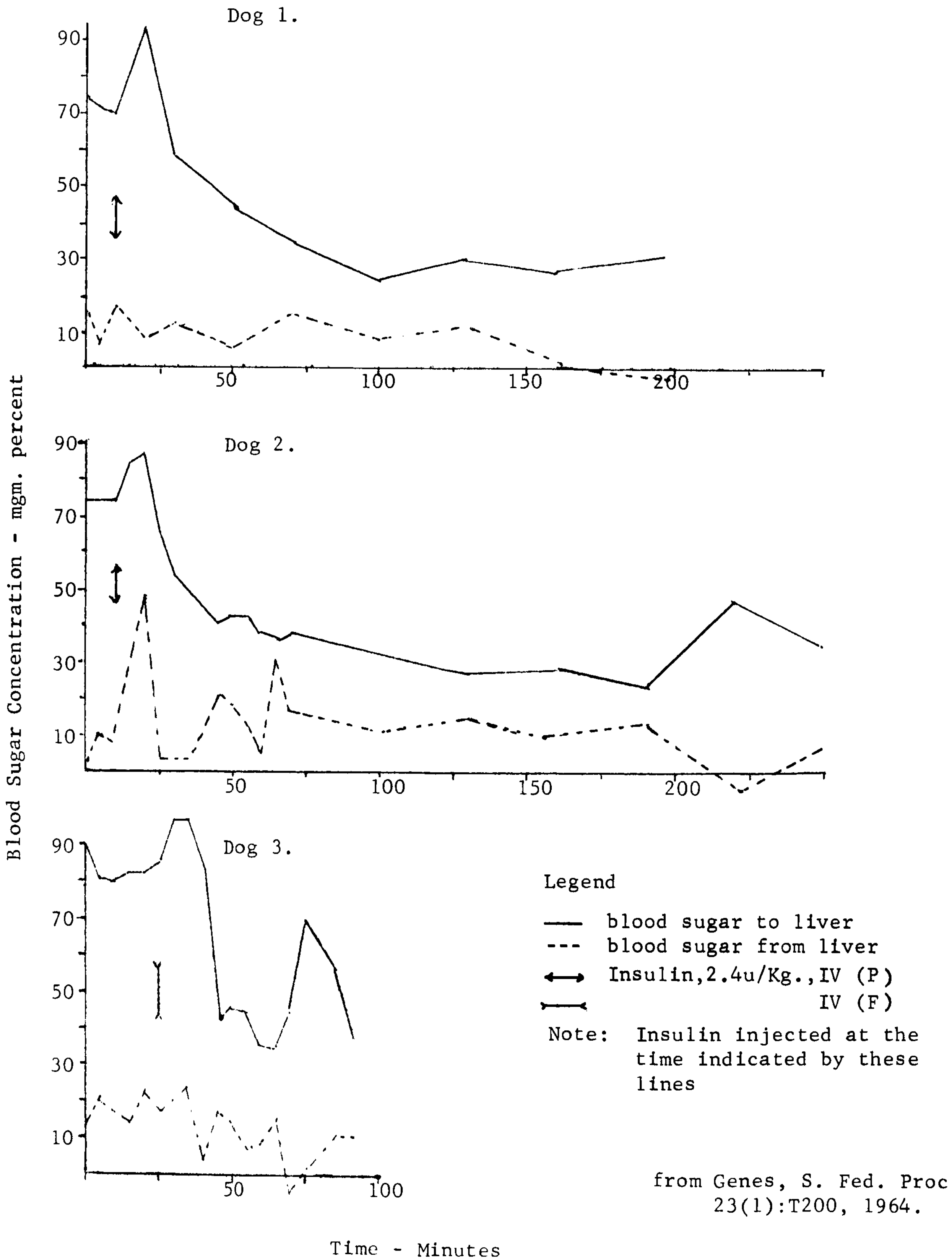

Figure 6. Pre- and Post-Hepatic Blood Sugar Concentration

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B. THE OXYGEN-CARBON DIOXIDE SYSTEM

Introduction

The vascular oxygen-carbon dioxide concentrations are of interest for several reasons. In accordance with the general hypothesis that biological regulation is achieved through dynamic oscillators, it would be expected that oxygen and carbon dioxide levels as well as other regulated blood components will oscillate. Also, in attempting to construct a model of the heat balance of the intact animal, measures of the heat production include the oxygen utilization, carbon dioxide production and sugar (fuel) oxidation. These data must correlate heat production as determined by arteriovenous temperature differentials and external heat loss (skin). In addition, the hypothesis that the circulating oxygen level acts as a choke on tissue metabolism is involved. A vascular oxygen cycle is likely the determinant of the tissue metabolic cycle. Since, oxygen transport is essentially by red blood cells, the earlier work on frog mesentery (1) and the findings in this report Section III C, on in vivo guinea pig muscle in capillaries, in which the rate of red cell flow was found to be oscillatory, is significant. The metabolic cycle may perhaps be ascribed to a red cell cycle resulting in a concomitant oxygen flow cycle. Considerable data indicates representative cycles in total blood flow. The source of the metabolic cycle requires further study, since the blood and several constituents exhibit similar cyclicality. This will be reviewed in part two of the discussion. Oxygen data further was of considerable theoretical concern to us since Urquhart (private communication) had measured oxygen concentrations and found only small A-V difference in a normal quiescent dog.

Method

The partial pressures of oxygen and CO_2 in blood were determined in vivo in guinea pigs and rabbits using a Beckman model 160 physiological gas analyzer with a modified miniaturized Clark micro-electrode. The electrode made possible continuous readings and recordings of oxygen tension in blood, body fluids and tissues. The carbon dioxide tension was recorded with modified miniaturized Severinghaus-type electrode, using silastic membranes over the electrode.

Determinations were made in the femoral artery and vein. The animals were anesthetized with sodium pentobarbital, 30 mg/kg, intraperitoneally, and the femorals exposed through a midline incision over the triangle. The electrode was implanted in one of the vessels and ligated in position obliquely, subcutaneously and cutaneously to permit free passage of the unhindered cable. All the early results indicated some degree of cyclicality of the continuously recorded pO_2. There were precipitous rises and falls in pO_2 with absence of regular oscillations. In one animal allowed to recover from anesthesia with the implant intact, the pO_2 oscillations became clear, regular and uniform, approximately one hundred minutes after recovery.

Thereafter the implant was performed under light anesthesia with recording of results approximately 4 hours after recovery from anesthesia. The modified technique was in agreement with that of Glover (2), who noted that in anesthetized, heparinized dogs undergoing operative procedures, the oxygen pressures immediately post-operative were erratic. The pO_2 and pCO_2 samples did show changes several hours after recovery.

Every precaution must be taken to avoid disturbance to the unanesthetized animal, because the artery becomes somewhat constricted and rhythmic contractions are damped or cease entirely on the slightest provocation. Indeed, it had been observed by Clark and Clark (3) that very phlegmatic animals were unsatisfactory for study of the rabbit ear artery since they were prone to sleep.

Early work by Wilson (4) had similarly indicated that rhythmicity was inhibited by anesthetics. Of the many tested however, morphine was not inhibitory and often increased the rate of contractile rhythmicity.

It is of interest to note that therapeutic amounts of morphine have little if any effect on the blood pressure, heart rate or rhythm. Minor changes which occasionally occur are usually secondary to diminished physical activity, narcosis and sleep. The vasomotor and vagal centers are unaffected except at toxic amounts. The cutaneous blood vessels are relaxed, and vascular action appears to be directly on the vessels.

There were several drawbacks in our experiments. Despite the use of micro-electrodes a considerable portion of the vessel lumen was occluded with a resultant reduction in flow and change in flow pattern. This may result in local stasis and a specific sample, in test, may not have the same oxygen tension or content as the average of all the blood normally flowing in the system.

Another problem was noted when the tip of the electrode was in close proximity to or in contact with the vascular endothelium. This caused sizable changes in the average value of the oxygen partial pressure readings which appeared to be in synchrony with the cardiac cycle. It is likely that there was mechanical or electrical coupling to the latter. The vessel wall problem resulted in up to a 30% change in mean tension readings.

Another possibility is that an electric signal may be picked up from the intima of the blood vessel, which has been reported (5) to be electrically conductive. (This suggests possible internal innervation of the blood vessels).

It should be stressed that we were essentially concerned with the physiologic variability of the blood gases. Also, that the electrodes primarily indicated changes in partial pressure values. The absolute values require extremely accurate calibration, performed frequently, on the same animal, as a basis for comparison. Our data has been compiled and averaged from several animals tested at different times and presented as a composite. However, this crude data provides a first indication of the dynamics of the oxygen-carbon dioxide blood levels.

Results

The results are presented in Table V. The variability in partial pressures of oxygen and carbon dioxide were within the bounds of values reported in an extensive literature. The data indicated only small A-V differences.

The arterial pO_2 ranged from 70-120 mm Hg., with a mean of 115 mm Hg. Distinct rhythmicity was observed and cycle frequencies were found at approximately 30-60 seconds, 100-200 seconds, 400-500 seconds and possibly 950-1100 seconds. The amplitudes in partial pressure associated with these cycles were of the order of 1-3 mm, 2-8 mm, 5-15 mm Hg. and 11-14 mm Hg. respectively, showing an inverse relationship with frequency.

The venous pO_2 ranged from 27-49 mm Hg., with a mean of 45 mm Hg. Cyclicality was shown with periods at 30-60 seconds, 150-300 seconds and a possible low frequency cycle at 15 minutes. Again an inverse relationship existed between frequency and amplitude, with the latter varying 2-4 percent, 7-10 percent and possibly 6-15 percent, respectively.

The arteriovenous difference was calculated to be approximately 4 volumes percent. This figure has been used in determining the heat balance based on oxygen utilization.

The arterial pCO_2 varied from 22-49 mm Hg., with an average of 41 mm Hg., while the venous pCO_2 ranged from 33-59 mm Hg., with an average of 55 mm Hg. Both arterial and venous pCO_2 exhibited similar oscillations, i.e., at approximately 1-2 minutes, 6-8 minutes, 30-60 minutes and 100 minutes, but did not show any specific pattern between frequency and amplitude. The absence of the inverse relationship found in the oxygen system, although amplitudes in the pCO_2 system varied from 1-15 percent, possibly indicates a difference in the mechanism of regulation.

It must be borne in mind that these data were not derived from the same animal in the same day, but represent a composite for calculation and preliminary determination of an energy balance.

The arteriovenous pCO_2 difference was calculated to be approximately 9 volumes percent and this figure was used for one calculation of heat production for the heat balance.

TABLE V. OSCILLATIONS IN THE OXYGEN-CARBON DIOXIDE SYSTEM IN THE FEMORAL VESSELS OF GUINEA PIGS

Animal		pO_2 Cycle frequency (sec)	pO_2 Cycle amplitude mm Hg.
guinea pig 18 0.99 Kg.	Artery	20-30	1-2
		100-200	2-3.5
		410-490	5-7
	Vein	30-60	1.5-2
		140-200	3.5-4
guinea pig 20 1.02 Kg.	Artery	30-60	1.5
		160-240	5-6
		450	8
	Vein	30-50	1
		200-300	4-5
guinea pig 21 1.04 Kg.	Artery	30-60	1-2
		100-150	2.5-5
		500	8-10
		950-1100	11-14
guinea pig 22 0.97 Kg.	Artery	20-40	1-2.5
		120-180	5-8
		400-500	8-15
guinea pig 25 1.01 Kg.	Artery	20-40	2-3
		80-140	3-7
		400-485	11-15

Arterial pO_2	70-120 mm Hg.	115 mm average
Venous pO_2	27- 49 mm Hg.	45 mm average

Animal		pCO_2 Cycle frequency (min.)	pCO_2 Cycle amplitude (mm Hg.)
guinea pig 26 1.0 kg.	Artery	1-2	Varied from 1-15% no specific pattern
	Vein	6-8	
		30-60	
		100	

Arterial pCO_2	22-49 mm Hg.	41 mm average
Venous CO_2	33-59 mm Hg.	55 mm average

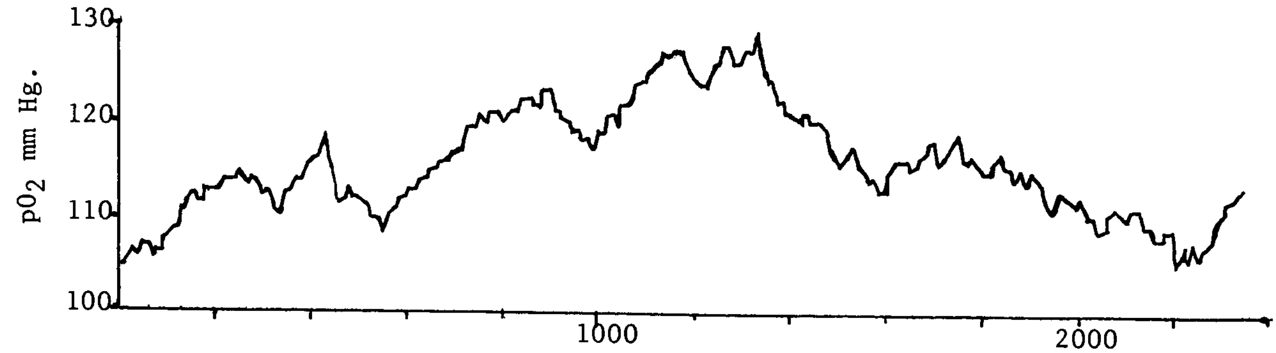

Figure 7. Guinea Pig 19, 1.01 Kg., Femoral Artery

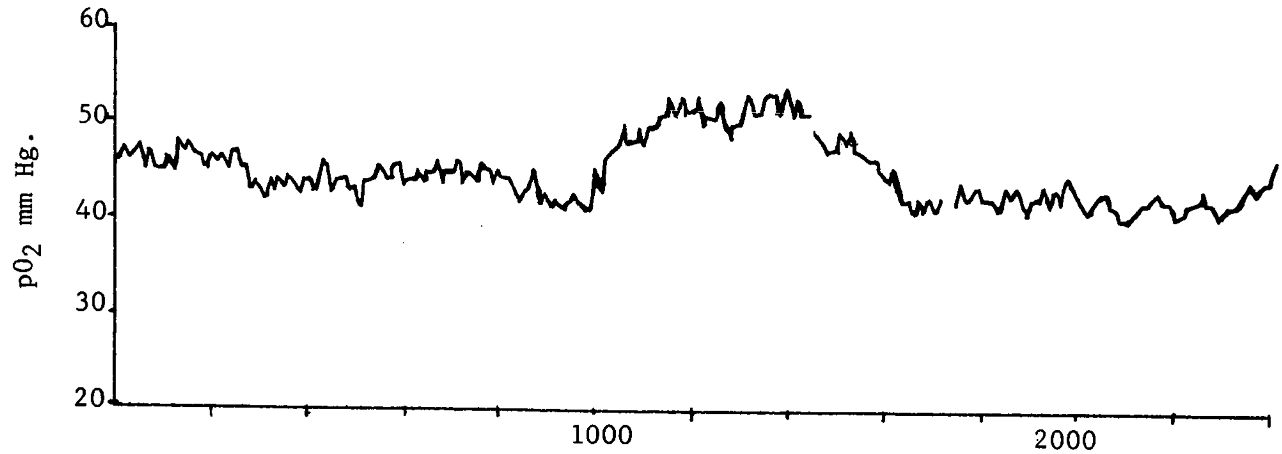

Figure 8. Guinea Pig 23, 0.99 Kg., Femoral Vein

Figure 9. Guinea Pig 24, 1.12 Kg., Femoral Artery

Time - Seconds

Discussion

Discussion of the oxygen-carbon dioxide system will be divided into 3 sections, ventilation, transport, and tissue, and the data considered in relation to our results.

Cyclic variations in ventilation was reported by Lenfant (6) who continuously monitored tidal volume, expiratory resistance, dynamic pulmonary compliance and end tidal O_2 and CO_2 in seated subjects. Simultaneous arterial blood samples were also analyzed for pO_2 and pCO_2. The arterial-alveolar gas tensions differences were calculated. All the measurements exhibited the cyclic variation of a sinc wave. The cyclic periods were between 1 and 3 minutes, and the amplitudes differed considerably between subjects. The alveolar-arterial O_2 difference ranged from 13-20 mm Hg. and the alveolar-arterial CO_2 between 3-5.5 mm Hg. A recent communication with the author indicated that the research and its evaluation is still in progress. This study further complements the work of Goodman and his students at Case Institute, and the work reported on earlier in this program (1).

During a study of the acid-base composition of the blood, Helding-Bjurstedt (7) recorded data which, by our analysis, demonstrated oscillations in the partial pressure of arterial oxygen and pH. The author did not refer to these rhythmic fluctuations in the text. The arterial oxygen saturation was loosely related to the pressure oscillations in normal, unstimulated subjects. Frequencies were analyzed at 3-5 sec. cycles, 20 sec. cycles and 60 sec. cycles with amplitudes respectively of 2, 5 and 8 percent.

A later report by Fox et al, (8) reported fluctuations in oxygen saturation of femoral artery blood which were believed to be associated with the respiratory cycle. These were observed while using the Evans Blue technique. The data showed respiratory cycles at 1 per 10 sec., and oxygen sat-saturation cycles at 1 per 10 sec., with an amplitude approximating 3-5%. These high frequency cycles appeared to correspond. An examination of the data in this paper showed a lower frequency cycle, at 1 per 65 sec., with an amplitude of approximately 10% of the mean.

Roddie et al, (9) demonstrated short duration records with a clear tendency to cyclical oxygen saturation in control and experimental studies of the forearm. Examination of the data showed 3-5 minute cycles and 20 minute cycles with amplitudes of 2-3% and 7-10% respectively. Since only short periods of data were presented there is some doubt about the validity of these low frequency cycles. Analysis of the original full length records would be more definitive.

Pories et al,(10) using dogs with shunt techniques noted that the degree of RBC aggregation in conjunctivo or in a shunt was not related to the oxygen tension in liver or kidney. The liver oxygen tension exhibited cyclical changes in value ranging from 3-12 mm Hg. Kidney oxygen tension oscillated from approximately 10-20 mm Hg. over a 160 minute test. The dog's blood pressure remained at 120-145 mm Hg.

High frequency cycles in arterial oxygen saturation only were noted by Enson and Cournand (11) who observed that the magnitudes varied with the cardiac and respiratory cycles. The amplitudes vary by as much as 10%.

Obliquely touching upon this subject, Carregal (12) studied the cyclic fluctuations of excitability of spinal motoneurons. The study dealt with rhythmic fluctuations of the response of certain spinal motoneuron pools to a constant afferent stimulus, which was locked to the respiratory cycle. Asphyxiation of the spinal cord abolished the cycling response. The author suggested that the fluctuations of excitability of spinal motoneurons were due to fluctuations of O_2 and CO_2 content of the blood irrigating the motoneuron pools. In a personal communication, the author stated that this work is continuing. In a more recent report, Gamble et al, (13) demonstrated 5 sec. cycle frequencies in arterial oxygen saturation with an amplitude of 3-7%.

The tissue metabolism also appears to correspond with the ventilatory and transport cycles. Although the evidence is scanty at present, some discussion is merited.

Solov'ev and Khodas (14) reported cyclic variations of myocardial oxygen tension which appeared to be correlated with arterial oxygen saturation. These in turn may have been related to oscillations in the arterial pressure. The cyclical variations in myocardial oxygen tension were attributed to "altered vasomotor regulation." The frequency could not be determined since the records did not contain any time scale or signal. The amplitudes, however, varied from 6-10% of saturation.

Using the open chest dog preparation, Yagi et al, (15) studied coronary and peripheral blood flows. Under steady arterial oxygen tension, the rhythmic variations of the coronary and peripheral flow were inversely synchronised. The authors suggested that the adrenergic function was to modulate the blood flow to resist the oscillations of increasing blood pressure, and the cholinergic function was to modulate the blood flow to the oscillations of decreased blood pressure. When the adrenergic or cholinergic actions were neutralized the oscillations appeared to be due simply to changes in blood flow resistance.

Whalen (16a) on intracellular pO_2 and function, indicated that in vivo mammalian muscle pO_2 is low enough to limit oxygen consumption. These findings are consistent with the hypothesis that in vivo pO_2 may regulate heat production in muscle and may control local blood flow. Subsequent work by the same investigator (16b) showed a mean intracellular oxygen calibration of 3 ± 1 mm Hg. in the resting guinea pig gracilis muscle. The intracellular pO_2 fluctuated rhythmically from 0 to 5-12 mm Hg., with 1-2 minute cycles, and was usually independent of changes in concentrations of the inspired gas. The independent pO_2 oscillations indicate blood flow in resting skeletal muscle is regulated to maintain a low oxygen tension which enables it to govern respiration. These experiments are the most direct evidence thus far, for an oxygen choke, i.e., that the tissue impedance helps to form the rate governing reaction of oxygen release.

Summary

Experimental data indicate oscillations in oxygen and carbon dioxide in both arterial and venous femoral blood in unanesthetized, unrestrained and apparently normal guinea pigs under quiescent conditions.

Analysis indicated arterial oxygen cycles of approximately 30 seconds, 2 minutes, 7 minutes, and 20 minutes with partial pressure amplitudes ranging from 1-15 percent. There was a general tendency for the higher frequency oscillations to show smaller cyclic amplitudes.

Apparent venous oxygen cycles were found with periods in approximately the 30-60 second, 2-3 minute, and 15-20 minute ranges with amplitudes of about 2-10 percent. Again a tendency toward an inverse relation between amplitude size and frequency was indicated.

The current weakness in these data is that they operate on the flat part of the oxygen-hemoglobin dissociation curve, since the animals have thus far only been tested at rest, so that these leg muscles are not highly active. The likely curve is indicated in Figure 10.

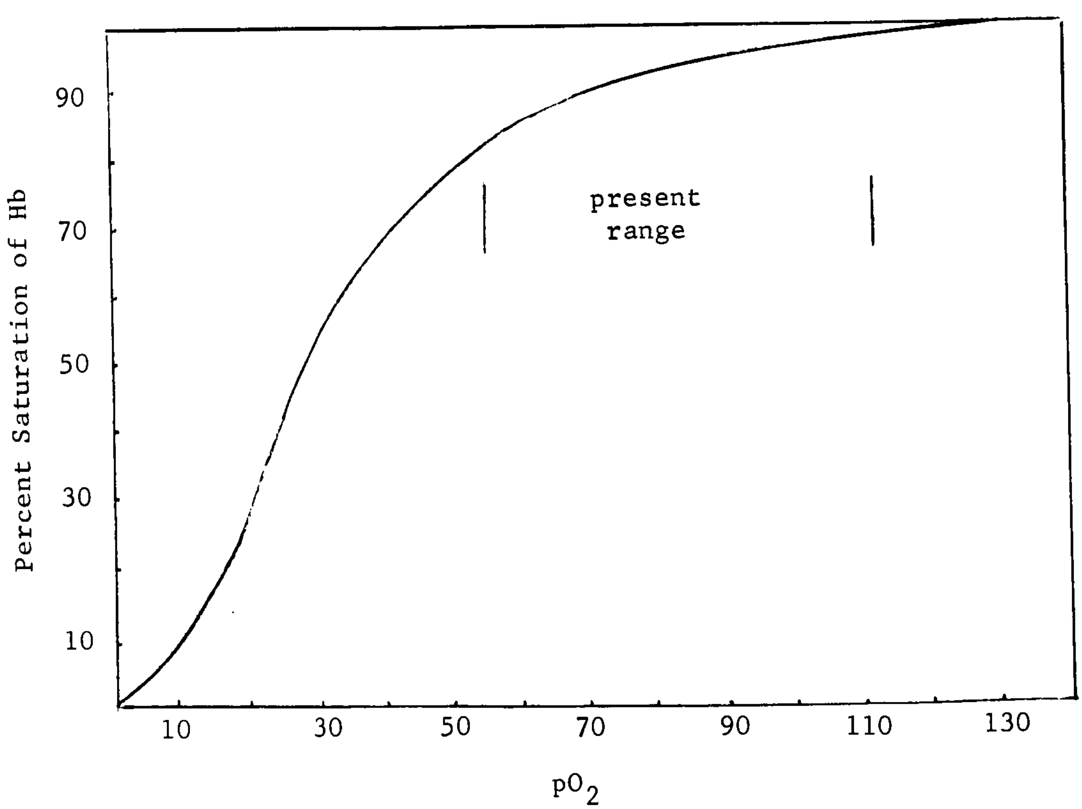

Figure 10. Dissociation Curve of Hemoglobin (at 38°C and pCO_2 = 40 mm Hg)

In the future, it is hoped that tests can be made with working muscle so that oscillations, if any, can be directly indicated with large A-V concentration differences.

Arterial and venous carbon dioxide cycles were comparable with estimated periods of approximately 2 minutes, 6-8 minutes, 30-60 minutes, and 100 minutes. The amplitudes ranged from 1-15%, with no apparent relation between frequency and amplitude.

Anesthetics inhibit the oscillations observed under normal physiological conditions. Anesthesia, handling, surgical intervention and possibly emotional stresses may result in effects other than these oscillations.

The frequencies and amplitudes are not sharply specific, but tend to warble. However their harmonic content over any observation period appears to be the same. The same result appears to be true for the sugar oscillations also.

It has been hypothesized that the muscles form an unstable system that would utilize all the oxygen available to it, and that the dynamic characteristics that would permit them to follow activity would require that they be involved with a cyclic oxygen choke. The present study has shown the cyclic nature of some main concomitants of the metabolism chain. The evidence of Whelan supports the primary idea of the oxygen choke in the surrounding tissue supplying oxygen to muscles. Hormonal mediation for these local oxygen cycles has been proposed.

The classic concept, originating from Landis and Pappenheimer, and illustrated in the Handbook of Physiology (17) is that there is a linear relation between oxygen consumption of muscle and blood flow of about 0.3 ml/min/100 gr muscle, in the rate at which oxygen is delivered to the muscle by arterial blood until plateaus are reached that are temperature or activity dependent.

Within the framework of our modelling, and the data assembled, we do not concede that the extra perfusion of blood that was used in test animals to derive the plateaus represented flow through nutrient channels. In our view, as will emerge further in discussion of experimental microcirculation data, the total blood flow shunts the capillary (nutrient) beds.

Thus in normal physiological operation, if the red blood cells made oxygen available to the muscle tissue, it would be used up. However, the oxygen is only made available to the tissue in cyclic intermittency (i.e., by an escapement). The tissue resistance acts as an oxygen choke to make oxygen available to the muscle fibers and thus provide the rate limiting step. The signal to the local capillary bed arises from central nervous sources to permit the muscles to follow an activity level that the brain has agreed upon.

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C. DYNAMICS IN THE MICROCIRCULATION

Introduction

In previous reports of this series, (1a,b,c) the thesis has been developed that the source of the two minute heat cycle was to be found in the muscle capillaries, with an oxygen choke as the limiting factor controlling the heat release. Accordingly, a demonstration was sought of the oxygen flow in the microcirculation. The flow of red blood cells in capillaries was selected as the simplest measure of the oxygen supply dynamics. With the guidance of Dr. E. Bloch of Western Reserve University, cell counts in preparations of the frog mesentery were determined and the measurements reported earlier (1d). The results demonstrated cyclic red blood cell flow. Our objections to these experiments were that the frog were deeply anesthesized, the tissue was mesenteric rather than muscular, the animal was not a homeotherm and the perfused externalized tissue was exposed to air, high heat and light. Our work was followed by Stow and Greenwald (2), Harris and Nicoll (3) and Johnson and Wayland (4).

Dr. Bloch suggested consideration of the mouse penniculus muscle preparation (a transparent fan on the back) and the rabbit ear window used by Williams. Dr. Williams suggested the guinea pig penniculus muscle with a single or bilateral window might be used for viewing. These approaches were pursued for development of technique though they would not fulfil the ultimate objective; the observation of active working muscle preparations. The bat wing was also considered unsuitable for the same reason.

The problem of observation in active muscle is maintenance of moving fibers and vasculature in the optical field. To obviate this, Iberall suggested observation at the point of insertion or origin of the muscle, or at a crossover between two muscle masses (e.g., deltoid over pectoralis). These regions would provide active muscle tissue which undergo minimal motion in activity.

The assistance of T. Jayne, who furnished advice on optical systems and collaborated in the search for window materials, is gratefully acknowledged.

Experimental

The experimental program was directed toward three goals: to develop window preparations into active muscles that would have long life and permit normal activity, to develop an optical system of sufficient resolution and depth of field that would follow red blood cell flow in capillaries, and to develop an exercise system to permit active operation of the muscle by the animal. The work is far from complete, but reports what progress has been made toward these objectives. (e.g., at present, the animal is wrong, the cell is not adequately transparent, the optics are not adequate. The animal could be exercised, but fortunately stands reasonably still).

The quadriceps muscle in the hind limb of the guinea pig was selected for study. The animals, approximately 1 kg. in weight, were anesthesized with Nembutal, 33 mg/kg, intraperitoneally. Using sterile technique, a circular section of skin, 1-1.5 cm. in diameter was excised superficial to the quadriceps and the fascia stripped. Initially, 100-125μ, plastic windows were sutured in place between the subcutaneous and cutaneous layers of the skin, using 0.003 inch stainless steel. Antibiotics were administered prophylactically and therapeutically, for several days, in dosages of 8000 units penicillin and 15 mg. streptomycin IM.

Kodaloid, a clear plastic was tried first, but it adsorbed moisture and clouded. Lucite and mylar were then used. The windows did not appear to interfere with normal locomotion. The high degree of light scattering and reflection prevented clarity when viewing the capillaries and cells. This approach was temporarily abandoned, although it is open to review with the use of thinner windows, to reduce the light scattering and reflectivity. One possibility is the use of spray coatings similar to spray bandaging. Another possibility is modification of the light incidence by liquid coupling to the windows. Thus, while the windows were satisfactorily compatible, permitted adequate motion, had quite long life, provided a window into active muscle, and allowed useful viewing, so far these were not satisfactory to permit viewing capillaries.

The plastic windows were accordingly removed and the skin circumferentially folded under itself and sutured to the subcutaneous layer to inhibit granulation tissue formation. The blood flow in the small vessels remained accessible (up to several days) as long as drying of the surface tissue was prevented by bandages and frequent moistening with physiological saline. The wound surface could be renewed by removal of the drying tissue. The wet open wound permitted adequate viewing of the red blood cell flow within small vessels, down to the resolution of the optical system.

For cell counting the unanesthetized, unrestrained animal was placed in a normal stance on a small platform, with the head, forelegs, and frontal portion of the torso in a perforated cardboard canopy. The animal remained quiet with his head in the partially darkened canopy with only occasional shifts in position and backward or outward movements. The most prevalent position was the normal upright stance.

A high intensity light source (Iota Cam Corp., Wakefield, Mass.) was used, coupled to a fiber optic pipe through a color filter (blue green or violet) and a water filter to reduce heat. The 200 power objective of a standard triple objective microscope was used. The light was directed almost perpendicular to the tissue. Contrast was increased by working in a dark room with a reduced aperture of the objective lens.

The number of cells per second flowing in a particular small vessel was visually counted. The vessels were approximately 15μ in diameter (estimated by comparison to a Zeiss stage micrometer and also to fixed red cells). The vessel was thus of the order of size of a small arteriole or venule, large capillary, or bypass vessel (if we accept the criterion for a capillary, that it be approximately the size of the average red cell, assuring intimate wall contact for optimum chemical exchanges).

The flow was estimated by a time marking for each group of five, or by making the markings for each five in the estimated aggregate number greater than five; whether the entities marked were actually cells or clusters is not possible to say at this time.

The animal remained relatively quiet except for slight respiratory motion for periods up to 10 minutes. Changes in vessel caliber and intermittency of flow were noted. Erythrocyte orientation varied considerably either as individuals or aggregates in the direction of flow. The vessel segments studied were several times the diameter. This technique is applicable to vessels where excessive cellular overlapping does not occur and is therefore size limited to small vessels less than 15-20μ. It should be noted that apparent RBC flow appeared to be slower than arteriolar flow. Also, fluctuations in arteriolar diameter were aperiodic with those observed in the small vessel segments used for counting.

The rates of apparent RBC flow varied from one to 28 cells per second with an approximate average of ten per second. (The conditions made it difficult to distinguish all the red cells individually with absolute certainty. It is therefore possible that groups of cells were being counted as single cells. The absolute values are not accurate but suggest oscillatory characteristics). The flow appeared cyclic. Analysis of the data shows several frequencies with periods of 10-15 seconds, 30-60 seconds, 100-140 seconds and approximately 300 seconds. The results are shown in the accompanying Figure 10.

Discussion

It should be noted that our results are considered to be estimates. Several cycles found in red blood cell flow in skeletal muscle vessels correspond to cycles previously observed in temperature and ventilation rate in mammals. In other experiments on direct determination of blood oxygen concentration, reported below, similar cycles are reported. It is clear that oxygen is supplied to the capillaries in an oscillatory fashion, and probably the supply to the tissue is similarly oscillatory. Thus, the heat production cycle could be established by the cyclical oxygen supply. Since similar cycles were shown in blood sugar and carbon dioxide concentrations, the existence of corresponding periodicities does not automatically establish a causal relation. Rather, the chain of argument; low oxygen storage, high oxygen utilization in muscle activity, relatively high storage capacities of fuel, carbon dioxide, and water in the blood and tissue compartments, lends credence to the oxygen choke concept. This was discussed in detail in earlier reports.

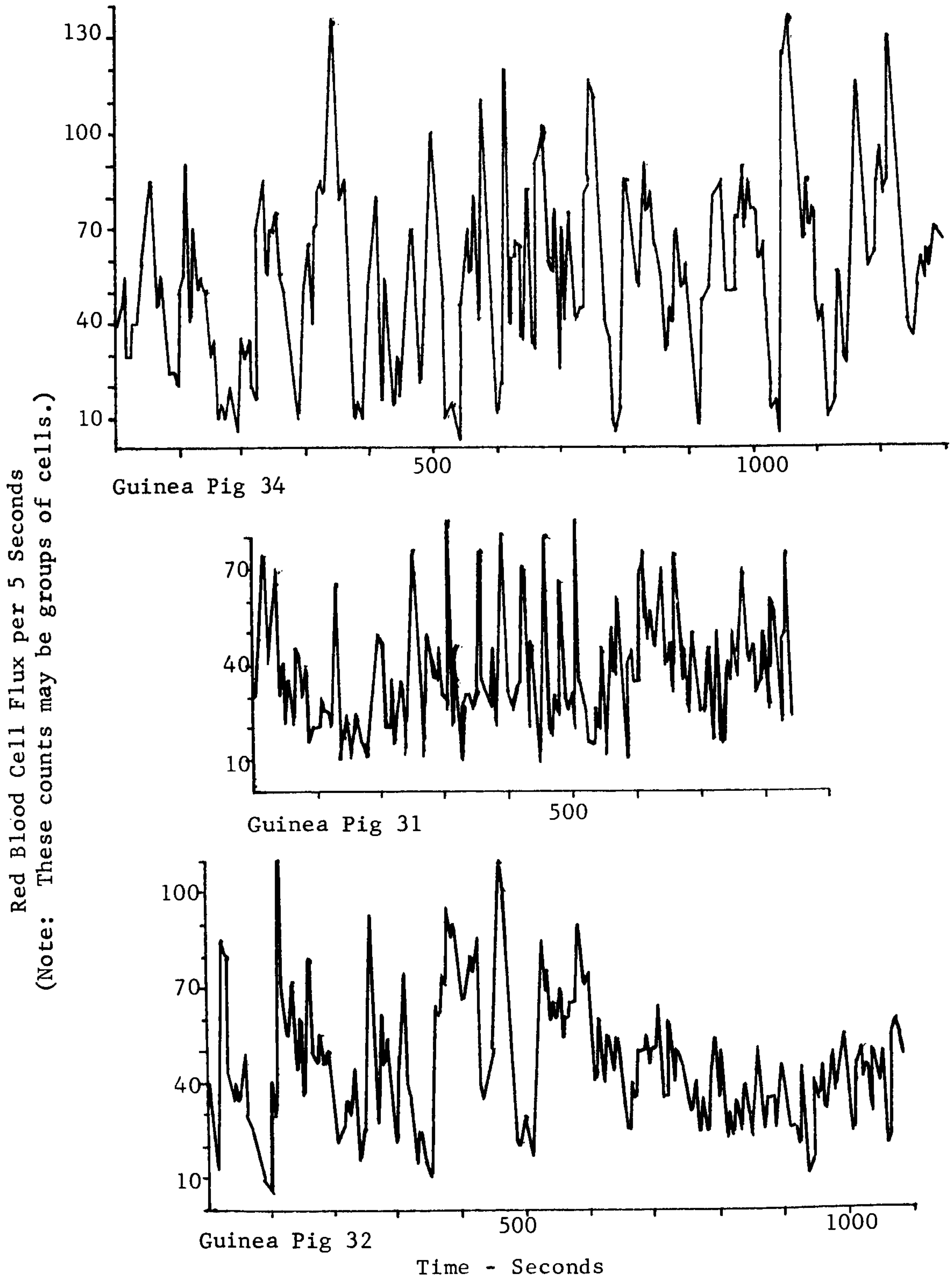

Figure 10. Variation in RBC Flow in Individual Skeletal Muscle (Quadriceps) Small Vessels in Unanesthetized, Unrestrained Guinea Pigs

The reality of oscillatory flow of red blood cells in skeletal muscle small vessels suggests that the concept of vasomotion may consist of oscillatory blood cell flow as well as, or in place of a more infrequent alternate opening and closing of individual capillaries. We have observed small vessels in the frog mesentery, rat lung, and guinea pig muscle. Specific mechanical opening and closing of the capillary per se, has not been observed, but rather a fluctuating flow. Mechanical opening and closing implies an all or none flow since the extent of capillary patency required for passage of one cell would be the same as for 100 cells. The periods of zero flow observed in our experiments exhibited extremely short durations. Apparently, some other mechanism for regulation of red cell flow, possibly electrical, in nature and possibly mediated by a hormone or hormonal group affects the capillaries and arterioles.

Comparison of the present mammalian results with the earlier data on the frog shows approximately similar frequencies in microcirculation red cell flow. The greater amplitudes in the frog mesentery may have been partially caused by the extreme damage involved in the externalized preparation. High light intensities and restraint and confinement have been found to influence blood flow in some tissues.

Summary

The rate of red blood cell flow in skeletal muscle small vessels (15μ) of the unanesthetized, unrestrained, quiescent guinea pig was found to range from 1-28 cells per second, with a mean of 10 cells per second. Experimental observations were such that the individual cells could not be definitely separated. The numbers possibly represent groups of cells.

The flow was oscillatory with frequencies of 10-15, 30-60, 100-140 and 300 seconds, generally, an inverse relationship existed between cycle frequency and amplitude.

A comparison was made with previous studies on the frog mesentery. Implications to the general concepts of heat production, and microcirculatory dynamics are briefly discussed.

Many aspects of the experiments require further improvement. It will be necessary to resolve segments of small vessels in the 5-10 micron - capillary size, to find better means of viewing through windows, and to develop better means for holding blood cells in adequate focus.

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D. DYNAMIC REGULATION OF BODY WEIGHT

A three day weight cycle reflecting a three day water balance cycle was first reported by Iberall (1) and discussed in (2), based on results in two individuals, a male and a female.

Similar cycles can be seen in data of Newburgh (3) (in an experiment in which he demonstrated transient imbalances between food intake and weight).

The suggestion was made in (1) that this cycle represents a water balance process likely regulated by hormonal processes. It is considered probable that psychological factors may exert an influence. Thus, continued study of this cycle is warranted in connection with both these aspects of the program.

The studies have continued with weight data being collected on nine subjects under physiologically and socially normal conditions. The objective is to determine whether the cycle occurs in humans and mammals generally, and what its characteristics and variability may be.

The subjects are members of our laboratory staff including one female and eight males, ages 21 to 50 and one adolescent female, 17 years old, ranging in average weights from 130 to 250 lbs. They are weighed every morning, weekends excluded, at approximately the same time, on a Fairbanks-Morse scale, Code 1204, with a three pound beam accurate to 0.25 oz., or approximately 0.02 lbs. The subjects are weighed to the nearest 0.5 oz., with shoes, jackets, ties, belts, and pocket contents removed. The experiment has been under way for three months; the results herein reported are for seventy four days.

Results

The results are summarized in Table VII.

Discussion

A clear cyclicality is found with periods of about 3.5 days with variations in amplitude ranging from 0.5 to 2.75 lbs. per cycle. There is indication of a 10-12 day cycle but more data is required to definitely establish this. The daily variation in some subjects was occasionally greater than the variation in amplitude of the three-four day cycle.

The overall weight changes during the three month period were nominal, approximately three to ten pounds. The general drift downward is possibly due to seasonal changes in going from cool to hotter weather. The test period has been March 29th to June 10th. Three of the subjects, AI, BH and ME are attempting to lose weight.

TABLE VII. VARIATIONS IN BODY WEIGHT OF HUMANS

Subject	Duration of Test	Range of Daily Change, Lb.	Overall Change, Lbs. Start-Present	Cycle Freq-uencies Days	Amplitude per cycle Range Lbs.	% Variation	Age	Weight Range Lbs.
AI M	74 days	0.1-2.2	-2.2	approx. 4	0.75-2.40	.35-1.1	48	216-223
SC M	74	0.25-2.5	-0.75	3.6	0.50-2.25	.3-1.0	47	228-235
ME M	74	0.25-2.0	-8	3.7	0.50-2.0	.2-0.8	40	245-254
TJ M	74	0.15-1.75	-2.7	3.7	0.50-2.0	.25-1.0	36	173-181
DY M	74	0.20-2.5	-0.5	3.6	0.50-2.5	.3-1.5	35	166-170
FP M	74	0.10-1.75	-1.7	3.6	0.50-2.0	.35-1.5	21	133-137
WB M	74	0.0-2.0	-1.5	3.5	0.50-2.5	.35-1.8	35	139-143
BH F	74	0.25-3.0	-2.8	3.6	0.75-2.75	0.5-1.8	50	150-158
TI F	43	0-1.70	-6.3	3.5	0.5-2.5	.35-1.8	17	136-144

The weight changes in one female shows marked variations around the menstrual period. A sharp drop of several pounds occurs within one day after the start of the menses with recovery in the next one to four days to the pre-menstrual level. Since data on only two females are included for this study, it is premature to draw conclusions. It would be most interesting to have data on a larger number of females over a greater age range.

One of the subjects, DY, exercises seriously and regularly; this apparently has not affected the cycles or their amplitudes (see Figure 11).

Indications that body weight may be cyclic in other mammals than man, may be seen in the work of Richter (4). Daily spontaneous running activity of normal male and female rats and food and water intake were determined. An approximate 3 day cycle is apparent in both food and water intake, in both sexes, with amplitude variations of approximately 6-10%. Body weight was recorded at 10 day intervals thus making it impossible to detect higher frequency cycles.

Similar results were noted for a rat with a sectioned bile duct. The ad lib water and food intake shows a 3.7 day cycle with variations in amplitude of 25 and 20%, respectively.

The 3-4 day ad lib food and water intake cycle is present in practically all the data in Richter. Despite this, the author concluded that any marked cyclic manifestation indicates the presence of a disturbance since a perfectly healthy, well integrated subject would not show any fluctuations in somatic or mental functions. This is contrary to our findings and to those in his own work.

One of his experiments merits special consideration. The food and water intake in a thyroidectomized animal shows an approximate three day cycle. The absence of daily body weight data is frustrating and exasperating. However, in (1), it was suggested that the thyroid hormones may be involved in the water balance cycle, and be reflected in the weight cycle. If this were true one might expect absence of thyroid to result in alteration or disappearance of the water balance cycle. Yet the water and food intake cycle apparently continued. To test the thyroid effect further, we have initiated an experiment on body weight in normal and thyroidectomized guinea pigs. Results will be reported later.

Ultimately, the objective of this program will be to determine the effects of disturbances, hormonal and psychological, on this cycle. In this way, it may be possible to determine what the physiological regulating mechanism is for body weight. If successful it may lead to a rational approach to weight control which appears to be lacking at present.

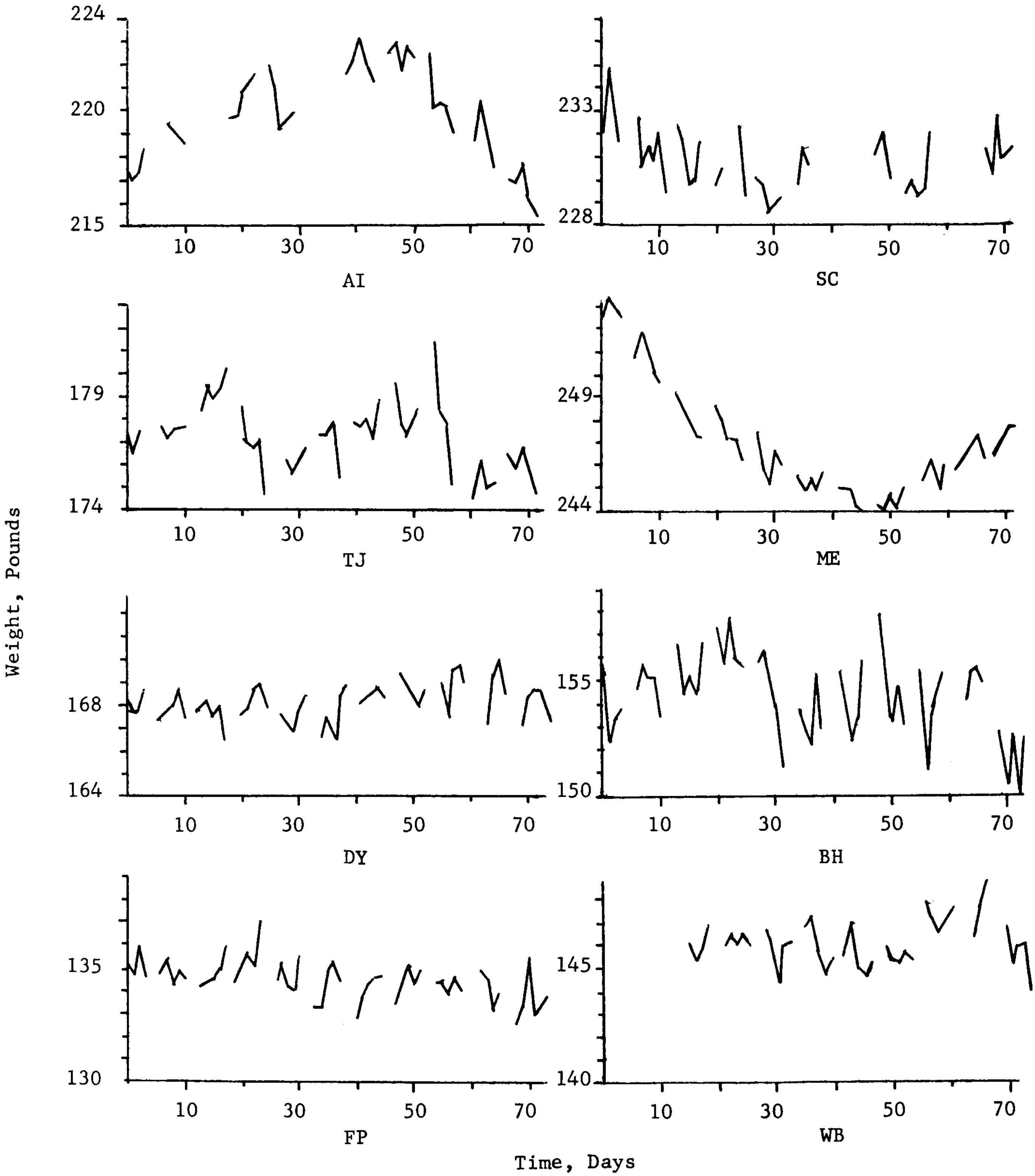

Figure 11. Cyclicality in Body Weight in Humans

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E. THE SHUNT MICROANALYZER

Introduction

We have undertaken the development of a 'window' into the blood system in the form of an external viewing 'cell,' permanently implanted as a blood shunt. It permits extracorporeal transit of normal, physiologically undisturbed blood and functions as an anastomatic junction, utilizing only a small percentage of the femoral or brachial arterial flow.

This technique permits application of electronic monitoring and spectrophotometric study of normal blood and its constituents during the circulation shunt from artery through cell and return to artery.

The system is particularly useful for the quantitative estimation of physiological systems and biorhythms during normal activity and stress situations. It can serve as a comparative analytic tool of normal versus abnormal for diagnostic purposes as well as prognostication of phantom or latent disorders as manifested in the circulating blood.

It is to be designed for use in the unanesthetized, unrestrained, freely roaming animal and will, in time, monitor oxygen, carbon dioxide, sugar, hormones, and other biochemicals in their dynamic chains.

Methods and Results

To date, experiments have been performed on 18 guinea pigs and 3 rabbits, to evaluate the approaches and techniques that will lead to a long life efficacy for a microanalyzer shunt.

Heparinized animals were anesthetized with Nembutal, 33 mg/kg, I.P. and prepared using sterile technique.

A branch of the femoral or brachial artery was catheterized using silicone tubing or siliconized polyethylene tubing. The efferent tip was inserted against the direction of blood flow, doubly sutured in place and externalized in a circular loop such that the afferent end was reinserted in the same vessel, in the direction of blood flow; approximately 10 mm distal to the efferent junction. The cross-over point of efferent and afferent catheter ends was sutured together for support and anchored to surrounding muscular tissue. This permitted maximal support of the externalized shunt with minimal distortion of the normal vessel pathway or normal blood circulation.

Care was exerted to compensate for the transition from the supine operative position to the normal upright stance assumed by the animal post-operatively, to avoid the problem of catheter flexion and subsequent obstruction of flow. Antibiotics were administered prophylactically and therapeutically for several days.

Venous catheterization was not attempted, at this time, because of the more complex difficulties due to the thinner, amuscular walls.

The preparations remained patent and viable for up to 7 weeks when the shunt was imbedded subcutaneously. Completely externalized shunts functioned for considerably shorter duration. All the experimental animals died due to clotting and/or infection, with survival rates varying from 3 days to several weeks.

Studies of the cell design included square, round and oval shapes, with clear plastic sides of various materials, for direct viewing, and sealed by bolts, screws, glue, etc.

The current microanalyzer cell is modelled of medical grade silicone, with optically clear top and bottom surfaces, with a central cigar-shaped passage for normal flow. A thinner by pass crosses the cell to permit unicellular transit of red blood cells for spectrophotometric or microscopic examinations. The cell thickness is approximately 2 mm to allow for insertion of the appropriate electrode sensors for investigation of various parameters, i.e., oxygen, carbon dioxide, sugar, hormones, pulse rate, etc.

The cells are tested prior to use to assure smooth, contiguous interior surfaces, to eliminate foci for eddying and blood stasis with subsequent coagulation. Cell leak tightness is tested with 65-75 mm Hg pressure overnight to ascertain effect of prolonged exposure to arterial pressure pulses.

Discussion

The red blood cells did not settle appreciably towards the periphery of the microanalyzer cell, indicating that vascular homogeneity was apparently maintained during patency. The absence of settling was at least partially due to the finish and contiguity of the inner surfaces, since minor changes resulted in varying degrees of stasis and vortical flow.

Several disturbing factors complicated the problem of shunt cell viability. The temperature differential due to externalization appeared to have an adverse effect, as well as the sudden change in velocity of fluid flow in the mid-section of the cell. Contributory disturbing influences were the variations in numbers, sizes and rates of flow of red blood cells which, apparently, caused some degree of turbidity.

Almost invariably, failure was due to either clotting and/or infection. Further work is in progress.

Experimental evidence has unquestionably linked stressors with altered physiologic functions, such that blood defects and performance capabilities are altered even though overt or grossly observable incapacitation did not yet occur. In addition, stressors can cause subtle changes in circulating constituents which become apparent by re-exposure to the same or another stress situation or body insult.

The evidence indicates that the compensatory and homeokinetic mechanisms of the body are affected, with the changes manifested in the blood system. Impaired pulmonary function or ventilation are also reflected in the circulating oxygen-carbon dioxide system.

The shunt microanalyzer could provide a rapid, ready technique for analysis of the physical and chemical parameters and constituents in the circulating blood.

IV. HUMAN BEHAVIOR

A. S. Iberall

A. SPECULATIVE MODELLING

This study (1) has created a new physical view of the biological system that should have its greatest immediate impact on physiology and more remotely on clinical medical practice. As physically oriented biophysics, it should not be different than the impact that chemical physics, as a foundation drawn from theoretical physics, had on physical chemistry or chemical thermodynamics. The degree to which the physiological-psychological complex known as the human has been modelled so far may be noted by inspection of the previous work (1). This report will continue the modelling.

In essence, the human biological system may be represented as an intermittently self-actuated powered system with an internal computer and accessory systems which reacts with its internal environment to sustain the chemical reaction sugar plus oxygen reacts to form carbon dioxide plus water over a long use life. There are many biological systems, and some mechanistic systems, which perform or are capable of performing the same function. Thus it is necessary to define the systems and means by which the human in particular performs this function.

(Though physical scientists may easily marvel in their large view of the biological system, its intricate development and enfolding, and its range that includes the concept of morality and religion, it is nevertheless necessary to undertake the task of explaining the detailed actions of the system. These different views are not in conflict and they should not be mixed.)

The problem of reproduction, or replication is an important one, from the biological point of view. However, the present concern is to describe the operation and functions of the existing generation, not how the existing generation replicates the next generation.

What is it that the newborn human infant can do? It has enfolded from a variety of coded elements - genes - which gave it a characteristic human form, with various internal systems, and capability of further maturational development. If growth takes place, certain other systems and system characteristics will emerge. If the environment has a valid range, a rather specific growth, maturation, and behavioral pattern will emerge. Yet all of the details are not established with great finality. For example, if the child is exposed to any of a great number of hostile environments, it dies.

All of these things are evidences of linear instability. (If one recalls Newton's first law - "A body in motion or rest remains in a state of constant motion or rest unless acted upon by an external force," it is clear that the infant is not a simple stable system that decays to a state of constant motion. Forces must be brought into play, dynamically.)

Now, a mechanistic system could be started from an assembly line with a complex learning computer so that its future behavior would depend on the course of environment that the system experienced. Thus what next happens to the child is not so remarkable, unless thought is given to the following subtlety. The mechanistic system would not have a very large repertoire. One would find that it develops a small series of common reaction patterns, and really has a limited capability for dealing with the environment. The faults in the machine that made it would tend more nearly to be replicated from generation to generation. (There would be diffusion into each new environment, but a similarity of pattern would emerge in similar environments.)

What of the human child? It has nearly no capability for dealing with the environment. Without a mother or mothering surrogate, the infant dies. How can such a system survive, and develop such a far-reaching viability? The essential element, it would seem, is instability. <u>The human is essentially an unstable system which reacts to increase its instability unless it acts upon a satisfying input in its milieu</u>.

(It is self-satisfying to arrive at such a central hypothetical concept for the human brain. However, it would be foolish to claim that it is meant to be completely original. Here it has been 'discovered' from a physical scientific point of view. It may have been enunciated by many other scientists from some other point of view.

A particular source from which this concept grew in the author's mind was the thought expressed during a Wright Brothers lecture a decade ago, by C. Draper, that the important step taken by the Wright brothers was not the development of aerodynamics, which would rightfully be traced back if desired to Da Vinci, and certainly received extensive development in the decade before the Wright brothers, but the appreciation that the airplane was not to be constructed as an aerodynamically stable system. All builders before had tried this. The Wright brothers built an essentially unstable system. It was the human pilot who manipulated the control characteristic response to disturbance to determine the relative stability of the system.

This concept, in the first place, helped change the author's view of feedback control, and provided a clue for the non-linear foundation for control theory. This idea has undergone further development until it has presently emerged as a foundation for behavior.)

The infant, as an introductory illustration, shows a build up of instability in the totality of elements that it can 'cortically' control. This may be viewed as 'anxiety'. (Its reality can be noted in a key remark of Anna Freud's (4), "Above all, to rid the child of anxiety proved an impossible task"). The saturation of this stage, in the case of no satiation of needs, is a euphoria, in that the anxiety state cannot be sustained. These elements - instability, anxiety, euphoria, relaxational phases - represent the functional themes that arise over and over again, and is thus representative of the kind of system that is in operation.

It is clear that the infant is dependent on the mother or mother surrogate (4, 5, 6). What does the infant gain from the mother? To use a catch phrase - it gains the knowledge on 'which way is up', and these early lessons are what the forthcoming adult keeps coming back to all the time, whenever consistency of interrelations in the total milieu is in question. (The total milieu will mean both the exterior and interior milieu that lies outside of the command and control centers. For mechanisms, it likely includes the regulatory centers of hypothalamus and pituitary, and includes many other portions of the mid-brain. However, this will not be discussed at this time).

In infancy, the cohesive interfacial input content that the mother makes available is food-water, anal-genital cleansing, warmth, and not much later an interpersonal coordination of play. (In an unpublished document "Philosophy for Mid-Twentieth Century", it was proposed that the evidence from which one might infer that the human brain is a computer, is the leisure time activities of sports, arts, and sciences as representing a 'spinning of the wheels', a continued practice of useful activities even without immediate need. It now appears, more fundamentally that such 'play' activity begins almost at the beginning for serious reasons. The mother-child 'play' at coordinate games. These involve

in pre-athletics - how to do things 'physically', involving motor activities

in pre-science - how to do things 'mentally', involving internal computer activity on 'real' referents

in pre-arts - how to do things that are not necessities, involving attention getting and internal computation, on referents of indeterminate status

and represent practice for the next moment, i.e., development and practice of a repertoire).

The mother thus forces on the infant both fulfillment of current needs and practice for future needs. It is clear that the mother does not have an extensive repertoire.

(The mother, whether primate or cat, as illustration, spends a considerable amount of time in body grooming, in the human,in body washing. The cat continues this kind of grooming, by self-licking, throughout life. However, how limited the mother's repertoire is, is well borne out by the incident in (6) where the solicitous mother-chimp has no other course for a sick offspring than offering the breast or licking, or cradling.

There is obviously a higher development of the human. In social organization, past a certain point - not in very primitive societies - the human mother has two other choices. She can manipulate artificial devices - treatment with medicines from the surroundings, or with surgical aids from the surroundings. She can seek out a more skilled human manipulator - a doctoring one, who can manipulate with greater skill).

The essential elements in the repertoire remain; reception of signals, undefined interpersonal attachment to the infant, memory of a repertoire, internal computer manipulation and external motor manipulation. However, the drive, even in the mother's case is the same unstable 'anxiety', seeking a means of discharge so as to obtain a 'satisfactory' state. The 'satisfactory' state is what has been learned by the mother as 'which way is up', i.e., the circle is completed back to infancy.

The infant itself has only the cues of activity, touch, sight and sound to go over at the beginning. Later on he will add a number of internal languages, starting first from the autistic, and then including dreams and various symbolic languages.

Now 'which way is up' is not highly consistent with all of physical reality, nor does it possess the greatest survival value. One must surmise that for the species or line or type that does survive, there is a considerable selection process that weeds out those who do not choose courses of great survival values. Thus, one would expect, similar to the Boltzmann theorem, that a convergence takes place toward an equilibrium population whose mother-infant teachings have high or optimal survival value, and that as a result, the existing population in any ecological region and era tend to be ergodic (i.e., the individual behaves much like the average of the population).

At the present time, it is not possible to name with certainty the apt selection elements that will account for the rapidity of convergence toward the population means. (One would suspect that the great flaring instabilities of new-infancy, and of adolescent sexuality represent two of the most potent drives to learning 'which way is up').

This view of highly non-linear instability suggests that none of the stabilizing influences - essentially linear - such as the integrative terms of memory and experience are sufficient to run the human. A <u>human by itself, acted upon by limited inputs - in particular inputs poor in human-like 'interpersonal' relations - will drift off toward 'unrealistic' behavior</u>. The human must be used by and used for humans.

One of the factors that lent impetus to seek out this program was the problem, (conceived in 1950 while monitoring pressure suits for the U.S. Navy), of man confined for considerable periods in pressure-space suits. Psychological help was sought but without much success. It was not considered serious at that time. Now, a decade or more later, it has again come to the fore. For example, in our suit development work, subjects were kept in as long as 24 hours, in extremely painful and trying situations during developmental fitting. Yet as long as the subjects were involved 'lovingly' in the problem, they could endure any torture. As pointed out in (5) emphasizing a whole range of affectional systems as a binding force in monkey and man, it calls attention to "the importance of ... affection as ... a leading .. social mechanism has been recognized ... long ... credit for focusing scientific attention on love belongs to Sigmund Freud ... His dogged persistence in publicizing ... love as the socializing force in human behavior left an indelible imprint ..."). However, the basic course of action is an unstable system of building up the tensions of anxiety, and then intermittently discharging them in a 'satisfying' way. This process develops into a fairly regular relaxation oscillator system, that persists as a fundamental non-linear dynamic regulator of human behavior.

However, a priori fortuitous, it represents the same course of action of practically all internal physiological systems.

A speculative dialogue is continued partially inspired by the last report (1) and partly by new ideas that have accrued as a result of scanning cybernetic literature and related material for a report on the information sciences (3).

The essence of human behavior is that it only knows 'which side is up' when it is constantly being pulled in many directions (i.e., its gain at zero frequency is undeterminate, namely the system is unstable at rest). In infancy, the mother and the learning to satisfy elementary needs is sufficient. Later, through most of life, the family relation is fairly adequate. However, if an individual divorces from society, he becomes almost unbalanced. Thus the system is nearly unstable, and responds mainly to derivatives and impulses.

The keying cues must be similar to those in the eye. The eye shows a series of saccadian motions, a continuous near-Brownian-like motion, measured in one case one morning as 1.6 saccads per second. If one tries to concentrate on an immobile eye position, the eye rolls off. Thus the eye 'positions' are so discretized. Is this how all systems work? Provisionally the reply is yes.

There must be a large cueing sensitivity that the body has to all sorts of input signals - visual, smell, temperature. (Under these circumstances, the hypothetical thesis proposed in (1) that there may be high temperature sensitivity in the hypothalamus - from the in-out nasal air passage has increased merit. However the same passage can also provide high 'smell' sensitivity. There is reason to pay attention to the thought that Dr. Elliot Hague voiced in private communication that in a long sustained search for the observations and mechanisms of photoperiodicity in mammals he has found the pineal body to be worth some consideration).

The ever present cues give rise to the ever present input signals that continue to excite such things as the saccadian drives.

The net effect is the continued relaxation oscillator type of action, of mechanism on top of mechanism, each with different flexible timing phases, and different discharge signals. Thus one oscillator may be shut down in dark or warmth or when free of smell, etc., yet there still remains a relaxation spectrum with some longer time constant, perhaps governed by a refractory period such as fatigue. Any particular action may show a large warbling frequency spectrum involving many disturbing causalities and phase shifts. In the absence of inputs, it may either verge toward longer time cyclic instability, sometimes viewed as 'free-running', or it may show a sustained spectrum. In a human, an unrelieved anxiety spectrum that builds up may be free running as a near aperiodic break-down to a catatonic state, which responds very nearly to external cues, using only internal ones. This may help explain why the human makes such little progress. So much effort must be expended to keep straight up. This is the price humans pay for an unstable system which is highly viable. Thus one may conclude that the human system is basically dynamically regulated by the voluntary system, the involuntary system is only used as an adjunct.

(Before this is rejected out of hand, consider the following question. Is anyone prepared to state what the operation of a human will be when involuntarily confined to a livable position - namely lying on the back, with no light, noise, smell, temperature change, but with sustained IV feeding, etc. We would venture the guess that such a condition would cause serious difficulties because of the absence of what appears to be fundamental for human life, the drive for voluntary motor-enervated action and manipulation.)

The system is basically a motor-enervated system in which electrochemical 'anxiety' builds up in the nervous system until it is discharged by motor actuation in 'satisfying' learned or maturation modes.

This mechanism is now proposed at every level - from the 10 cps nervous level, to the 10 cps neuro-muscular vibration level, to the few cps red blood cell jitter in the capillary, to the 1 cps heart beat, to the 1-2 cps eye saccad, on up to the circadian rhythm, the three day water retention cycle, the near three day sex urge cycle, to the menstrual cycle, to plant growth cycles, moulting cycles, etc., on up to that one single relaxation 'oscillation' that represents the entire life period. (Another source who independently has been collecting data for a long time illustrating these relaxation oscillations is Richter (2).)

What is fundamental is that the 'pressure' that is built up in the timing phase is irresistable, and it is only a suitable motor activated outlet that must be found to discharge. Thus the instability is real and must lead either to sustained oscillation or to catastrophic breakdown.

(There is no wish to overdramatize the issue. The reason that every system doesn't break down in one episode of oscillations is usually because there is a cascade of buildup and discharge systems. It is only in a limited number of cases that only a single discharge system is available).

It is likely then that all of the body regulation has this voluntary character.

(There is an interesting point involved here. When we presented our first thermoregulation paper at an ASME meeting, Benzinger pointed out that the sustained respiratory and thermal cycles which had been found were a good illustration of Pavlovian response. We rejected this thought as missing the point of the work which showed a sustained limit cycle in the human with no apparent 'voluntary' control. This view is still held. However, while the spectrum showed is believed to be characteristic of the voluntary human in a 5 hour resting state, it is no longer so certain what the response would be of a human who has had a much widely different motor-enervation course. Thus the operating physics of the system is a description of operation in a particular milieu of past environmental conditions and experiences both for the individual and the group. It seems perfectly valid to grant that the 'involuntary' systems seem to have a much greater permanency in the group; but not to consider the possibility of change in the group also would be fatal. For example, if a few successive entire generations had to constantly chase up and down stairs rapidly all their lives, one might suspect to find some changes in the progeny they produced - by selection).

This is not proposed as a nonsensical picture of the involuntary system. It simply represents a system with indeterminate 'gain' at zero frequency. The system is unstable in a quiescent milieu and will hurl itself into action to seek out a more 'satisfactory' state.

Thus we believe we can undertake to build a motor-enervated simulating model (MESM) by building suitable unstable systems to represent its physiology and by endowing it with an elementary Freudian guiding algorithm also based on suitable unstable systems to represent its psychology. The tentative feeling is that while many of the individuals so built would be catastrophically destroyed (namely, it is not visualized that they be provided with sufficient memory banks and learning capability) their mean action would represent normal 'human' or 'rat-like' neurotic behavior. Furthermore, while much of the action would be harsh, all of its failings would be minor to its instructiveness, and that it would furnish the basis for extended development.

It may be interesting to inquire what detailed ways humans, or higher biological species, use to achieve smoother quality of performance.

Out of the work in attempting to elucidate and determine the energetics and control of the muscle complex as a motor system, and the operation of the vascular system, a glimmer was seen.

It must be noted that there are three kinds of information flow interfaces in the body. First there are the localized ones such as eye vision, nose smell, aural hearing, oro-nasal temperature; second there are the surface ones such as temperature, radiation, pressure, chemical fluxes including water; third there are the body ones such as body forces illustrated by gravity, and motional concomitants of acceleration, velocity and displacement.

There are likely a number of maps of the entire system imprinted in the brain. Consider some of the candidates.

1. Temperature - if one closes ones eyes, one is aware of surface temperatures of the body (at the present, the issues will not be raised whether these are cold or warm sensitivities), and quite aware of very subtle gradients. It is not impossible that this grades over to a learned extreme awareness of certain 'lumped' temperatures, namely the hands and feet temperature and the breathing passage temperature. One should note the breathing passage temperature gives a sustained 'error' signal of A.C. form of near 1 per 4 seconds to compare ambient temperature with the regulated deep body temperature. Thus even if the others were D.C., or slow A.C. or even aperiodic, this is one pressing A.C. signal that is always available. We have argued in the past and demonstrated that 'comfort' states of the human are associated with sensing of temperature of the extremities (see (1) Part 2, Ref. (1)) and the maintenance of a certain uniformity of temperature over the body. (Work not reported in these references was done on bathroom shower controls, where the psychological difference of response of different people, typically females, to gradients in wall temperature could be demonstrated, but by a particular temperature maneuver, these initial sensitivities could be wiped out, as 'hysteresis' in a mechanical sense, and then the same comfort temperature sensitivity of all humans shown. The data on water immersion sensitivity was consistent with the much more difficult to achieve measures of air immersion sensitivity. The optimal surface temperatures are not the same in the two cases but the heat losses are much more nearly so). Furthermore, we have been impressed by a neglected study by Jenkins (see (1), Part 2, Ref. (3)) that demonstrated detailed mapping of the temperature sensing taking place at the skin.

How this maps into the brain, is not known to us at present. However, it is quite obvious that this represents one view of 'up' and 'down', and that the mother, in the body warmth, huddling response that is certainly associated with breast feeding (see (5) or (6) for typical primate pictures), or, in modern form, in the endless preoccupation in the nursery with swaddling clothes and blankets and temperature. (One may consult a picture of the swaddled child in a recent popular piece of folklore, "How to be a Jewish Mother," to sense the mother anxiety).

However, it is equally clear that the motor-enervation is not purely psychological but mother-learned from the differences in response patterns in later life to warm-cold paths. This is not to say that there are no physiological drives but it certainly is true that there is 'adaption' of a psychological nature to temperatures as far-ranging as the nearly nude Indian at the tip of South America to near-zero (^{o}C) temperatures to the highly covered Bedouin at near-45^{o}C. The resultant is somewhat 'amazing', for whatever the temperature, the 'psychological' adaption is to an average activity pattern that only represents a moderate increase of metabolism over quiescent metabolism. (i.e., the kind of courses that Scholander and others have shown for various Arctic animals or small animals, or that have been discussed in (1)). Other 'normal' individual behavior is then represented by a moderate twinkling performance around that mean pattern.

This suggests that there are optimal living strategies, consistent with the involuntary systems, by which the voluntary systems produce a regulation out of the dynamic instability. At the present point, the issue is that it seems to be taught by the mother to the infant for the existing milieu.

Assuming this is true for a moment, the valid question might be what is the time scale for such meaningful learning? Is it the individual infant - fraction of the life-span, or is it the seven (or five?) generations to make a gentleman? The best guess is based on the number found in a study on technological forecasting (3), taken from a 1937 report on Technological Trends and National Policy that showed a mean time delay at the beginning of the 20th Century of about 175 years from the first voicing of an idea to its first meaningful investigation. In "Philosophy for Mid-Twentieth Century Man" on the other hand, it was estimated that there is a likely delay of about 2000 years between the first significant voicings of a humanly important 'moral' idea and its first significant applications. These numbers 200-2000 years are not that far apart in providing a measure of the time delay in the introduction of 'ideas' or 'behavioral' techniques to the human biological species.

Thus the optimalization of a behavioral pattern which mother transmits to infant is not a rapidly changing thing even for the human species. The temperature mapping in the brain, or the portion representing extremity temperatures, or the portion representing the A.C. oro-nasal temperature signalling is relatively slow changing from generation to generation, and is used in a fairly subtle fashion to guide behavior.

2. Neuromuscular awareness. This grades over from a surface awareness, to a volume awareness, to the awareness in certain lumped elements such as the auditory, the vestibular, and the kinesthetic. One should start from the observation, highlighted in (1) Part 1, and Part 5, that the muscles are in a <u>sustained state of microvibration, which by itself provides little or no return signal, but which, upon the slightest amount of movement, provides an A.C. limning of the body movement.</u>

3. Neurohumoral awareness. This also grades from a surface awareness to a volume awareness. The mechanism, we propose for tentative consideration, is the movement of fluids, such as in superficial capillaries or other tissues, by which sufficient pressure change is pumped around - relative to the high mean central pressure, particularly in the vicinity of arterioles, see (1) Part 5 for suggestive sources as to the change of mean pressure within the microcirculation - to create afferent signals as to changes in the capillary supply system. According to this model, the capillaries could be doubly used, once afferently to provide hydraulic signals of mechanical leads near muscle masses, and second to be controlled efferently so as to become the

oxygen choke to the muscles. (It is fascinating, in CLASSICS OF CARDIOLOGY, Vol. II, Dover 1961, to read the observations and techniques of Quincke, who long preceded Lewis, directly on the pulse in superficial capillary beds, to get an appreciation of the sensitivity of this hydraulic system to change). It is clear that a specialized A.C. awareness is provided throughout the system by the heartbeat, first to outline the entire system, but then by its changes, to limn the changing regions.

4. Neuro-chemical awareness. In an even more diffuse fashion there is likely a selective mapping of selective chemical signal at the body interfaces - in surface distributed form of the skin, of the internal stomach tube and respiratory tube, ranging from its lumped specialization at the mouth and nose, and in the lungs and stomach (selective partial pressure exchanges of membranes of gas components, and even water are illustrations), and of selective signals throughout the body volume at various organs.

5. Neural awareness. It is possible that the nervous system is itself limned in the mind.

6. Neuro-hormonal awareness. Finally the hormonal states may be mapped into the mind.

At this point, it is hard not to believe that the body is outlined in fuzzy fashion by at least a vector mapping into more than one region of the central nervous system, and that these mappings provide learned signals for the motor-enervation of the system according to certain undetermined optimalization principles.

7. There is then the more specialized awareness associated with the eye (extending the radiation-temperature sensing), the ear (extending neuromuscular sensing), and taste and smell (neuro-chemical sensing). These lumped elements provide various mappings of the exterior milieu with greater or lesser exactitude.

The suited motor manipulating responses that fit the changing patterns of these mappings is mostly what constitutes the content of behavior that the mother teaches the infant. From this the child learns 'which side is up'.

One may continue just one step afield and point out that here lies the beginning sources of the great philosophic abstractions that have confronted man for many thousands of years - truth, morality, beauty, etc.

'Truth' is to be discovered from the individual 'sense', and from the common 'sense' of these mappings. Objects fall down, fire burns, leaves soak up water, quinine cures malaria fever, are all observations that may so be determined. Alcoholic life shortens life, obesity shortens life, sewage in drinking water shortens life, individual rigid aggressiveness doesn't suit a community, common defense does, are observations that take much longer. (As the poet W.H. Auden said in a February 17, 1966, New York Review, book review," ... when one considers the behavior of large organized social groups throughout human history, this much is certain, it has been characterized neither by love nor by logic." Yet (5) points to the necessity of love or affection in primates. How are these to be reconciled? It is simple. For the optimalization of behavior for social groups in those ages in which the milieu and the technology does not permit relaxed easy behavior, competition is violent and vile in the group. Thus the more subtle 'truths' are discovered within the context of the milieu).

'Morality' can arise when the harshness of survival does not require an exhausting motor-enervation in search of optimal mapping patterns. Instead the system evolves cooperative endeavors, using each other or other objects as cooperative 'tools'.

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'Morality' or 'moral posture' is a strategy that utilizes the motor-enervation of the system, to manipulate its internal mappings into accordance with learned patterns, when its internal communications channels are not so loaded with motor-enervating signals because of a troublesome exterior (or interior) milieu that there is no spare computational capacity.

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The most promising thought to us, from a mechanistic view - just as the significance of electrical communications proceeding through the characteristics of the nerve synapse was viewed by others - is the added communications response that might be attributed to stretch-like receptors for every watery compartment, such as water involved near muscles, water in the capillary, etc. This provides a hydraulic actuator as a motor element and the basis of an electromechanical monitoring strain gage. Thus the body may be outlined twice by its internal water system - in the enervated motor system, the muscle, and in the distributing cardiovascular system.

Thus we accept for the present the vague picture that the body image is projected up into the brain in more than one way - possibly muscularly, humorally, hormone enzymatically, electrically, and chemically - that this creates a rather redundant, even though crude picture of the lower 'mind' and body imprinted in the mind, that sensory input then provides finer detail for control purposes, that all of this is fractured as a sequenced set of 'moments' (a concept that was well identified by John Stroud in 1958 in (7)), as in a moving picture. We have preferred to detail this idea by the concept of a 'posture' as a complex of systems that are coordinated into the moment, i.e., the body computer controls one posture per moment, it appears, by definition. (Stroud's moment lies in the 0.05 to 0.2 second range, which agrees with these ideas. For example, it does not appear that one can play more than 20 musical notes per second with any quality, a task as rapid as one can generally be called on to perform).

Thus we see a system that is constantly motor-enervated by its instability through the signals representing the difference between an 'ego ideal' imprint of the body mappings and the actual body mappings, in such a weighted summing response, that might be considered the 'libidinous' flux, to discharge the measure of cumulative flux by motor action, which is represented by a smooth change in posture from moment to moment, but whose learned repertoire consists of many orbital paths which the motor system locks into, by using a prerecorded 'analogue' for its input guidance signal. <u>The system is always in process of becoming more anxious.</u> This seems sufficient preparation to seek the experimental foundations for behavioral foundations of such a thesis.

(One may note the tracking in this program thus far.

1. In the first instant some rudimentary control idea of the system was sought.

2. Then an attempt was made to track it through the shadowy neurologically backed psychopathology of Freud.

3. Then a brief view of the actual neuroanatomical information was attempted.

4. Now we approach the behavioral-psychological view for confirmation of the modelling ideas).

B. EXPERIMENTAL PSYCHOLOGICAL VIEWS OF BEHAVIOR

For a start consider (4). Since the beginning of psychoanalysis, it was hoped that the preoccupation with the early happenings in life would make analysts experts on childhood. Attempts at application began after a few decades. It seemed feasible to attempt to remove many of the detrimental parental influences that seemed to be involved in adult neurotics by enlightening parents. Sexual enlightenment, permissiveness instead of authority, less compulsion in toilet training, demand feeding, etc., were some of the many easing techniques that were introduced. However it proved impossible to relieve children of anxiety. Parent attempts to reduce children's fear of them resulted in increased guilt feelings in the children - of their own conscience. In turn, if the severity of superego was reduced, children become most anxious, humans unprotected against the pressure of their own drives. It was true that children growing up under psychoanalytic education were different from earlier generations, but they were not freer from anxiety or conflicts, and thus not less neurotic. This wouldn't have come as a surprise if enthusiasm for clinical prevention had not triumphed over the strict application (and further scientific development) of psychoanalytic tenets. Neuroses cannot be prevented wholesale. The division into id, ego, and superego presents a psychic structure in which each part has its specific derivation, aims, and modes of functioning. "By definition, the various psychic agencies are at cross-purpose with each other, and thus gives rise to the inner discords and clashes ..."

(These remarks are some of the most pregnant in the history of human behavioral thought. No physical systems scientist can avoid the obvious description of system instability, and its internal build-up. Having recently come to understand the point, before reading Anna Freud, a review was begun of the behavior of people around us. They were asked to jot down the general psychological cast of their behavior. The most prominent thing found was a serial skipping from issue to issue, typically

sleep
food-hunger
anxiety
motor activity
anxiety
food-hunger
motor activity
euphoria (reading a newspaper to get away from problems)
anxiety

Such a moderate list, give or take a few items, was characteristic of daily 8-12 hours of behavior. The periods of anxiety were marked by a serial scanning of all of the problems around and building them up to an exhausting tension. Periods of euphoria were marked by an exhaustion which sought relief, by attempting to focus attention, i.e., be driven by some external irrelevant cues.

This is illustrative of the hours structure of behavior; in addition there are the more fleeting moments of behavior, and certainly the longer periods of behavior. However the cascading waves of anxiety and euphoria, of motor activity, and of sleep, make up the predominant structure of behavior.

That a learned guiding algorithm, a 'super-ego', exists also seems to be beyond question. Thus 'psychological' determined behavior must be quite real and localized in the brain. This statement is not made fatuously. What it says is that such a prominent Freudian, as Anna Freud, out of a profound amount of experimental experience with children, and with adequate motivating to present psychoanalytic teaching and education in most favorable light concluded that

1. A child with parental guidance; i.e., well defined rules of behavior, grows up with anxiety.

2. A child with permissive parental guidance; i.e., external admiring rules of behavior, grows up with more anxiety, self generated.

3. A child with indifferent parental guidance; i.e., no guidance except purely by self, such as in divorced, or mutual hostile parents, or indifferent parents, etc., grows up with the greatest anxiety, all internally generated. The closest physical analogue, is a vortex sheet; the child curls all of his resources up into himself. The extreme case is schizophrenia.

This means instability. This means a learned guidance. This means an ability to track and schedule motor activities. This means developmental analogues. This means synchronization and replication. Q.E.D. The psychologist-psychiatrist has been right.

However, the task remains of convincing such people that the physcial scientist has mechanisms and concepts that may be able to help in understanding the system. This is why the concordance in concepts is necessary).

The first question that comes up is: What is the steady state of the brain in the face of cues? This is known. It must be the normal behavior with which one is surrounded. Then what is the steady state in the face of minimal cues? As one begins to formulate these ideas into an experimental program, it must be realized that it means no light cues, no temperature cues. (Thus even a 0.1 ^{o}C. difference between in and out breathing may be significant. Thus it may be necessary to use water baths at body temperature), no gravity cues, no pressure or muscular cues (these tend to be somewhat contradictory, because man is brought up in a gravity environment with various pressures, etc., and not as a free-floating form in some indeterminate space. Thus moderate minimal restraint is required. To many readers to whom all of these specifications may sound either foreign, irrelevant, or old hat because of the man-in-space program, one may now note that it was in such laboratory tests we were making in 1948-1950 in the interior of pressure suits that the background for such problems arose), etc.

One must speculate on the disorienting nature of such an environment (we were brought up with the vertigo of aircraft flight), the acute enhancement of cues, the possible degree to which internal operation would govern, the ideė fixe that the brain would take, the possibility of anxiety and terror states, and the nature of the ego ideal that the mind might latch on to.

It was found that such experiments had at least been begun in a very thorough way by Lilly (8).

Return now to the 'normally' operative individual, first by starting with (5). The Harlows make the following points:

1. Love or affection (interpersonal attachments) has long appeared to be a binding socializing force in humans. Freud may be credited for focusing scientific attention on such a force.

2. Freud's clinical studies led him to the aberrations produced by interference with the biological libidinal satisfying drives (i.e., 'libido' producing). The prominence of sexual deviations relatable to frustration or suppression of the biological sex drive led to the connotation of sex drive for libido, and much less to Freud's broader concept of a life force.

3. Cultural anthropologists have stressed satisfaction of the sex drive in theories of the origin of human societies. Field studies of social groups in which to test the sexual theory of social organization turned to

such simple groups as subhuman primates. They confirmed that sex was the key to primate social organization, and this theory flourished as late as 1960.

4. In 1961, baboon field work by Washburn and DeVore (9) showed little support for sexuality, but for interpersonal relations in social binding. Other pertinent primate data was to be noted in Jane Goodall's studies on chimpanzees (such as (6)); Schaller's studies on gorillas (10); or work at the U. of Wisconsin (11).

5. It appears that social learning and interpersonal relationships are needed to explain primate cohesiveness. Love is to be viewed as a series of affectional systems. In the rhesus monkey, they have identified five such systems, each which develop in a series of orderly stages.

6. "Anatomical and physiological characteristics underlying each system predispose the individual to react in particular ways, but the general capacity of the individual to learn with experience also plays an important part."

7. The affectional systems are

infant-mother
peer
heterosexual
material
paternal

They seem to fit in also with known human data.

8. Infant-mother. At birth, in monkeys, there appears to be a reflex to cling tenaciously to the mother and inch up until restrained (at the breast level.) Other reflexes orient the infant toward the nipple, to open its mouth, to grasp the nipple, and to suck. The first few weeks are primarily reflexive, voluntary action appear only later. Contact, per se, appears to be a primary factor, even superceding nursing. Ape babies are less mature and cannot cling as effectively, human babies have only a vestige of a clinging reflex.

In its second stage, there is an awkward range of voluntary motion - much later in higher primates. In the third stage, a stage of security is reached through a complex combination of maturation and learning. However its activities are motor oriented. Strange objects become fear objects, and the infant only relaxes when it contacts the mother. In the fourth stage, the infant is then emancipated from its mother some time after the first year of life (apes after 3-4 years, humans still later).

9. Peer affectional system. Infants with mothers or artificial mothers play quite vigorously during the first six months. If peer children have been associated from the first month of life, the animals seem socially normal. If they are isolated from their mothers for 4-8 months, their play

is then wary in contact and aggressive. When deferred 8 months, that group is more fearful and hostile, with these characteristics lasting even in the third year and probably permanent. If there is no mothering and peer experience in the first year, the animal is socially inadequate. If monkeys are isolated for 3 months from birth, there are no later scars; if for 6 months, the animal is fearful with only rudiments of play; if for 12 months, all potential for socialization is destroyed. The animal is fearful and lacking in aggression and play. In normal relations, there is speed and enthusiasm in the spread of contact in a group. Males and females associate early in life, but gradually separate; physiological differences then appear to make the male more active and aggressive and female sedentary and submissive.

10. Heterosexual affection. This system appears to develop out of the play of infants, which leads to an acceptance of body contact, a requirement for heterosexual activities. These monkeys show maturation of fear by 3 months, mild aggression by 6 months, and true aggression in the second year. If social experience is delayed, they may show both fear and hostility in later life. The heterosexual adjustment appears to require inhibition of fear and aggression with consequent acceptance of body contact.

Why, in mating, some potential partners are rejected and others accepted are questions not answered in the field studies. (One might presume that it is only Freudian explanations, related to specific characteristics of the early relations with mother and father that lend directions to the choice).

Human and subhuman primates cannot be separated on the basis of differences in the development of heterosexual behavior. In both, sex behavior has its origins in infancy and develops according to the restrictions imposed by social conditions in the culture.

11. Maternal affection. This also has its origins in infancy. Birth to a normal female sets in motion a sequence of behaviors that protects the helpless newborn. In the monkey, it is close attachment, and the mother will accept all infants. From a continuous attention for the first 3 months, dominated by cradling and holding, there is total acceptance with no punishment, and a gradual relaxing of hold as the infant gains control of movements.

In a second stage, after 3 months, the mother will reject other infants, and begin to punish her own, although she is positive and tender. The infant learns to anticipate rejecting responses and spends more time finding solace with its peers. Peer ties grow. The mother-child relation is the closest that a primate experiences in its lifetime.

Those infants raised with no mothers or social contacts - in the laboratory - become cruel or indifferent mothers. With second children, they become adequate mothers, as if socialized by contact with their first infants.

12. Paternal affection. The affection of young adult males for the young of their species has no special physiological circumstance, yet the

pattern exists. Generally there is a gentle, tolerant attitude of dominant males toward infants. Early social deprivation appears to be a factor in the abuse of the young.

(A physicist would have to infer from this description that the formative behavioral structure is Freudian. As has been surmised, it is a likely concomitant of the biological instability that certain standard instability motions - 'reflexes' contact clinging, head-hand-mouth motions, etc., lead in two directions. One, to implant into the brain a sequence of body images, and some 'libidinous' measure of what images are satisfactory - in which various physiological oscillator signals, concomitant to their regulating functions, make up the imprint; and two, to actuate the motor-enervated system into an action made up of 'postures' by 'moments', consisting of rapid alternations of posture and motion. The undiscovered elements are, the basis for memory - although memory by analogue is proposed - a systematic description of the location of memory banks and access thereto, and the nature and physical locations of the elements that make up the satisfying algorithm.

However, that behavior is made up of the interpersonal relations stressed by Sullivan, and the entire theoretical construction discussed in (1), Part 4. The present discussion represents further detailing of this model of orbital synchrony that was postulated for the biological system.

The child is ready for the mother and the mother for the child. Warmth, temperature, soft pressure, involved motor actuation, i.e., directed motor enervation that elicits satisfying responses, internal chemical secretions are the manipulated elements involved in the relation.

When this gross orbital synchronized pattern is broken by the mother rejecting it - likely for physiological reasons - in favor of a more open behavioral pattern, and the infant by the increased motor capability that can no longer be saturated or 'satisfied' by the limited mother-infant movement possibilities, the child is driven toward peer interactions. These mirror images of himself fit an unstable system. There is "speed and enthusiasm of their contact with one another ..." This is a description of an active system which is interacting by locking into all sorts of temporary orbits, i.e., there is 'play', there is 'practice'. However, the thing that is quite remarkable is how weak the orienting bonds are. It is only in pathological states, or in newly emerging states, that the bonds are 'intense'.

This might persist 'forever'. However there is a next maturation element, adolescence marked by sexuality. The 'playmate' orbit opens again, and this time looks on serious play for subsequent reproductive purposes. It appears clear that reproductive activity could begin anytime after the onset of this next phase instability. However, apparently in monkey, ape and man, social pressures in the particular group and culture determine a period of such boy-girl play until reproductive activity takes place. The birth of a child with its considerable endocrine involvement, and the socializing process of play among these young adults, then triggers the mother into a next orbital relation of mother-infant, and closes the circle. Where does the father come in? In this view, as seen experimentally, he has not yet come into clear focus. Here again the Freudian link must still be used as a hypothesis. There is an intense 'sexuality' involvement between the adult 'boy' and the adult 'girl'. Its foundation is still body contact, warmth, clinging response - and of course the intense pleasure focus of actual copulation - and infant memories. There still remains the more lumped intense pleasure centers of oral, genital and anal activity.

The configuration mother-infant-adult male 'father', or temporary consort is unstable. For an 'unknown' reason - possibly the childhood experience as the socializing influence - the adult male is not aggressive. He works out an orbit, the external ego image for the child. Human experience suggests that the orbit has the following advantage. It blends the mother's image of infant and male so as to focus attention, and involve minimal motor energy on the mother's part, and achieves the maximum attention in the competition on the father's part. Why monkeys are so tolerant, we do not know.

It was quite appropriate to have been told about a TV fragment from the night of February 14, 1966, in which a panelist asked a rather apparently well known person with extensive zoo experience whether it was possible to bring up different kinds of animals together, and he answered yes, with the use of ample affection and caressing.

One can hardly propose that this has modelled the complete psychodynamics of infancy and how the transform takes place to maturity. However we believe the rudimentary elements from a physical view are here.

To assist with a formal background it may be useful to provide a verbal structure into which a model may be fitted.

1. A complex biological system - at or near the human level - develops momentary postures out of his motor-enervated system.

2. These postures are drawn from a repertoire, which is rigidly learned.

3. The posture itself is made up of many posture set elements that are derived from the physiological system states determined by their regulating oscillators.

4. Some of the posture set elements are reflexive, established by genetically coded maturation elements. Others are established by socializing guidance and practice.

5. There is a projection of the regulating oscillators into the brain. These projections are organized loosely into a hierarchy of systems.

6. There is an internal computer and a memory. The computer uses an internal language, and has a guidance algorithm that is adaptively formed out of the social guidance and practice. The memory is mainly stored as

minute circulating analogues. It is obvious that our specification here is most weak, and purely conventional. It is this element that requires the greatest amount of improvement in description. However, for convenience, one might view the system as having pleasure and pain centers, that these are strategically embedded in the projection field of the oscillatory systems hierarchy, so that their sequential actuation or lack of actuation is what provides computational end points.

7. The socialization process, starting from birth, in the mother-infant phase, is a training of pattern by guiding reflexes and other maturation elements into satisfying repetitive patterns. The endless repetition of these elements gradually forms internal analogues for these actions in memory, and an internal computer language for describing the process by one-to-one correlation. The guide mechanisms seem to be the instability of internal anxiety and the discharging stabilizing effect of clinging and contact.

8. All of the systems used seem to exhibit the following kind of instability: if motor activity is held in abeyance or locked into a repetitive pattern, there is a slow buildup of an internal posture set that may be identified as anxiety. This is discharged by motor activity, which includes in its enervating feed-back loop - it is believed at this time, in this context, that there is a significant use of control functions, rather than simply dynamic regulating functions - an internal flux through the brain regions associated with the various body images. These initially shifting patterns are coordinated with the pleasure and pain centers.

9. Without guidance patterns, governed at first from the primitive 'painful' signals of hunger or cold to provide 'anxiety' signals, and 'satisfied' by clinging, contact, warmth, and warm chemical food signal, and then 'socialized' into a growing complex of motor responses, and correlating internal language, the system would likely hunt unstably until it saturated its motor activities with a euphoria of fatigue, then anxiety, etc. With guidance, a socialized pattern is developed that fits, or nearly fits, the maturation pattern. The problem of fit is most strenuously made evident to the adult when he faces emergent adolescence. Adolescence is not to be planned for but endured, says the psychiatrist.

In between the extremes of very good socializing guidance and none, lies the average near-human.

10. The complex of guidance patterns that can be developed depends on the complexity of the brain system. What the mother and the culture can teach the fly, ant, worm, fish, cat, dog, horse, dolphin, monkey, ape, or man-child differs. However most of the basic principles need not differ.

11. We believe that a system could be built today that would operate on these principles with a life repertoire as complete as some of these animals possess. The present discussion reinforces this belief that was first expressed in (1), Part 5.

12. One must note how the repertoire of postures is enfolded in time. There exists at every moment an input state which represents not only lumped sensory signals, but also lumped systems signals such as heart, breathing, stomach, particular skin nerves, stomach, bladder, kidney, bowels, etc., as well as various body images. In response to these input states there is a choice of an orbital synchronous path that involves these systems by motor activity. Stability is such - this element is yet far from clear, and it certainly varies from individual to individual - that the particular time scales being used in these orbits varies. When anxiety is high, one may tend to believe that the cycles become faster, not necessarily the very fastest, but what has fitted the more primitive infant experience.

As a literary observation - based on only a little data - with extreme anxiety such as crisis, weight, in response to food eating, and anger increase, while sex and affection decrease.

13. At the other extreme, there is the mature adult strategies that involve long range orbital paths - marriage and career - which then fall into daily, weekly, seasonally rhythms that follow the sun and the human social calendar. One may note that these long range 'stable' orbits are based on a regularization of all other shorter range orbits. There is a time to eat, and to perform body functions, a time for love, a time for work, a time for children, etc. If the input signals are not too disturbing, and can be handled as near routines, <u>each society attempts to optimalize its orbital synchronous paths so that they are in harmonious unison with the optimal states of their physiological oscillators</u>. (At the present, one would have to say that it is not yet known how to work off the long time buildup of aggressiveness in the young males in an entire society, if the milieu has been not too strenuous for their entire adolescence, except by the orbital synchrony of war. All scientists should think seriously about this. Shall society send the youth into far distant places in social service, as a substitute?)

Consider (4) again. Anna Freud concluded that personality can be penetrated both by direct observation of child behavior as well as the more detailed probing of the unconscious that had been the psa (psychoanalysts) tool. Of course if the ego mechanism involved in a particular problem is repression, nothing is visible on the surface except absence of behavioral patterns, or reaction formations which transform the repressed counterpart to some other overt manifestation. Such expectations were realized, particularly in oral, anal and urethral character types. (One can accept the idea of lumped interfacial foci, as being orienting, and can recognize a strong primacy of oral, genital, urethral, and anal controls. However a physical scientist is in no position, at present, to take a stand for or against such Freudian derived theses. This is stated obviously not from fear of taking sides, but from a pure confession of ignorance of clinical observations and interpretation).

Child behavior appears transparent with regard to anal and phallic strivings. During bodily illness, other manifestations permit conclusions - pleasure in body care, anxiety as a result of guilt feelings, of sickness as a self-induced punishment, anxiety behavior as a result of poor earlier mothering.

Observations in play again point to anal, urethral, and sexual preoccupation. Behavior toward food is more telling than just its oral fixation in which the child's greediness (also in old person's) is the most obvious manifestation. Eating disturbances are more broadly tied to developmental disturbances. Behavior toward clothes is another valuable observational area - exhibitionism in form and nature of coverings, and repression in neglect. Further areas are in the home and school.

However these observations are not to be used therapeutically. This would ignore the ego defenses, and the entire apparatus which psa has discovered guards against the easy availability of the unconscious content. However, adding an adequate knowledge of psa does permit fruitful observation.

The ego control over motor function, speech, the content of memory, intactness of reality may be tested for. The synthetic function (the synthesis of ego) cannot be so determined. In young children, direct observation may be used. (Reference is made to the valuable general source (12) or to Piaget's books (13)). Another valuable source of observation are effects on the child of institutional or creche upbringing.

One difference between adult and child psa treatment is that adult analysis has the curative tendency that a striving for 'normality' holds out promise of success in sex and work, while drive satisfaction, as soon as directions are produced in analysis, results in a wealth of fluid motion. "Libido and aggression are in constant motion and more ready ... to flow into the new channels ... opened up by analytic therapy. In fact, where pathology is not too severe, the child analyst often will query - how much of the improvement ... as outcome of his therapeutic measures and how much ... to maturation and to spontaneous development moves. However, it is the urge to complete development that is so strong in the immature.

(It must be stressed again, that we do not intend to become psa, nor at this time can we evaluate such psa tenets as the primacy of an oral, anal, urethral, and genital personality, or phase of personality. However it is clear that there are a considerable number of systems imprinted in the brain. It would do neurophysiological and cybernetics colleagues injustice not to admit to the extreme amount of data processing associated with other lumped signals of the visual, the smell, the touch system, etc. The psa may no doubt say that these are not primary in ego development. On the other hand, the cyberneticist may say forget the nonsense of ego, id, super ego and concentrate on automatic regulation and control, and data processing problems. We do not agree with either view. Both sides will say that we, the physical scientists, are much too ignorant, and must learn enough of either field to be convinced. This may be, but we cannot accept this as a working hypothesis. We must stay close to a physiological-physical foundation, carefully trying to feel a way out to these other fields from this base. Thus as a substitute for detailed clinical psa, or clinical neurophysiology this program searches for the broad principles that lead from physical to physiological to psychological mechanism. There is a thrill, for example, in the needling of Klüver who gently chides such search in (14), but then proceeds to provide his clues in (16). "It is only when we come to the mammals that the sense of smell becomes dominant, it becomes ... the sense," but " ... the sense of smell is poorly developed in the higher primates, including man. However ... large parts of the 'olfactory brain' or so-called rhinencephalon are not directly ... concerned with mediating olfaction ... We are faced ... with the problem of the 'untenanted rhinencephalon' ... Who, then, are the other tenants? ... at least two other tenants ... 'sex' and 'emotion'." He points out that Freud proposed the theoretical speculation that the decisive step in development that led to the threshold of human civilization was made when pre-man got his nose above the level of the female genitalia and assumed upright position and bipedal gait, with the result that olfaction became secondary and vision the supreme sense. Klüver offers a reference by Schloeth (1956) on animal encounters in different species who found for example that in lemurs the first contact was naso-nasal, in monkeys and apes, after first visual contact, the contact was naso-genital and naso-anal.

In summary of limbic functions, Klüver concludes that olfactory, emotional and sexual phenomena may be considered as phenomena involving fluctuations or oscillations, nearly devoid of constancies, but involving nearness.

This study will call attention, piece by piece as they are found, to the ideas that there are contributions to the body images in the 'mind', that these body images are real, that they represent changing states of the body system, that these represent the source inputs for driving the 'psychological' or learned responses, that the responses are generally represented by motor enervation and internal 'retrospective' and 'prospective' computation, that most of the paths are 'learned' routines that try to bring about satisfying states, that these routines are used as synchronized orbits. One cannot yet sharply characterize all the body images. It is reasonable that a body image exists of the endocrine system. It is not reasonable to believe that it is sharply outlined near consciousness levels. However it is not yet possible to accept that the signalling from a primitive oral, anal, urethral, and genital phase - except as names for a complex of maturation responses involving all of the systems - become the drive toward the developmental algorithm. Yet it is not impossible that these signals provide the signpost of 'up'. During each phase the monkey-ape data seem to indicate four developmental phases, two of them certainly physiological - the infancy mostly 'anal' response, and the adolescent mostly 'genital' response. The other two, the peer play response, and the authoritarian father response are not so clearly in focus, with regard to physiological causality. Yet these are not impossible from the point of view of an intrinsic kind of driving instability within the brain.

Klüver proposes that what is needed is both poetry and cybernetics. We are doing our best to satisfy him - but as physical scientists).

Technique with children may not use free association. All children are uncompromising in an inability or unwillingness to cooperate. Play acting has been used, but is not a valid substitute. Thus the analyst's task still remains to interpret unconscious material.

In adults, analysis deals for long periods with material under secondary repression, with undoing defenses against id derivatives which have been rejected from consciousness. Only from these does it proceed to elements under primary repression, which are preverbal, not part of the organized ego, can't be remembered, but only relived.

The ego of the young child has the developmental task to master orientation in the external world, and also the chaotic emotional internal states. It gains its victories whenever such impressions are grasped, put into thoughts or words, and submitted to the secondary process.

(In these studies, the charge has had to be considered that it may be reading more in to Freud than he really meant, and that his students may certainly not have the same view that is being proposed here. These words and descriptions belie these charges. The program is gradually formalizing more than ever a view of dynamic body images in the brain, as representative of Freud's id; an integration of these body images, as representative of Freud's ego, and an operative algorithm for the motor system and internal computer that has developmentally formed as representative of Freud's super ego. It has had to recognize the importance of an internal computer language, well described by Sullivan as developing in steps from its autistic form to its ultimate linguistic form. It has had to accept the particular computational forms that proceeds from a very primitive patterned analogue made up, likely, of reflex arcs, to the more complex secondary response involving memory, delays, analogue computation, 'repression', 'dreams', sublimation', 'transference', 'abreaction', etc. To this are added the primitive idea of instability, discharge by action, and generally by search for routine analogous orbits.

As an aside, one can add an additional interesting speculation. It may be noted that there are a variety of inputs that put one to sleep; illustratively boring discussion, which results in a yawn; boring writing, which results in dozing; or fatigue, which results in dozing. All of these resemble one stage or type of euphoria. As a first approximation, one is led to the view that if something arises which the system can't synchronize with, then instead of continuing to build up a jitter rhythm, one synchronizes with the rhythm of sleep, by disconnecting various parts of the computer.

All of these ideas in one present opinion attempts to bring a cybernetic, physical view to the better known portions of behavioral sciences).

A. Freud discusses resistances in children, transference, the analyst as a new object to the child hungry for new experience. The analyst is externalized and involved in the child's intersystemic conflicts. Infantile dependency or independence of the parents as a separate psychic structure is of theoretic importance. From the child's chronologic age (in the present culture) his dependency state can be assessed by the consecutive uses he makes of his parents.

Quite interesting are the comments on the balance between internal and external forces as seen by the adult and child analyst. In the adult, the power of mind over matter (i.e., control of motor activity) is presented in the changing view of their real life brought about by unending mood swings from elation to depression. The analyst becomes a firm believer in psychic, as opposed to external reality. The analysis of children, on the other hand, points always to the powerful influence of the environment, i.e., he is dominated by the object world.

(All of this points to response to body images by more direct motor and computer activity, and to a higher degree of instability. The system is not yet stabilized by a fully developed guidance algorithm).

Four characteristic differences between the child and adult are the ego-centricity which governs the infant's relations with the object world; the immaturity of the infantile sexual apparatus, the relative weakness of secondary (controlled) process, i.e., id (image) derived rather than ego (integrated) responses, and the different evaluation of time at various age levels.

A prototype developmental line has long been postulated and is being explored increasingly.

1. Biological unity of mother-infant.

2. Fluctuating object images in memory space form under the impact of imperative desires, and withdraw upon satisfaction.

3. Object constancy.

4. An ambivalent relationship characterized by the ego integrative attitude of extreme manipulating of love objects.

5. Object centered phase, characterized by orbital extremes, with regard to the parent of the same sex.

6. Transfer of orbit to other-than-parents (contemporaries, community, teachers, etc.) in search of libidinous (pleasure-pain, love principle, or affectional system responses).

7. Pre-adolescent fluctuating image space, and ambivalent manipulation in search of need - fulfillment, a return toward infantile attitudes.

8. Adolescent breaking of the tie to infantile objects, with a genital maturation and libidinal cathexis (object and body image, affectional system response) formed toward objects of the opposite sex outside of the family.

This 8 point program of form and functional action phase or the lesser 4 stage affectional system described previously, differ only in technical details. One must consider the projection of body images, and external images, the maturation, the instability, the non-linear fluctuations, the locking into orbits now as being 'proven' elements as part of a cybernetic hypothesis, and proceed from there to details).

These developmental lines toward independence are illustrated in such activities as progress from suckling to rational eating, from wetting and soiling to control, from irresponsible to responsible body management, from egocentricity to companionship, from the body to the toy, from play to work.

Regression is also a principle to be recognized in normal development (remembering that the behavioral system development proceeds by lines to build up a complex secondary computer-like algorithmic structure that its course is different from the smoother physical systems development and maturation and involves 'fixations' and regressions). Three types are recognized - topographic, which moves back from 'rational' motor actuation to 'irrational' internal near-sensory hallucinatory wish fulfillment; temporal, which works back to older psychic structures; formal, which uses more primitive methods of representation to take the place of the newer ones. The general rule appears to be that what is older in time is more primitive in form, and topographically nearer to the perceptual end.

Fixations and regressions are interdependent. Fixation points may be caused by traumatic experiences, or by excessive frustration or gratification associated with the primitive signalling interfaces.

(This represents the fixing of portions of the behavioral algorithm on specific kinds of analogues which lead to particular kinds of orbital entrainment paths around a key point as a focus).

The pathology sections and therapeutic sections are not at present interesting. Suffice it to note that the development disturbances found in children are found early in four areas - sleep, feeding, elimination, and wish for company.

For some brief background on the status of the unconscious before Freud, in the domain of two earlier centuries of European thought, one may refer to (15). Its virtue is that it lays down a history of some of the philosophic-psychological-biological background of the 'unconscious' character of behavior accepted before Freud by an author who is not pro-Freudian, but which will still permit a jüdgment of the importance of what came before and within Freud's total concept. (It is of passing significance to the previous statement that ideas usually have a long history, even when they appear to come suddenly to an individual, that the general conception of unconscious mental processes involved its development in Europe over a period of two centuries, 1680-1880. This time scale was the same mentioned in (3) for technological development. In reviewing this book, the feeling develops that the decisive advances that Freud made, in the present frame of reference, is unequivocal, rather than lending strength to the thesis of the author of the book).

As a transition to behavior, those who may look with doubts on Klüver's discussion in (14) may examine MacLean's earlier discussion of the responses in the limbic system of a monkey in (16) (or, as commonly referred to, the rhinencephalon structures). MacLean points out that the system is concerned with the self-preservative activity of feeding and the species-preservative activity of sex. The study impetus stems from Papez' (1937) classic paper on a foundation for emotion (which Klüver references, too). Intermixed in response are the elements pertaining to feeding, angry and defensive behavior, body grooming, and sexual function. There is closely related organization of the oral and genital regions, though in the body the areas seem so remote. Ten years earlier, it would have been speculative to indicate the convergence of these (intero-and-extero-ceptive) systems. Old's comments, "I can't help becoming enthusiastic when I hear a man talk about the limbic system and its relation to the various drives and hypothalamus and the midbrain tegmentum. I always have the feeling that everyone is making out a case for a common denominator of function ..." What emerges out of their subsequent discussion, is that whereas the concept of rewarding and punishing centers had received considerable play and criticism at the earlier First Macy Conference, now it seemed better that at cortical levels stimulation arouses attention, a "what is it" response, which will receive attention a few times but then dies out. However subcortical stimulation, is much more demanding. It can elicit response or attention for hours, almost without fatigue, it is urgent, demanding, "far beyond anything else that we can stimulate by means of presented external objects" (Lilly).

While all of their discussions seemed to be devoted to the 'episodic' content of stimulation (if a 'posture' is held for a 'moment', an 'episode' runs through a series of postures from a repertoire in an orbital entrained or an aperiodic path), there is a considerable continuity with the clinical observations that a psychiatrist, Dr. D. Bond contributes.

(The neurophysiological situation is perhaps approaching closer to the description that McCulloch has stated, that most parts of the brain function are known - in detail, except possibly for the reticular formation).

Reference (3) on information science lists a somewhat extensive cybernetics literature on the brain. The discussion on this topic will be deferred.

An apt introduction to the standard earlier sources in psychology are Shipley (17) and Herrnstein (18). With these for perspective, a more nearly up-to-date review of current psychological trends is Wolman (19).

Various interested colleagues have proposed many more references that should be read, and we are trying to cover them as fast as possible. However for this phase, it is proposed only to mention four more; Hill and Parr (20), an excellent symposium that can serve as in introduction to encephalography; Luria (21), " ... a major document in neurophysiology ... a monumental contribution. Nothing of this scope exists in the Western literature of this field ... on the cerebral cortex ... marks a farther and decisive step toward the eventual coalescence of neurology and psychology, a goal to which only a few laboratories in the East and West have been devoted over the last decades" (since this is the goal chosen, to span the stretch from physiology to neurophysiology to psychology, such a book should serve quite well as a preliminary guide. Namely, we have selected the spectral range 0.1 second to four weeks as being the preliminary stage on which the psychological drama unfolds. As justification for this view, we cite Stroud's view of the psychological 'moment' on one hand, and the corresponding insight that the human system can control 'postures' or 'posture sets' nearly at that rapid rate of ten per second. On the other hand, there is growing evidence on cycles such as are mentioned in a letter to the N.Y. Times (23), "Several universities are currently completing studies validating three long-term cyclical patterns called 'biorhythms': a 23-day physical cycle, a 28 day emotional cycle (unrelated to the menstrual cycle), and a 33-day intellectual cycle")); Arnold (24), which attempts to bridge psychology, neurology, and physiology; and Carthy (25), which defines the role of aggression.

Preliminary discussion has been opened with three well known encaphalographers. A fair summary of the position they hold was given by W. Gray Walter, who said that there is no significant behavioral content in the EEG, only a long detailed listing of 'administrative' functions. No sharper conclusion can be found in Hill and Parr (20), or any other source thus far examined. One can thus grasp why psychologists are not enthusiastic about looking at the 'evoked potential' level.

Possibly the most advanced thought existing presently is Walter's contingent negative variation, the 'expectancy' wave, which he presented at a May 1966 Bionics Conference in Dayton. The surface of the brain shows a negative pulse form nearly one second before an event (the brain is expectant). This may be found in patches over the frontal lobes. The frontal lobe is an intrinsic part of the sensory system, via the pathway of the reticular formation. In Walter's expressed opinion, this is the closest that he has been able to get to the "grammar" of the brain.

One can infer that only pieces of involved mechanisms are known - the sensory system (with the kind of decoding that Lettvin has been able to do for the eye, and the kind of specific anatomical verification that Lipetz has been able to furnish); the neural nets; the poorly defined (as yet) localization of function in the brain structures, the connection to the endocrine system, and the endocrine system. (For example, in private communication, we have been told about beginnings of functional dissection of such a structure as the hypothalamus that has identified at least 5000 functional networks. However this is hardly yet in focus). It is clear that the functional relations are not known to the point of identifying a chain of causality, in the physical sense, to explain action.

Luria (21) doesn't help either. His book is really directed at "the disturbances of higher mental functions caused by local lesions of the brain". He replaces the ideas of localization of function and centers of function by a dynamic complex autoregulating system involving many different levels of the nervous system. "In essence, it implies that no formation of the central nervous system is responsible for solely a single function ... functions are localized, not in fixed centers, but in dynamic systems ... the center, or aggregate of central apparatuses necessary and adequate for the function, consists, in most cases, of cycles of interaction between more or less widely separated ganglion cells ... The 'center' of a complex function is a constellation of harmoniously working ganglionic areas, mutually exciting one another... The concept of the systematic structure and dynamic localization... clarifies several observations ... difficult to explain on the basis of ... isolated, stable centers in the cerebral cortex. For instance ... Brown ..., Grünbaum, Sherrington ..., Leyton and Sherrington ... stimulating the same point of the motor cortex ... elicited diametrically opposite effects ... depending on the strength of stimulation and on previous stimuli ... Head (1926) was able to declare long before all the findings just described had been obtained that '... cortical activity, even when aroused by electrical stimulation, is revealed as a march of events with a definite temporal relation. The response obtained from any one point, at a particular moment, depends on what has happened before ...' ...individual areas of the cerebral cortex ... are 'staging posts' or 'junctions' in the dynamic systems of excitation in the brain and that these systems have an extremely complex and variable structure".

Yet all that comes out of this very appropriate beginning is a large number of fragments of motor-sensory and fewer 'intellectual' disturbances.

Arnold (24) is quite exciting. The two volumes form an interesting beginning toward present objectives. Yet with its strong psychological beginning in Vol. 1 and its descent to physiology in Vol. 2, the system still does not come into focus. The references evoke empathy.

Yet it is certain that the basic thing that is needed is some sort of orienting hypothesis. Not departing much from Arnold, there is a need to integrate the key ideas of such thinkers as Freud, Pavlov, Wertheimer, Head, Hebb, Ashby, McCulloch, Pitts, Lettvin and others.

For example, in a May 1966, Bionics talk on the nose coding, Lettvin declared apropos of all neural modelling, that none of the models put forth have anything to do with neurons, that no description by input-output functions has had any pertinence to date. Basically what the nervous system cell seems to have is a "point of view". The neuron doesn't fire on the basis of a voltage or current governed oscillation, it behaves as a very non-linear oscillator. It multiplexes in time, and no one can say what are its rules. It has a "point of view".

To this manifesto, we respond with enthusiasm. It quite appropriately interlocked and triggered off our own views. While quite crude, as yet, and not completely original, nevertheless these views part in outlook with some good friends. The object, which it is believed would be shared with Lettvin (also physically trained) is to get away from human 'teleology' on one hand, and to get away from logical systems level 'teleology' on the other hand. The McCulloch-Pitts logic is not adequate for the nervous system, nor is perceptron theory, nor does it help, as von Foerster is attempting to do, to change the search from a calculus of propositions to a predicate calculus, to a calculus of relations. These ideas are too premature.

What is first selected, in agreement likely with Hebb, is that there exists marginally stable loops, that can easily be unstabilized to become transiently 'reverbrating', i.e., van der Pol relaxation oscillators. This puts the problem within the domain of connected networks of non-linear loops. Such a complex shares its content in part with Ashby's homeostatic networks.

However, it does not pay to think of these networks in 'teleological' terms such as excitatory - inhibitory, etc., as a description of fixed loop function. Each loop has a variety of possible inputs, governed topologically by its location and its contiguity to other loops. This is governed by growth and signal excitation. Its 'stabilizing-unstabilizing' margins themselves change in time, and mostly go through a developmental phase.

Now arises a basic question. How can it be that many animals - the cat, guinea pig, gorilla - lead such dull lives? (In Schaller (10) one would say that the major course of the animal is 11 hours of sleep, 5 hours of working and feeding, 2 hours of resting, 6 hours of moving and feeding; defacating; urinating; a little play; a little sex. On one hand this may be regarded as over simplified. On the other hand, it is a description of the gross behavior). Yet, the human, dog, chimpanzee, rhesus monkey, dolphin - particularly in limited observational regimes - show so much patterned variability. Clearly, it is not only the size of the brain, or the class of nervous system elements that governs.

One can only guess that it must be the patterning complexity that can make the difference, and the only way that the patterning complexity can come into being is by the variety, complexity and rangeability of the 'stabilizing-unstabilizing' margin of the individual neuronal loop. It is very likely the developmental rangeability and complexity of the stability contour that counts.

Re-examine this one more way. The question was addressed to a cybernetic psychiatrist colleague, who is perhaps out of sympathy with psychoanalysis, but certainly in sympathy with clinical problems, as to how many type personalities he might identify. (The question is used over and over again to psychiatric colleagues, particularly with clinical interests, to try to see the human through their practicing eyes). He offered

> those out of touch
> those in touch too much
> the ideè fixe type
> detached types
> types who are internally polarized (such as by 'good' and 'bad')
> types with narrow world views.

(As to what people 'think' about, he offered

information-boredom
search for sensory signal
language to reinforce identity
search for contact
matching of environment (with an internal view?)
shifting of content and body image).

Yet each of these types of people can operate quite successfully with a suitable environment.

On the other hand, the music that comes out when Heifetz plays, as contrasted with the poor beginner appears tremendously different in integrated content, although very similar numbers of elements are organized. (If this is doubted as lacking in evidence, one can compare the speech pattern of Olivier, say in Othello, with some crude coarse gutter joke, and require that its 'artistic' differences be established).

The basic differences can only be in patterning 'texture', in those elements that can 'compose' the nervous system response, and at that only in the topological richness of patterning texture.

In the limit, it is conceivable that this model would require no formal 'memory', other than the formation of patterns.

Consider the system in the following view. The genetic coding results in a certain cellular unfolding in a highly regulated environment. The coding is sufficient to produce some very complex oscillator systems. A primary formative signalling complex may be fourfold; the chemo-electric unfolding of lipid and protein linings along hydraulic paths; the hydraulic system unfolding under the stimulation of sonic-vibrational signals; the growth and specialization of cells through genetic coding, including long time delayed maturation elements; and the formation of two types of oscillator loops - chemo-electric cell aggregates, neural elements, and hormonal chains. It is not certain that these all don't use the same governing chemo-electric step, but with different geometry and topology.

The net effect is that the system is delivered at birth with different systems. Many tight or short chains are already set and their unstable oscillator loops are in operation. What is 'free' is the largely unpatterned neural loops. Obviously they are easily triggered, but their development is not complete. Thus there is a common experimental order in which the network is shaken down socially. The Australian aborigine child, the upper class American child, the Appalachian child does not receive the same child-mother education. You cannot take a grown African primitive and satisfactorily train him to function 'like the others' in a complex industrial society. The difference must be the texture of nervous system patterns, and this can only mean the stability-instability contours distributed through the brain.

The chimpanzee, the dull child, the cat, the brilliant English scholar fearful of logical problems, the brilliant physical scientist fearful of undirected creative activities, all have pattern limitations, and perhaps some system connectivity relations. Yet the number of element complexes is comparable. Thus it can only be patterns that are different.

It is clear that these patterns appear as organized complexes to the observer, whether layman, localizing neurologist, or psychologist. _It is clear that none of them have broken the logical 'code' of behavior._ It is clear that this is what the scientists have tried to do. It is timely to consider putting away the search for systems logic, until a clearer idea emerges on how the networks operate. (Consider a reference like Smith (22). He offers the line James, Semon, Prince, Hebb and Bugelski, and contends that the neural circuit hypothesis be abandoned. Yet he offers an essential network theory. Circuits are not formed through learning. They are already there. Transmission of impulses in the cortex is random. Whether true or false, the brain logic is still not thereby exhibited).

In the area of this problem, we are more qualified to make a judgment than many groups involved, because the problem is an abstract problem of non-linear mechanics, and not of psychology, neural networks, or electrical networks, etc. The most we know at present, is that stability in a non-linear network is always very specific to the type of network, and its boundary conditions, and outside of classifying topologically the kinds of actions one might get, it is not possible to develop a combinatorial 'algebra', or 'calculus' in any general fashion.

Yet, of such non-linear network complexes must emerge neurology and psychology. The EEG can only hint at the complex of its abstract properties.

The governing algorithm of the complex human will be defined as its patterned nervous system response, by which external and internal patterned signalling inputs sweep through the nervous system nets and result in various stable-unstable loop responses which are conducted and field propagated through the system. It is now proposed that there is no specific 'memory' other than the topological richness of 'preferred' connectivity, and that the preferred connectivity, in Pavlovian sense, develops from input-output directed behavior.

In response to the question as to what 'directs' behavior, the most limited possible teleology will be assumed, that whatever is most satisfactory in discharging the system of input signals to a taught-in-childhood rest state helps form the preferred patterns. However, the system is unstable enough that the inputs are constantly exciting patterned response, i.e., lack of motion will begin to excite internal loops into internally preferred patterns that lead to preferred motor action patterns.

There are fixed systems, which are autonomous oscillators, namely, they are short wired, or have strong enough inputs that they will govern themselves. These physiological oscillators include

heartbeat
ventilation
neural loop discharge
sleep
fuel oscillations (intake, storage)
water oscillation (intake, storage)
sex
red blood cell fluctuations
electrolyte and metabolite fluctuations
stomach peristaltic action
endocrine fluctuations
oxygen fluctuations
carbon dioxide fluctuations
metabolism
body image

There are those that are at least partially taught in childhood

activity
anger
anxiety
attention
pleasure
signal seeking
body contact
temperature orientation
language use
admiration
power manipulation
fear
aggression

There are 'poles' of behavior, as they were being sought from the beginning of this program. However it is no longer believed that they are unique. They are the 'poles' of behavior around which the human brain commonly wraps its orbital orientations - that 'polarize' the internal connection patterns.

Thus in rather a discouraging fashion we are moving away from the psychological, logical, communications view of the system. What remains as the possibility? It still remains that behavior can be examined for its temporal organization, for its spectral characteristics, not so much phenomena as learning or forgetting curves, but the characteristic frequency responses. It is such characteristics that tell around what material the textured response of the non-linear networks of the brain forms and swirls.

It may be wondered why such a negative view is taken just at a time when modelling by so many is under way - by the cyberneticists, by the network and systems engineers, by the computer logicians, etc., all who have wide skill in ascertaining systems response. The pessimistic counter is the 2000 years of philosophic thought that has been devoted to the question and for which it doesn't appear that the physical answers are apt.

One finds a relaxation oscillator view of civilization in which each generation often considers the next generation as 'going to the dogs'. This can only mean that patterns are locked up in each generation, and the next generation self-patterns for itself.

It is found that psychoanalysis is very hard to chew and swallow. (It is not conceded to be impossible, only difficult). One finds that working psychiatrists cannot use all of their taught 'theoretical' constructs, only a limited number of them, which they empirically (clinically) discover as providing them with a limited guide. This can only mean complex and ill-defined patterns that have hardly fully formed out of function. This again is why there is so little content in the EEG (except about such instabilities as epilepsy).

Thus in the end it must only be the major physiological oscillators that stabilize. The entire early training (whether extensive in some animals, or limited in others) are sufficient to develop patterned responses around the long term preservation of the metabolic reaction, including self actuation and propagation. The motor mechanisms are available to effect the resultants of search movement and propagation. A rich texture may form with 'language', whether internal or external, but it hardly counts (except as rich texturing).

Thus the insistent signalling complexes of

oxygen level
carbon dioxide level
water level
fuel level
motor instability
rest-wake instability
sensory demand instability
sex demand instability
nervous system (internal 'language') instability

are close to furnishing a primary list of physiological oscillator complexes which dominate the gross texturing of the responsive adaptive nervous system. This then develops into its patterned response, driven by fixed cues of the day, the year, the 'decades' of life, with their emergent maturing, likely partially genetic; then the emergent 'social' epochs of the week and month (there is no doubt that a combination of physiological instability and social instability helps determine the 'necessity' for these social periodicities); and then the strong aperiodic socialized and socializing cue of the mother or mother surrogate.

This casts a new light on civilization. On one hand, it explains why there is the broad range of 'opinion' of radical-liberal-status quo-conservative-reactionary, reflecting opinions from change to new to change to old. There is no single 'best' response. Whatever the milieu and society evolves into, the human will pattern and adapt. From time to time, or age to age, which adaptive patterning is best suited, or which individual (living entity, or species) has the little differences in patterning capability to best fit, can vary. There is no fixed formula for Nirvana. The systems are solely self-adaptive to the environment. There may be better survival value or not to a particular genetic coding, and the development of particular patterned responses, but it is almost impossible to tell.

With regard to the genetic capability, an extremely beautiful statement of R. Fisher's views of the integration of Darwinian selection and Mendalian genetics may be found in (26).

> "What Fisher showed is that it is not mutation that controls evolution, but selection which governs the speed, direction, or cessation of evolution in accordance with ecological conditions. Mutation has no immediate evolutionary effects at all; what it does is to fill the genetic material of the organism with genes that mostly become recessive (and therefore do not show their effects under existing environmental conditions, unless inbred) until such time as changes in the other genes (which are organized into what is known as a gene-complex), or the environment, or both, make it possible for some one or other gene, by the sheer opportunistic play of ecological events, to exert effects even slightly beneficial. After this they become dominant (in the way that Fisher showed and E.B. Ford proved) and are incorporated in the standard genetic legacy from one generation to the next. This is not mere theorizing, but experimentally demonstrated fact. The vastly superior power of selection over mutation in changing an organism (selection pressures can now be measured, and no mutation has the slightest chance against any adverse selection), and astronomically large possibilities of heritable variations resulting from segregation and recombination ("re-shuffling") of previously accumulated mutations, make it possible to say that if, fancifully, all mutation were to stop today, there is already in the various species sufficient potential heritable variation for natural selection to work on and to force evolution along in the future for as long as it has forced it up to now".

Thus the richness of latent genetic coding changes for the maturation elements, the numerousness of the species (not the 2-4 billions commonly thought of as having lived in the past, but the nearer to 70-100 billions of humans pointed out by von Foerster) provides the rich adaptive patterning that man's (and a few other animals) particular nervous system permits. All that must be given up is the claim to fixed behavioral patterns. The species, and the members adapt. If you want to see more nearly 'human' behavior (namely what we have become culturally accustomed to) crowd a pliable species together. Within their nervous system patterning adaptability, they will become 'socialized'. It is more nearly contiguity that determines society, than society determines contiguity. If one wants to see less 'human' behavior, put the 'savage' human family in an isolated primitive milieu, without a broad host of cultural memories in the mother. This must be food for thought.

As an overall view of the human, we are amused to see that we have returned home to the epigenetic view that we were taught, as a very young student, in which the genetic material unfolds, generally in carefully nurtured or regulated environments - from whence a more nearly constant response (pattern) develops. However, the pattern would change in response to changes in milieu, as well as what genetic mutations might become more dominant or common. Finally, the maturation unfolding - particularly sexual maturation, with its urgent signalling toward mate configuration and reproduction - furnishes time delayed check points that urge the pattern formation toward preferred directions.

Since the language-ridden 'intellectual' reader may consider these views rather negative, it is useful to expand, with some personal references, on its rationale.

In the past few years, we have made some rather exciting intellectual progress on problems that have all had long perplexing histories. We were brought up technically, as an applied scientist, by the technological myth, "If you build a better mousetrap, the world will build a path to your door", and its corollary that good works will be rewarded. We have learned what must be an age old lesson. Nobody pays attention. Ideas must fit the power structure, or if one has the strength, one can fight his way into the power structure. These issues are not the dominant ones that are of immediate concern. What is of interest is the following:

1. In 1965, we performed a management study on using research to make advanced technological progress, in which the rate of science and whatever society management was involved came into focus. It was rather shocking to realize, in reviewing management sources and the experience of research directors, that human behavior - in management - was irrational, contrary to the premise of all planning documents. (This, was a working conclusion, not a bar-talk hypothesis. It is very easy to get people to say, "Well, of course that's true. Everyone knows that," or "You're talking like a crackpot. Basically, managements are quite rational, and well directed toward their goals." The empirically observed fact is that they are irrational, and in sophisticated ways that T.C. Mits is not familiar with, unless it were explained to him in great detail). This was personally disturbing because of attempting to devote a career, 25 years, plus 20 years more of study, to reason. Yet only now has the truth been learned, a truth laid down probably many times in the past.

> "This experience gave me an opportunity to learn a fact - a remarkable one in my opinion. A new scientific truth does not triumph by convincing its opponents and causing them to see the light, but rather because his opponents eventually die, and a new generation grows up that is familiar with it."
>
> Max Planck

> "Time makes more converts than reason."
>
> Tom Paine

"It is virtually impossible to get a new applied scientific technical idea assessed on its merit in government today."

1965 Report

2. There has been the occasion to learn in the performance of this contract. This contract is interesting because we are physical scientists coming to biology - crossing disciplinary lines. As a result it has been possible to observe all of the conventionalized responses that one might already be unconscious of in one's own field (this does not mean to denigrate biologists, management, or humans. It is only trying to gain insight and perspective). First, it provokes resentment. "Why don't you stay in your own field." It arouses insecurity. Second, as the scope of inquiry was opened - not knowing where answers lay - it was found that most scientists operate within a very narrow surround of historical background. Basically, they deal with what 'mother' taught them. It is very seldom that one finds broadened horizons. The broadened horizon chaser is a rebel who is attempting to avoid mother's confining apron strings. Third, one finds that the broad generalist is also viewed with suspicion. "It takes me an entire career to ferret out the facts in this narrow area. How can he possibly understand them?" Yet the number of independent ideas one has to deal with is really quite small. Fourth, abstraction is a very painful process. One could well understand that biologists were in the main anti-mathematical, and anti-tightly organized logical structure. However, it comes as a surprise to us that they as well as physicists, and mathematicians were perturbed by abstractions presented in some novel fashion other than to which they were accustomed. (For scientists who doubt this in particular physical problems that they might immediately insist were 'rightly' controversial, one need only ply them with new 'shocking' abstractions in the creative arts - in painting, music, theater or politics, for example - to see the difficulty in accepting abstractions). 'Up' is the way mother taught. Fifth, one cannot introduce new ideas. They will not be taken seriously. This was found in some recent hydrodynamics study, in which a 'new' demonstration for the mechanism of turbulence was offered. So far it has not been possible to get one hydrodynamicist to examine and discuss the thesis seriously. "It is too difficult to understand ... Any idea that takes so many pages to explain can't be right ... It isn't enough to prove where a new idea is feasible, you must also show us where our old ideas are wrong."

3. The essence of the matter is that the 'intellectual' profession of scientists are not really any more rational than any other set of humans, even in their so-called rational activities. This is of course heresy, and we could not have made the statement, or even understood it when less experienced. (The irrational certainly extends to cover us, we prefer to be the first to hasten to explain).

4. It must therefore be concluded that there will be nothing more found for human behavior than this rich textured response to adapting inputs; that what the human has ultimate recourse to is where the incessant spatial cues of his internal physiological oscillators and their 'homeokinetically'

governed variables lead him via the spatial cues furnished by the oscillations produced in his specialized sensory systems by virtue of the temporal cues contained in his proximal milieu; by the adaptive temporal 'conditioning' of his nervous system provided by 'mother' and by his interpersonal space-time contacts. This of course sounds existentialist, however there is a broad area of 'common sense' in any slowly varying external milieu that permits adaption patterns to develop. A personal belief is held for a humanistic morality. If one had to chase one moral 'goal' for humans, it would be that they texture their responsive search to maintain a metabolic reaction with compassion for their own kind.

C. BEGINNING A NEW CONSTRUCT-PATTERN PSYCHOLOGY

From the studies thus far conducted, it is clear that only a limited view is possible for human behavior. This breaks with many investigators by declaring that at the present the only safe hypothesis is that there are no values in behavior, only internal patterns in the nervous system. The main pattern of behavior is modelled around the primitive signals afforded by the physiologically governed oscillators, and this is largely devoted to the preservation and maintenance of the metabolic reaction. The rest is what is guided by the interpersonal maturation configurations of mother-child, mother-father-child, child-child, boy-girl, continued then by the 'round' of life, and the patterning richness that can develop in the particular nervous systems.

Illustrative of evidence for these are such items as:

1. A person quits an intolerable position. There are others who will take up the position, without any real reference to what the previous one had experienced. (The individual is 'willing' to run the course, regardless of how disastrous the 'pin-ball machine' path had seemed to the previous runner).

2. Various cynical managements, both national and industrial, have put up individualistic job requirements, regardless of how difficult, or degrading, etc., and one could find, by a sequence of trials how close the job would be performed.

3. The lack of 'transfer' and 'communication' between generations, past a particular age.

4. The historical repetition of undesirable events, like war, rape, crime, etc., again and again (as if they develop as particular patterning responses that are most easily formed).

5. The speed with which 'tradition' builds up.

The 'psychological' (i.e., individual 'learned') behavior is shown in the patterning that develops around the stable space-time patterns that 'socially' develop. It is the ecological-physiological interactions which set up a motional instability. This may be seen as follows: unless food, warmth, other needs are immediately 'here', as for example, oxygen may be, then the organism goes into a searching instability. In a complex industrialized society, there are related searching instabilities which force the organism toward the development of orbits. Employers like employees to come in on time, restaurants and stores have to meet time schedules, etc. Thus the logistics of supply, the regularization by driven cycles (night-day, spring-summer-autumn-winter, the weekly calendar, etc.), mass and flux balances (food grows cyclically, etc.), time delays, the interaction with emergent physiological mechanisms, etc., all help to establish standardized (temporarily) patterns around which the individualistic patterns can thread.

All this has no dynamic content, at the moment. It represents the beginning construct of the 'kinematics' of behavior. A pattern psychology will have to proceed to search out what seems to be the suited dynamic laws.

The lapse of some time between the writing and printing has permitted discussion and gestation of ideas. In presenting the theses to some biological colleagues, it has emerged as a richer and more cohesive point of view. In particular, we are pleased to comment on what emerged from an intense dialectic discussion with Dr. F.E. Yates.

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

Each endocrine gland seems to put forth a spectrum of hormones, and it has been a little discouraging to attempt to exhaust by long lists, their apparent multiplicity of functions. Yet major functions emerge, and the spectrum covers functions that are usefully adaptive. However it also emerges that more than one gland may put out hormone components that collaborate at common functions. In reviewing time constants it appeared fascinating that, while the spectrum is rich, it tends to appear finite in number. Thus the concept of time fracturing of physical-chemical chains seems to roost on a more specific perch. Any particular ductless gland may contribute hormonal elements. However most of them will be involved in chains with a small number of time constant ranges. (For example we might propose some typical numbers 0.05-0.1 second, 0.5-1 second, 5-10 seconds, 20-30 seconds, 60-120 seconds, 300-500 seconds, 20-40 minutes, 3-4 hours, 20-28 hours, 3-4 days, 20-40 days.) It is not the case that they must be involved in such time ranges. However, those that can be entrained in chains that have considerable adaptive value have greater survival value for their species. Thus the hormone patterns are interlocked - from gland to gland - to form a matrix of chain function (sugar metabolism for example) and time. It is this highly locked-in matrix that exists in the endocrine system, the nervous system, etc. that provides the underlying functional structure of the system. The patterns then form and wrap themselves around these more permanent poles. The final ingredient, of course, is that these salient polar times fit, by small numbers, and interact with the A.C. cuing of the environment. The night-day cycle is a most powerful polarizer. The breakdown of time ultimately to the 1-2 minute or the 0.05-0.1 second cycle time is of course more subtle. The 28 day menstrual cycle drive is quite real, and the breakdown into 4 weeks is reasonable. It is disconcerting to consider cues for a 3½-day water cycle. Which is causal for which?

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

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