

ACCUMULATED STRESS, RESERVE CAPACITY, AND DISEASE

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by

Peter A. Levine

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### ABSTRACT

The underlying theme of this paper is that the accumulation of stress affects the reserve capacity of an organism, both in the maintenance of its functional integrity and in the resolution of subsequent exposures to stress. Stress is defined in terms of a reaction resulting from stimuli which sufficiently activate the autonomic nervous system (ANS) and is either resolved or accumulated depending on whether the pre-stimulus baseline is re-established or not.

Accumulated stress profoundly influences the totality of organismic functioning, and is expressed essentially through three bi-polar effector systems: In the realm of the autonomic, the effector system is the sympathetic and parasympathetic visceral outflow. For the somatic, it is paired movers, like extensor/flexors; and metabolically stress is expressed (though less distinctly) by, for example, catabolic/anabolic and inflammatory/anti-inflammatory endocrine reactions.

The response to stress is defined as occurring sequentially in two phases, charge and discharge: When the charging (sympathetic) phase is followed by a parasympathetic discharge of equal magnitude, then pre-activation homeostasis is re-established and the stress is said to be resolved. On the other hand, it is shown that under certain physiologic

conditions (and behaviorally where mobilization--i.e., somatic response to stress--is blocked), the charge phase is no longer balanced by rebound. In these cases activation is not resolved and the stress becomes incorporated within the organism, as a diminished adaptational capacity.

The basic physiologic relations of the autonomic, sympathetic and parasympathetic, can be represented by a simple mechanical analogy (the "Zeeman Machine") which exhibits properties described by a relatively new branch of mathematical topology, Catastrophe theory. The visualization gained by this re-presentation offers new insights into the nature and mechanisms by which stress accumulates. It also suggests 'paradigms' by which stress, once it has already become internalized, may be successively resolved towards re-establishing a fuller adaptational range/reserve capacity.

In this regard, various holistic systems of healing are seen to focus their efforts towards detecting and treating these accumulation imbalances and reduced capacities even before they become symptomatic and pathologic. It is the view of this work that a wide range of "stress diseases" with varied symptoms and obscure aetiologies are the final--pathologic--expression of this loss in resiliency.

That the accumulation of stress is the underlying stratum in certain disease syndromes is tested by measuring autonomic levels underlying certain blood pressure responses of a hospitalized population. It is not possible, however, to measure the sympathetic and parasympathetic components directly (since they are expressed as a single output vector,

blood pressure). For this reason a systems analysis of the cardio-vascular system, based on well known experimental parameters, but with variable set point and gain levels, is constructed. A set of blood pressure response curves is generated and compared with the hospitalized population. The fit of these with the experimental data is surprisingly good. In addition, the prognosis for five groups in the hospitalized population is predicted accurately by the model, whereas no such predictions could be made on the basis of the raw data.

The accumulation of stress, defined in terms of the autonomic nervous system, influences many, if not all, other systems. The concept of an autonomic hypothalamic "hub" around which behavior is organized and executed is illustrated to clarify some of these extended relationships. Specifically, the hypothalamic links between autonomic-endocrine, as well as somatic mobilizing systems, are examined in this context. In addition, examples illustrating the potential for the wide and varied symptomatologies of their "mis-integration" (autonomic-endocrine-somatic) in the stress diseases are presented. Some possibilities for pre-symptomatic diagnosis, whereby stress accumulation is detected before the development of debilitating symptoms and tissue pathologies, are investigated as well. These stress diseases are shown, in a selected set of examples, to have underlying patterns of unresolved stress that can be understood in terms of their topologic configurations in catastrophe space.

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## PART I. ACCUMULATED STRESS

### Section A. Autonomic Stress: Introduction and Definitions

The term "stress," despite its universal appearance in the nomenclature of biology and medicine, has been and is used without precise or even consistent definition. This unusual state of affairs must be due to a need in these sciences to describe significant groups of phenomena which simply are not covered adequately by other generic terms or concepts. In Mason's (1976) words: "The controversy over the definition of the term 'stress' does not bear upon the validity of the underlying scientific observations or concepts."

One of the areas where stress has variously been considered is in its relation to disease. The accumulation of "stresses and strains" has in many instances been indicated as a contributory or even primary factor. Diseases such as hypertension, ulcers, asthma, heart conditions, and even various neoplastic growths and certain types of diabetes are widely recognized as having "constitutional" and "emotional" stress components. More and more, these factors have been acknowledged by members of the medical profession and sciences. Yet there have really been few, if any, systematic means to separate and study these stress factors and their cumulative effects.

The use of the concept of homeostasis in the analysis of stress can be useful in eliminating some of the vagueness from the term, and in suggesting a working definition. The

idea derives from Claude Bernard, who proposed that cellular survival, and therefore the survival of the organism itself, depended on its ability to maintain a constant "milieu intérieur," in the face of an ever changing environment.

Cannon (1904, 1939) extended these ideas of Bernard and coined the term "homeostasis". The organism was pictured as a closed system in which a number of physiological processes maintained dynamic equilibrium. Forces which produced a displacement from the constant set-point of any system triggered reactions which tended to restore its original state. Within certain limits the body could easily and automatically adjust its metabolism to internal and external environmental changes.

Cannon proposed that these self-regulating mechanisms freed the organism "from the necessity of paying routine attention to the management of the details of bare existence." Without these mechanisms we would be "always on the alert to correct voluntarily what normally is corrected automatically." In addition to "routine" control mechanisms, Cannon also studied ones which were involved in alerting or responding to extreme or threatening environmental conditions. In these cases, Cannon believed that the organism developed a special device: the adreno medullary system. This was not, in the previous sense, a homeostatic device which would bring the organism back to a set point. Rather, it would prepare the organism to remove--or to remove itself from--threatening situations by "fight or flight." He felt that this system organized the animal's resources for

mobilizing energy in the anticipation of extreme muscular exertion needed for the "life or death" struggle in these emergency situations. It is of no use for the animal to maintain an internal consistency if it is eaten in the process. On the other hand, survival in the face of emergency, if the organism is unable to return to the previous non-emergency equilibrium, diminishes the capacity for internal regulation.

The basic idea to be built upon here is that activation of the emergency response and the functions of efficient cellular activity are often, if not basically, incompatible. Further, they are timed and balanced dynamically to the service of organismic survival, the acute adaptive response of Cannon's sympathetico-adrenomedullary system having temporarily a higher priority than the ongoing activities of cellular homeostasis.

In studying factors controlling the adrenal medulla, Cannon and his students found that the control of this gland was carried out by the Autonomic Nervous System (ANS). It was also being discovered that regulation of such automatic control functions as blood pressure, temperature, ventilation, osmolarity, and energy balance were also in the province of the ANS. Since the activity of the adrenal medulla is regulated by the sympathetic branch of the ANS, this meant that the same division of the ANS participated both in an array of minute, continuous internal adjustments as well as in preparing the organism for flight and fight

reactions. Only during these extreme conditions, he reasoned, did the sympathetic division "take over" and temporarily suppress the normal delicate regulation of the internal milieu and restitution of cellular function (which he felt was served by finely graded reciprocal shifts between autonomic states, i.e., both sympathetic and parasympathetic).

The "shades of grey" wherein the organism may not be able either to fully "mobilize" towards meeting emergency conditions or to make completely the transition back from emergency to "normal" situations with their much smaller and more precise requirements, were not derived in Cannon's era. It is the classification and understanding of these phenomena that is a primary concern of this paper.

A major shift in perspective comes about when one considers that patterns of autonomic function are plastic and therefore subject to modification by experience. And, while Cannon's discoveries apply to animals in the wild, they are almost certainly not sufficient in understanding "modern civilized man" or even animals in a laboratory environment.

As Smelik (1972) aptly puts it:

"It could happen some twenty years ago, that animals were transferred to the experimental room to undergo a stressful procedure, and that the experimenters were not aware of the fact that the simple opening of the cage and handling had already activated the adrenal system. It appeared that actually not only the harmful stimulus or the life-endangering situation elicits the adaptive reflex, but the anticipation of danger already triggers off the alarm reaction."

This anticipation, which occurs both in humans and in

wild animals, is of obvious natural survival value. In humans and laboratory animals, however, the usual mobilization which follows in the wild is suppressed or absent. Only the perception of this reaction, which, in humans, is probably fear, is present as an acute state. Chronic anxiety<sup>1</sup> can have profound autonomic and hormonal influences--a fact fully agreed upon by most clinicians and researchers in the field of psychosomatic medicine.

Thus it will be of great importance in the study of the various stress syndromes, to understand the potential mechanisms for "accumulation of stress," i.e., for the transition from an acute response towards a chronic limitation in overall organismic function and efficiency.

Yet understanding of the role of stress as an underlying factor in the process of health and disease has been in such complete disarray that it has recently prompted a re-examination of this crucial arena. The initial volumes of the newly formed Journal of Human Stress (Vol. 1; Nos. 1, 3, 4) contain a discourse between two of the most prominent figures in stress research today: Hans Selye and James Mason.

Two basic issues dealt with in this debate are the generality vs. specificity of stress, and whether the concept is more properly tied to stimulus or to internal

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<sup>1</sup>Anxiety, it is assumed, derives from a chronic transformation of the emergency arousal response into an internally activated set.

response dimensions. Selye defines stress wholly in terms of a specific stereotyped response (pituitary-adrenocortical) which is evoked, generally, by all noxious stimulus agents. Mason sees this same response, however, as but one of several endocrine reactions to what he considers a relatively specific group of stimuli--those which have "psychological components."<sup>1</sup>

It will be worthwhile to outline, in single steps. the meaning and scope of "stress" and its relation to health and disease, as it will be used in this dissertation. The facet of stress to be dealt with here is its effect on the autonomic nervous system (Autonomic Stress)<sup>2</sup>, the mechanisms by which it accumulates and its relation to an organism's potential or reserve capacity to meet further stress; as well as the eventual pathological breakdown and manifestation of the various symptoms of the so-called "stress diseases" as this capacity becomes sufficiently diminished. This is not to imply an absolute threshold relationship between the

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<sup>1</sup>The term "psychological," as used by Mason, is mostly to differentiate complex stimuli and "higher" integrative responses--in contrast to Selye's more "physical" or simple stimuli. In this work only the term "behavior" will be used and defined as specifically as possible, in terms of somatomotor components.

<sup>2</sup>While it is AS which is being considered primarily, it will be demonstrated how the autonomic capacity is a measure relating to the performance of the entire organism and that accumulation of AS leads gradually to neuro-behavioral-endocrinological "brittleness" which leads predictably to pathologic breakdown--stress disease.

In Part III the concept will be extended to include the involvement of other systems.

accumulation of AS, the eventual breakdown in disease and the manifestation of symptom pathologies. It does imply the existence of lawful processes in the transition between health and disease, which can be understood with a degree of quantitative rigor.

The next step is to formulate and define the phenomenological and neurological mechanisms by which AS accumulates over time, and how that leads progressively to limitation in an organism's capacity to respond appropriately to further stress (dis-ease) and then finally to the appearance of the "stress disease."<sup>1</sup>

Stress is defined as a process whereby a stimulus elicits activation of the autonomic nervous system (ANS) to such a degree that return to the homeostatic balance can be interfered with.<sup>2</sup>

Stress is then further defined in terms of a dichotomy which divides it into two forms: resolved and unresolved or accumulated. In a particular situation it is both the nature

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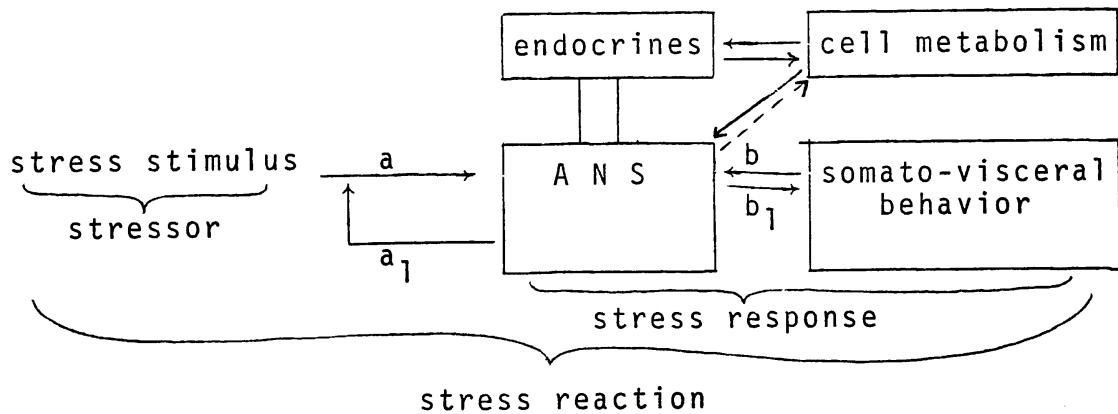
<sup>1</sup>The term "dis-ease" (with the hyphen between "dis" and "ease") is used to denote a continuing process which can eventually lead to the specific symptoms and behaviors of the comparatively abrupt pathological states associated with the stress disease (no hyphen). As a trivial, but illustrative, example, the person suffering an ulcer attack cannot be said to have been healthy the day before that symptom appeared. Common sense dictates that something was already amiss.

<sup>2</sup>Stress is thus distinguished from arousal, where return to balance necessarily does occur. Also implied in this concept of stress is the adrenocorticoid response of Selye, which is concurrent with activations of the ANS (e.g., see Mason 1968).

of the stressful stimulus and the present "capacity" of the organism to "respond" to this stress. This will determine whether the situation is resolved or whether it becomes "internalized" within the organism as a decreased capacity to resolve future stress.

It is proposed, in other words, that stress be defined in terms of a pattern of autonomic reactions which are not necessarily reversed. When initial conditions are re-established, the stress is said to be resolved. On the other hand, when the autonomic stress response is evoked but does not return to its initial state, it is defined as accumulated, and consequently, the autonomic response characteristic to subsequent arousal is fundamentally altered.<sup>1</sup>

I. The stress reaction can be defined in its most general terms as follows:

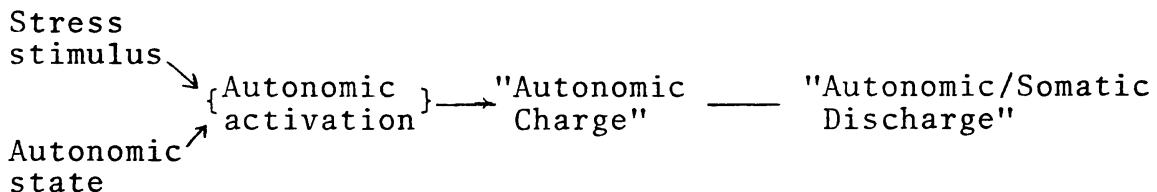



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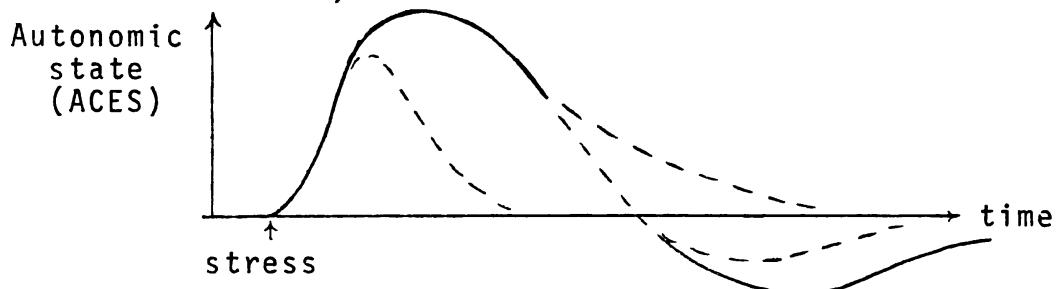
<sup>1</sup>This is not to say that the alteration cannot be reversed--the conditions under which this can occur are central to theoretical understanding of the treatment of stress imbalance and disease.

In addition to the involvement of the ANS in this reaction the figure illustrates that not only somato-visceral behavior but endocrine responses participate as well. The two way arrows allow for more generality. In addition, the two way flow  $a, a_1$  illustrates that the state of the ANS, as well as the nature and magnitude of the stimulus influence one another.

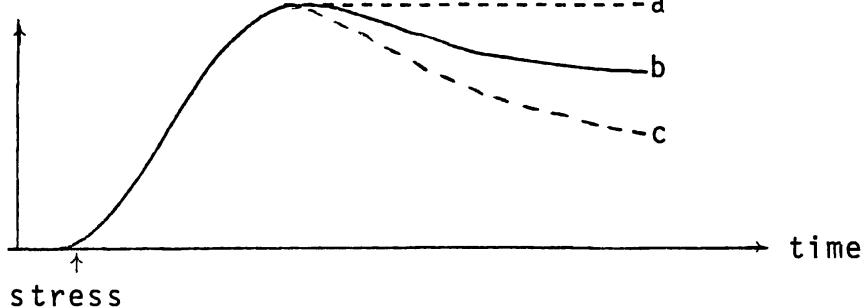
The cycle by which stress is resolved is then defined as follows:



And is portrayed in the following diagrams; for resolved stress, where ACES is taken as a construct of the level of activity in the central autonomic system:



And below for a stress response which is not resolved, i.e., is accumulated:

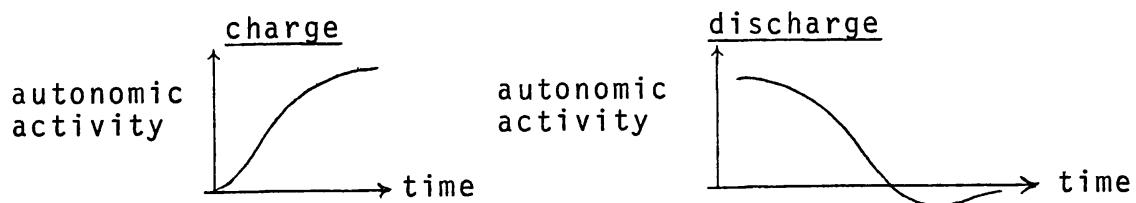


Curve a represents a totally unresolved stress residual, while b and c are partially accumulated.

In summary, then, for a stress to be resolved the shift of autonomic activity evoked by the stimulus must be restored to the pre-stimulus value. If the level does not return to that baseline, the stress reaction is said to be unresolved and a residual stress accumulates, modifying the baseline of autonomic activity.

The mechanisms by which stress is accumulated are central to the development of this paper, and are intimately related to the fact that autonomic activity is expressed, at the effector level, by the interplay of two component branches, the sympathetic and the parasympathetic division.<sup>1</sup>

For reasons which will become clear as the theme of this dissertation is further developed, the autonomic stress response is divided into two primary components, charge and discharge, as shown below:



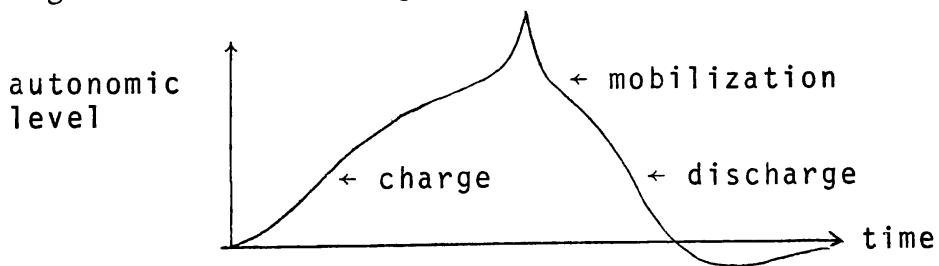

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<sup>1</sup>It will be demonstrated how this organization can be represented by a form of mathematical and systems analysis. This model exhibits a range of interesting and non-obvious behavior which is based only on elemental, well known, properties of the ANS. These basic properties, it will be argued, generate some rather astounding consequences for the mechanisms of stress accumulation and their effect on adaptive range and organismic function.

While stress has been defined in terms of autonomic activities, care should be taken not to think of the autonomic system as a functionally distinct efferent channel isolated from the central nervous or peripheral somatic systems.<sup>1</sup>

As early as 1925 Hess distinguished between 'ergotropic' (E) and 'trophotropic' (T) reactions. The former consisted of sympathetic discharges which were always combined with heightened activity of the somatic muscular system and cortical arousal, while the latter involved parasympathetic discharges and inhibition of somatic and central functions. Indeed, the major function of the autonomic charging was, as Cannon first realized, a preparation and mobilization towards flight or fight. This depended upon the capacity for intense and highly organized motor behavior. As this behavioral response was terminated, a return to the pre-stress autonomic baseline would serve again the ongoing homeostasis.

Thus the complete cycle by which stress activation is regulated can be diagrammed as follows:



The magnitude of the discharge is considered to be determined primarily by the intensity, rate and duration of

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<sup>1</sup>These will be dealt with explicitly in Part III.

the charge phase, the mobilization being more of a catalyst than entering into the dynamics of the discharge phase directly.<sup>1</sup>

Cannon's emergency reaction can be restated, then, in terms of the cycle, as a three phase response involving: (1) autonomic (sympatheticoadrenal) activation; (2) motor response (mobilization) and (3) return to pre-activation levels.

Normally (in the wild) these three phases would occur sequentially, each one leading to the next: the activation evoked by threatening stimuli is supported by and organized into appropriate motor response. This is followed by the phase of discharge into neutral equilibrium again.<sup>2</sup>

It is only in this context of the organismic adaptive response that autonomic activation "makes sense"; the various components are appropriately phased so as to reinforce an integrated response and to insure a return to the pre-stress level of ongoing cellular maintenance. Thus the development in the course of evolution of highly specialized mechanisms to respond to and organize for extreme emergency, with their obvious survival value, would have required parallel machinery

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<sup>1</sup>It will be shown, in section III, D, that mobilization acts upon the autonomic level in a phasic rather than tonic way so that it can trigger a response which might be absent or diminished without it.

<sup>2</sup>Hess, recognizing the unity of autonomic, somatic and central action in integrated behavior, used the terms Ergotropic (E) and Tropotropic (T) (ergon=work; trophon=nutrition; tropic=orientation) to describe these patterns.

to have evolved insuring that these responses acted only during the time when threat was actually present.

The normal mechanisms by which this balance is established appear to be basically similar to those discovered by Sherrington in his pioneer work (1906) for spinal reflexes. He found that changes in the state of excitation are followed by compensatory phenomena. This inhibition of a reflex by its antagonist subsequently enhances the contraction of the agonist. In Sherrington's words, the "inhibition is followed by a rebound to super activity." Similar phenomena also occur at higher levels of the CNS, particularly in the hypothalamus, and involve both the ergotropic (E) and trophotropic (T) systems.<sup>1</sup> These effects, studied by Gellhorn and associates (1943, 1958, 1959a,b) can be summarized briefly as follows (Gellhorn, 1969):

1. Excitation of the ergotropic system: Brief supra-threshold stimulation of the ergotropic division of the hypothalamus which increases blood pressure and heart rate during stimulation is followed by a sudden decrease in blood pressure and heart rate immediately after stimulation. This trophotropic rebound is directly related to the intensity of the preceding sympathetic excitation regardless of whether increasing degrees of excitation had been produced by changes in voltage, frequency, duration of stimulation or similar factors.
2. Excitation of the trophotropic system: Stimulation of the intralaminar thalamic nuclei with currents at a low frequency (3 to 5/sec) which produces recruitment (waxing and waning of potentials in thalamus, caudate nucleus and cortex) is followed after stimulation by a typical arousal pattern in

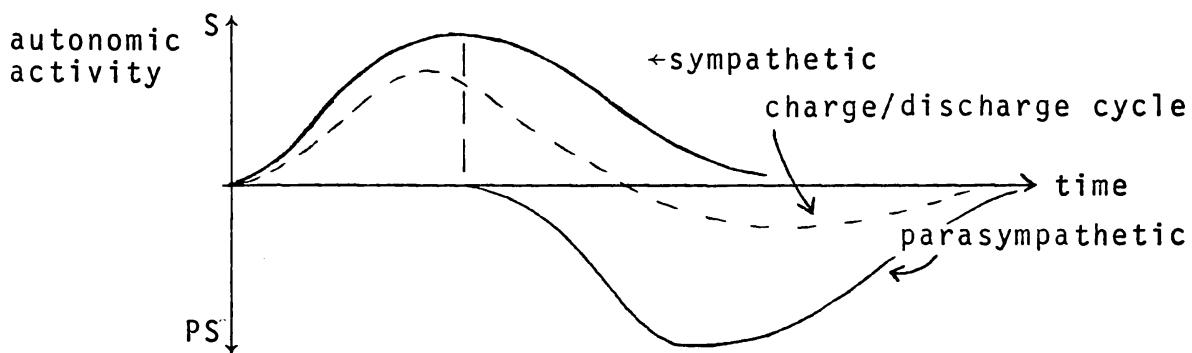
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<sup>1</sup>Equivalent, as used in this sense, to sympathetic and parasympathetic, respectively.

the cortex consisting of potentials of low amplitude and high frequency.

It may therefore be said that ergotropic patterns elicited by diencephalic stimuli are followed on cessation of stimulation by trophotropic patterns and vice versa. These rebound phenomena tend to maintain ergotropic-trophotropic balance.

Thus the processes of charge and discharge can be viewed in terms of the hypothalamic response to excitation: the process of charge being the build-up of central sympathetic activity and its shift to the parasympathetic:



It is the normal reciprocal relation of sympathetic and parasympathetic, then, as we see in the above figure, which insures homeostatic return to baseline autonomic activity.

On the other hand, Gellhorn (1937, 1968a) has found numerous cases where the above homeostatic processes are effective only to a limited degree, and a "tuning" of either branch, at the expense of the other, becomes evident. For example, recall, if the hypothalamus is stimulated at one ergotropic (sympathetic) site, with a brief suprathreshold stimulus, a characteristic rise in blood pressure (BP) and

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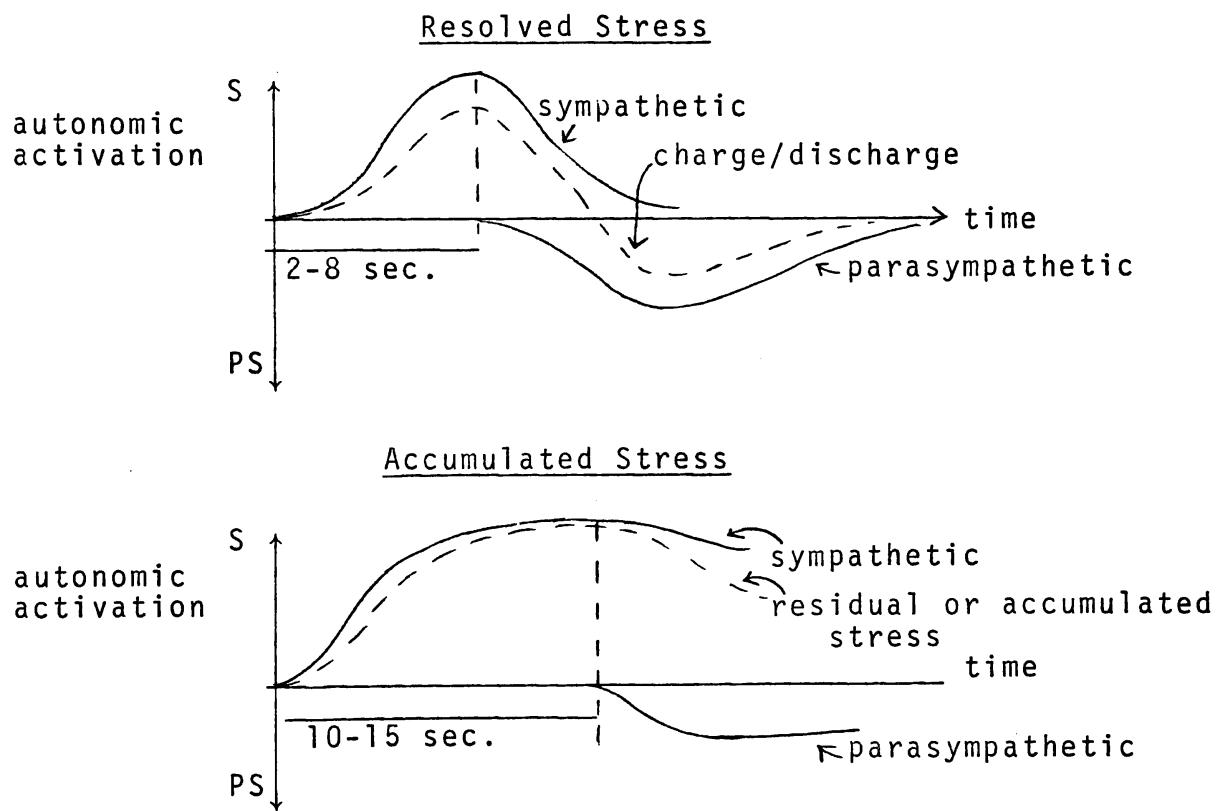
<sup>1</sup> Including a wide variety of physiologic as well as electrical stimuli.

heart rate (HR) will result. This is followed by a trophotropic (parasympathetic) rebound (decrease of BP and HR). If at another ergotropic site in the posterior hypothalamus a more prolonged, near threshold stimulus is applied, little or no ergotropic discharge occurs. When, however, the two stimuli are combined so that the brief suprathreshold stimulus is applied in the middle of the prolonged subthreshold one, the normal supra-stimulus does not produce a trophotropic rebound. The minimal subthreshold ergotropic excitation counteracts the trophotropic discharge which followed the suprathreshold one when it was applied alone. (The explanation might be that normal suprathreshold stimulation of the ergotropic system inhibits the trophotropic and then trophotropic rebound is a release from inhibition. But if it is not inhibited enough in the first place no release excitation occurs.) Further, in those instances where the trophotropic rebound does not occur, ergotropic "afterdischarges" do. That is, instead of the ergotropic stimulation being followed by a trophotropic rebound it is followed by its own reactivation.

These observations suggest that ergotropic afterdischarges produced by various combinations of increasing frequency, intensity, or duration of hypothalamic stimulation might also counteract the homeostatically acting rebound phenomena.

To test this hypothesis Gellhorn applied hypothalamic stimulation with increasing duration. Two phases were observed: if the ergotropic stimulation is terminated in from

two to eight seconds, the tropotrophic rebound is increased along with the magnitude of the preceding ergotropic excitation; but with stimulation periods of ten to fifteen seconds (or more) the tropotrophic rebound is progressively reduced while the ergotropic afterdischarge increases (Gellhorn, 1959). These two responses, along with their respective charge/discharge curves (C-D) are compared in the following figure:



We see above, then, the possibility of a physiological mechanism accounting for the accumulation of stress in a failure of the charge-discharge mechanism to complete a full cycle.

This imbalancing effect can readily become progressive due to a phenomenon Gellhorn calls "tuning": "In a state of sympathetic tuning, the reactivity of the sympathetic division of the hypothalamus is enhanced and that of the parasympathetic division is lessened. Similarly, in a state of parasympathetic tuning, the parasympathetic responsiveness of the hypothalamus is augmented, whereas its sympathetic reactivity is lessened." (Gellhorn, 1967a). Simply, if one branch of the ANS, for whatever reason, becomes dominant,<sup>1</sup> then the responsiveness of the other becomes diminished over a period of time; which is to say that the tuning has become enhanced (and will lead to further tuning of that branch). In this way the restorative homeostatic potential is diminished. In addition, Gellhorn notes phenomena whereby one branch becomes tuned to such a degree that "reversal" occurs: Stimuli which normally evoke an ergotropic response will, in a trophotropically tuned situation, elicit instead a trophotropic response.

Obviously, understanding the dynamics of these processes and the "real life situations" which initiate (and which block) them will be important to the understanding, prevention, and treatment of clinical conditions deriving

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<sup>1</sup>There are a number of ways in which the hypothalamus can be experimentally tuned: for example, through Sino-Aortic reflexes (Gellhorn, 1957); by stimulating other afferent nerves such as the sciatic; through changes in the internal environment, as for example, by asphyxia or CO<sub>2</sub> inhalation; and by pharmacological and physiological changes in hypothalamic function.

from this loss of reciprocal capacity.

It will be argued in subsequent chapters that situations which militate against the resolution of stress (and for its accumulation) can be grouped into three basic types, which are not meant to be absolute but broad and partially independent classes:

- 1) Those in which the level of activation has become so intense that the organism's central processing machinery is unable to integrate the stress into an appropriate mode of discharge.
- 2) Those in which the buildup of charge is so slow (i.e., as in chronic low grade "environmental" or "social" stress) that the mechanisms of rebound are not activated and in which a more acute (though by itself moderate and resolvable) stress response is evoked on that background and becomes accumulated.
- 3) Those in which the somatic (motoric) component of the discharge has been blocked from full or appropriate expression.

#### Section B. Catastrophe Theory

The question is how can the existence of accumulated stress be "proven," as well as its level measured in humans? To do this requires that the various parameters of stress be first defined in a mathematical form so that specific quantitative as well as qualitative predictions can be formulated and specifically tested. The strategy taken in

the subsequent sections will be to look at mathematical-topological properties which can be expected directly from the most basic (and minimal number of) well known physiologic properties of the ANS.

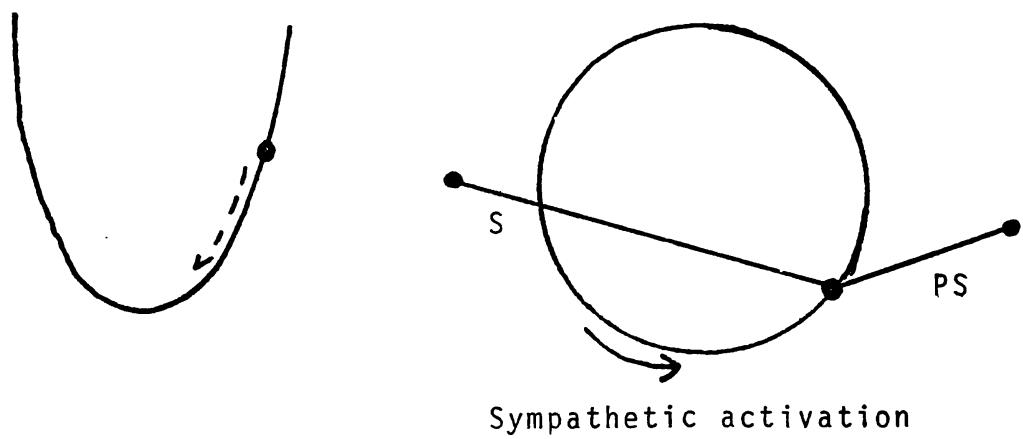
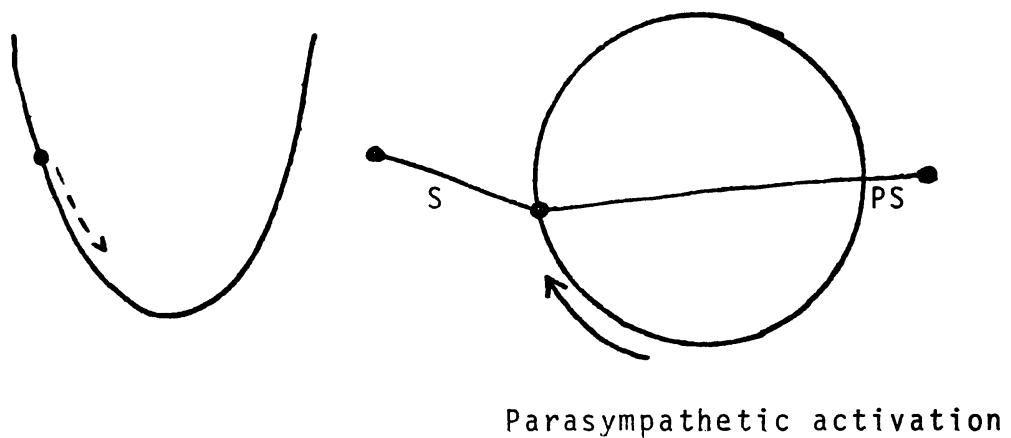
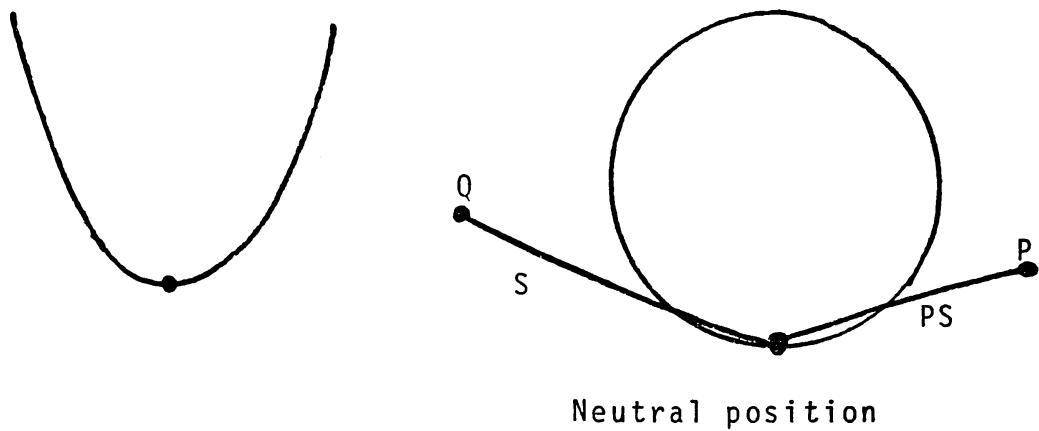
To begin, one of the most fundamental properties of the ANS (and of the nervous system in general) is the phenomenon, demonstrated by Gellhorn, that stimulation of either branch with brief electrical or natural stimuli evokes compensatory rebound of the opposite one; i.e., sympathetic stimulation evokes a secondary parasympathetic response and vice-versa.

Reciprocal activation of sympathetic (S) and parasympathetic (PS) autonomic components does not take place instantaneously but with a significant measurable delay and with only a small degree of overshoot. It exhibits, as an energy system, then, properties characteristic of a high degree of frictional damping.

These basic properties, i.e., reciprocity, friction and delay, can be represented by the following simple arrangement of an inertial disc, pivoted at its center "O", and with two elastic bands fastened to a point on its circumference, the free ends of which are held at points along a straight line through O (figure I).

The sympathetic (S) and parasympathetic (PS) activity are represented respectively by the two bands. If the disc is twisted in a clockwise direction, then the band representing parasympathetic activity is stretched or "charged,"

Figure I.



while a counterclockwise turn activates the one labeled sympathetic. Stretching ("charging") one (by rotating the disc) diminishes the other's charge or tension in a manner described by Gellhorn, and when either a clockwise (PS) or a counterclockwise (S) turn is released, it will--depending on friction and the disc's inertia--return past the neutral position, discharge into the opposing branch and then tend towards the neutral position, illustrating also the phenomenon of rebound.<sup>1</sup>

Description of this "machine" so far gives no added information on the relations of the autonomic components (S and PS) in the accumulation of autonomic stress (AS). It is, though, with some malice to forethought, that this ridiculously simple machine, similar to one invented by Zeeman, exhibits certain essential behaviors described by "Catastrophe Theory," a branch of mathematics theory new to this decade. This theory, in conjunction with control systems analysis, will set the foundation for a model of the ongoing process of health. Health is defined in terms of full autonomic range; dis-ease as a lessening in this capacity; and disease as the abrupt discontinuous changes in behavior and energy metabolism which characterize pathologic stress diseases. Towards these ends, basic ideas from Catastrophe theory will be explored, and some less than obvious,

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<sup>1</sup>The fact that secondary discharge of the original branch rarely occurs in Gellhorn's experiments, except at very high levels of stimulation, suggests that, in terms of this model, the frictional damping forces are high.

unexpected mechanisms for the accumulation of stress developed.

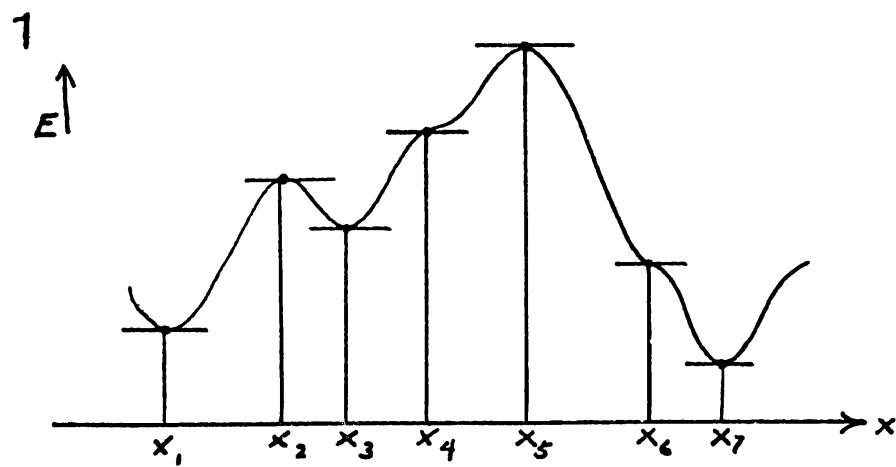
René Thom, in what has been termed "an intellectual revolution," (Stewart, 1975), has developed a theory which comes to the conclusion that almost all systems, which--in a mechanical analogy--have a high degree of friction, fall into only seven types. Thom calls them catastrophes to accent the quality of sudden change. The theory itself is quite elaborate and its proof rests upon "techniques of great sophistication." Fortunately, there have been, in spite of its newness, two very excellent expiatory articles by Stewart (1975) and Zeeman (1976), which are drawn on in this section.

The behavior of a system, in Thom's theory, is governed by an "energy function" E--which is not necessarily the actual physical energy. If we suppose that the state of the system can be described by a single variable  $x$ , a graph of  $E$  against  $x$  can be plotted. Figure II, 1 is an example. The equilibrium states correspond to values of  $E$  where the graph is horizontal. There are several "stationary values" on this particular graph: minima at  $x_1$ ,  $x_3$ ,  $x_7$ , maxima at  $x_2$ ,  $x_5$  and inflection points at  $x_4$ ,  $x_6$ . The minimum points correspond to stable equilibria, i.e., to regions to which the system will return after a slight disturbance, while maxima and points of inflexion correspond to unstable equilibria.<sup>1</sup>

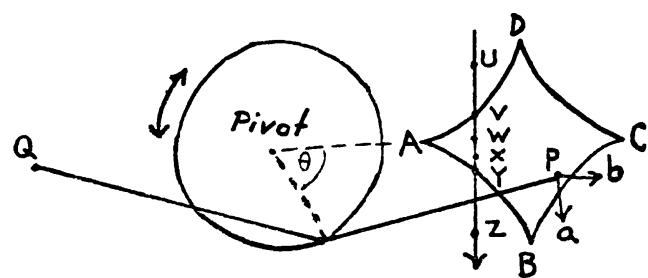
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<sup>1</sup>The analysis has been carried out rigorously by T. Poston and T. Woodcock (1974), Proceedings Cambridge Philosophical Soc. 74:217 ff.

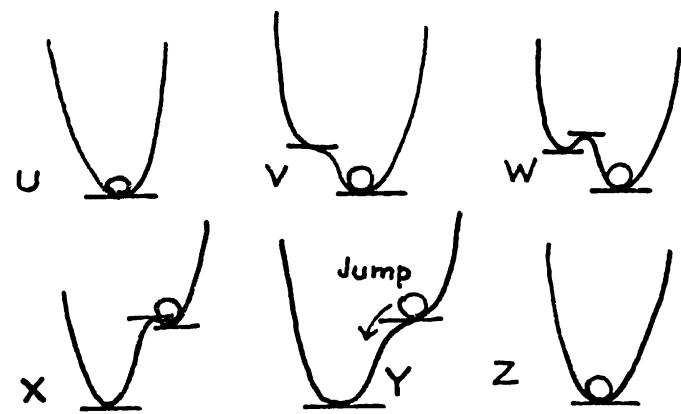
Figure II.



2



3



About the only requirement for the system is that it tends rapidly to a steady state equilibrium. Thus, frictional mechanical systems (force is proportional to velocity rather than acceleration) provide a good specific example with which to illustrate the basic tenets of the theory.

A simple physical model which displays all the relevant phenomena is Zeeman's "Catastrophe Machine," illustrated in figure II, 2: the device, made up of a circular disc, pivoted at the center and free to rotate, with two elastic bands attached to its edge, has already been described. In the formal machine, however, the remaining end of one piece is fixed at point Q, while the other end P is free to move in the plane of the machine.

Experimentally, it can be shown that the diamond shaped area ABCD has the following property: if the free point P is outside ABCD, the rotation angle of the disc ( $\theta$ ) has only one stable equilibrium position; but if P is inside this region there are two stable equilibria. Thus, if the disc is twisted or rotated by an external force, it will return to the same position (if P is outside that region), just as a ball rolling down the side of a closed trough will settle to the bottom. If, however, P is within ABCD, the disc will fall into one of two positions. In general, if P is moved smoothly, the equilibrium position of the disc will (in the absence of any additional forces) also change smoothly. If, however, P moves across the edge of the region enclosed by ABCD, the disc may make a sudden jump from one equilibrium

position to a completely different one. In figure II, 3, as P moves along the path UVWXYZ, a jump occurs in the position of the disc as it passes out of the diamond at Y (but not as it enters at V). If the direction of the path is reversed, that is, as point P is moved through ZYXWVU, the disc still jumps when leaving the diamond area, but now this occurs at V. Thus, the behavior of the disc exhibits hysteresis and does not reverse when the path traced by the free end P is reversed.

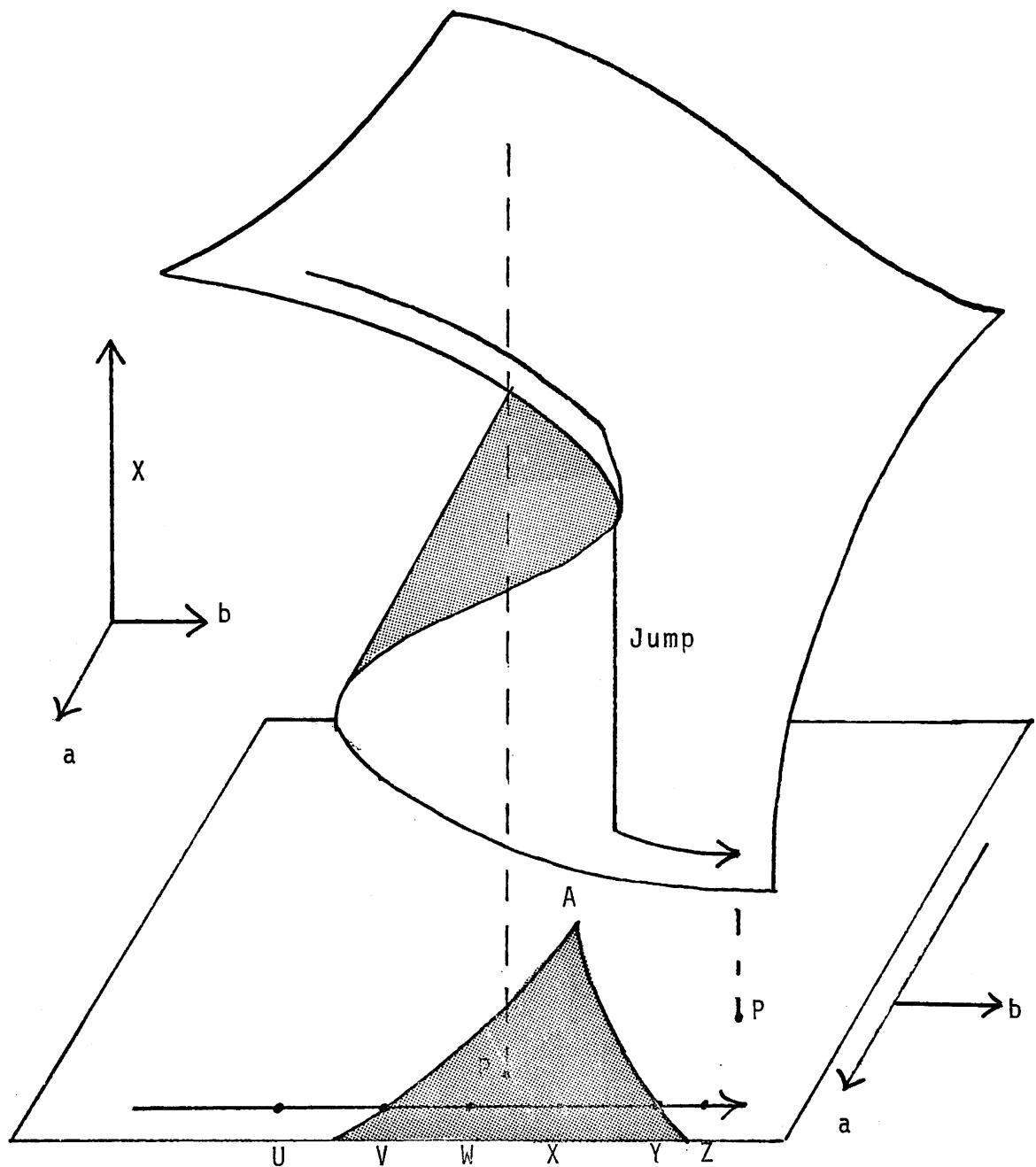
This behavior, which seems mysterious at first, is readily understood if we look at the energy function E (which, in the case of the Zeeman machine, represents the energy stored in the elastic bands) for positions of P traversing along the line UVWXYZ (fig. II, 2). When the point is moved outside the diamond area (e.g., around Y or Z), there is only a single minimum. Inside the area, at W or X, there are two minima on either side of a central maximum. At the edges Z and Y, one of the minima has now formed into the maximum, giving a point of inflection. Immediately, as P moves outside the diamond, this inflection disappears completely, so that as P moves from U to Z the disc starts off in the initial minimum position and, because of the friction, stays at that minimum all the way across to Y. At Y, however, as this minimum disappears, the disc is "forced" to jump suddenly into the only remaining minimum, which is some considerable distance away.

This process can be visualized by drawing a three dimensional graph of these equilibrium positions as a function

of the position of the free end P. A mathematical analysis of the machine leads to the graph depicted in figure III. The folded surface represents the equilibrium values for x, and is called the "Behavior Surface." For any given position of P(a,b) (control points), a vertical line can be drawn, which cuts the behavior surface at 1, 2 or 3 points. The lower plane is called the "control surface." The vertical height of the line corresponds to the equilibrium value(s) of x. If the control point P lies outside the shaded region, then only one value of x is possible. (The shaded region corresponds to part of the diamond shaped region in figure II, 2.) If, however, the point P lies inside the shaded region, there are three values that it can take because of the fold in the surface: one on the upper sheet, one in the middle, and one on the lower. Thus, as point P is moved along the path UVWXYZ (i.e., the control surface), the state of the disc is represented by a point on the behavior surface vertically above P, and "friction" causes this point to stay on the same sheet of the surface as long as this is possible. As P moves through V no trouble occurs, but when P finally moves through Y there is a fold in the upper sheet and the disc location falls off the edge, onto the lower one, with a sudden jump. It can be shown that all the jumps which can possibly occur are incorporated into a single simple geometrical picture like figure III.

In summary, then, the energy which is minimized in this system is the potential energy stored in the elastic bands.

Figure III.



The disc, therefore, rotates until the tension on the two bands is at a minimum. At that position the machine is said to be in a stable equilibrium, and unless energy is appropriately added, the machine must remain at that equilibrium point. The process that keeps it in equilibrium is called the dynamic, and relates the dependent behavior surface variable(s) to the independent control surface variables. The dynamic has two functions: First, it holds the behavior point firmly on the top or bottom sheet of the behavior surface. That is, if the disc is rotated by an external force and then released (as in the sympathetic-parasympathetic analogue described in figure I), it is the dynamic which brings it sharply back to one of the two equilibria. Secondly, when the behavior point crosses the fold curve, it is the dynamic that causes the catastrophic jump from one sheet, that is, from one behavior, to another. So it is the movement of the control point along the control surface which, through the dynamic of the system, results in the path taken on the behavior surface.

Thom studied much more general situations--systems that could be described by a finite set of variables, X, Y, Z... (behavior variables) and controlled by a second finite set of variables, A, B, C... (control variables) under an energy function E which varied with A, B, C... and X, Y, Z... . Thom's theorem says that with only a small group of exceptions, it is always possible to effect a smooth reversible change of coordinates in such a way that in the neighborhood

of a given point the system exhibits one of seven types of behavior.<sup>1</sup> Thus, through catastrophe theory, one can deduce the shape of the entire surface merely from the fact that the behavior is bimodal for some control points.

The Zeeman machine and the basic topology of the Cusp Catastrophe is a very simple system; and the question, of course, arises as to whether the theory applies realistically to much more complex systems such as the central nervous system. An energy minimum in a physical system, e.g., the Zeeman machine, is a special instance of a concept called an "attractor." This particular case is an example of the simplest kind of attractor, the single stable state. It is like a magnet or gravity acting on a trough well. Everything within its range of influence is drawn toward it. It is under the influence of this attractor that the system assumes a state of static equilibrium.

More generally, the attractor of a system, in dynamic equilibrium, consists of the entire stable cycle of states through which the system passes. The bowed string of a violin, for example, repeats the same cycles of positions over and over at its particular resonant frequency. This cycle of positions represents an attractor of the bowed string system (Zeeman).

While attractors can be single states, they are more likely to be stable cycles of states, i.e., "higher

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<sup>1</sup>Their geometry has been studied in detail by Woodcock and Poston (1974) using computer graphics.

"dimensional analogs" of stable states. As various parts of complex systems, such as found in the brain, influence one another, these attractors would wax and wane with varying degrees of rapidity, one attractor giving way to another. As this process goes on, the stability of the system also undergoes alteration, and there is the potential for a catastrophic jump in state. According to Thom's theory, though, ALL possible jumps between equilibrium attractors are determined by the seven catastrophes. This applies strictly to the subset of point attractors, but nonetheless the elementary catastrophes can, according to Zeeman, provide meaningful models for behavior as complex as the brain: "The models are explicitly and sometimes disarmingly simple, but the powerful mathematical theory on which they are based implicitly allows for the complexity of the underlying neural network."

Zeeman lists five characteristic qualities common to all cusp catastrophes: 1) Bimodality of behavior; 2) sudden transitions between states; 3) hysteresis: the transition between top and bottom sheet behavior does not take place at the same point; 4) an inaccessible region; and 5) divergence (large differences in the final state of the system resulting from small perturbations of the initial state).

Now, independent of the complexity of a system, according to Zeeman, "if any one characteristic is apparent in a process, the other four should be looked for, and if more than one is found, then the process should be considered a

candidate for description as a cusp catastrophe."

Of these five criteria, the role of the autonomic systems in stress behavior and disease meets at least two of them and possibly four. (Using the concept of behavioral motility (bm), the fifth criterion, an inaccessible region, is not measurable.)

The first criterion, bimodality, is the basic behavior of the sympathetic-parasympathetic system. That sudden transitions occur both between and within these systems is demonstrated both by the physiological work of Gellhorn and from the wealth of animal observations by Konrad Lorenz and other ethologists. For example, the dynamics of "decision" whereby an aroused animal either fights or takes flight, i.e., exhibits fear or aggressive behavior, has been demonstrated by Zeeman to conform with the predictions of a simple cusp catastrophe. Also, many stress diseases exhibit discontinuous remission or abrupt changes in symptoms such as extreme excitability and depression, as well as being triggered often by events which appear relatively minor to individuals who are not so predisposed. Even the phenomenon of hysteresis seems to characterize the disease process. In a simulation of anorexia nervosa (see section IV, A, The Stress Diseases), Zeeman clearly demonstrates this property.

In summary, despite the vast complexity of central integrative processes, and perhaps because of its discrete division into bipolar output elements, the involvement of the autonomic nervous system in "stress phenomena" appears well suited to catastrophe theory.

### Section C. The Model

Towards relating autonomic and accumulated stress behavior, we look at the Catastrophe diagram, shown in figure IV. The control variables are sympathetic (S) and parasympathetic (PS) activity, while the behavior variable is labeled behavioral motility (bm).<sup>1</sup> The neutral point of the system is the baseline level of autonomic activity ( $S_0, PS_0$ ), corresponding to a behavioral level  $bm_0(S_0, PS_0)$ , which is neither active nor quiescent, but in "restful alertness" (with the potential for a shift in either direction).

Let us first examine the behavior of the system for the case (1) of low to moderate levels of sympathetic activation. The behavior curve and its projection onto the control plane (see figures V and VI) follow Gellhorn's observations of parasympathetic rebound from sympathetic excitations (solid line). In figures V and VI, the dotted curve represents the behavior resulting from a higher level of sympathetic

<sup>1</sup>The implication is that the motility of behavioral expression is controlled by the autonomic nervous system. This at first appears contrary to most modern neurophysiological thought, which accents the role of the higher cortical centers in the programming and execution of behavior. It is certainly not necessary to presume that behavior is generated by the ANS (although the idea of behavior developing on an autonomic matrix will be discussed in a later section), but that overall intensity and excitability are a direct consequence of autonomic activity. This has been more than amply demonstrated by Hess, Gellhorn and others, and is reviewed in section IIIA. In addition, it is not even necessary that the control variables be restricted to two factors. The model can be extended to allow for a multiplicity of factors by compounding the simple cusp into higher order catastrophes. Zeeman (1976) presents a concise discussion of this.

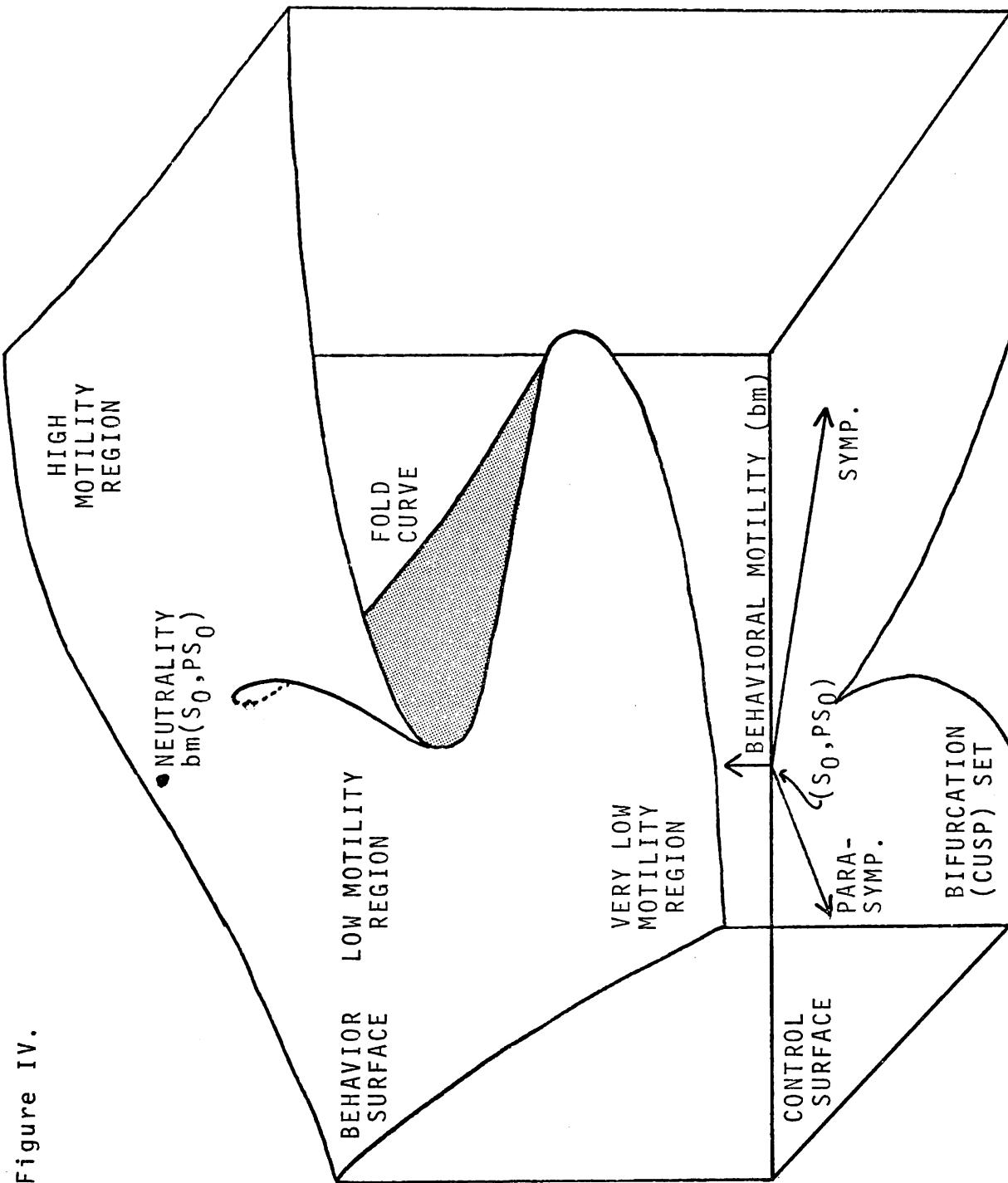


Figure V.

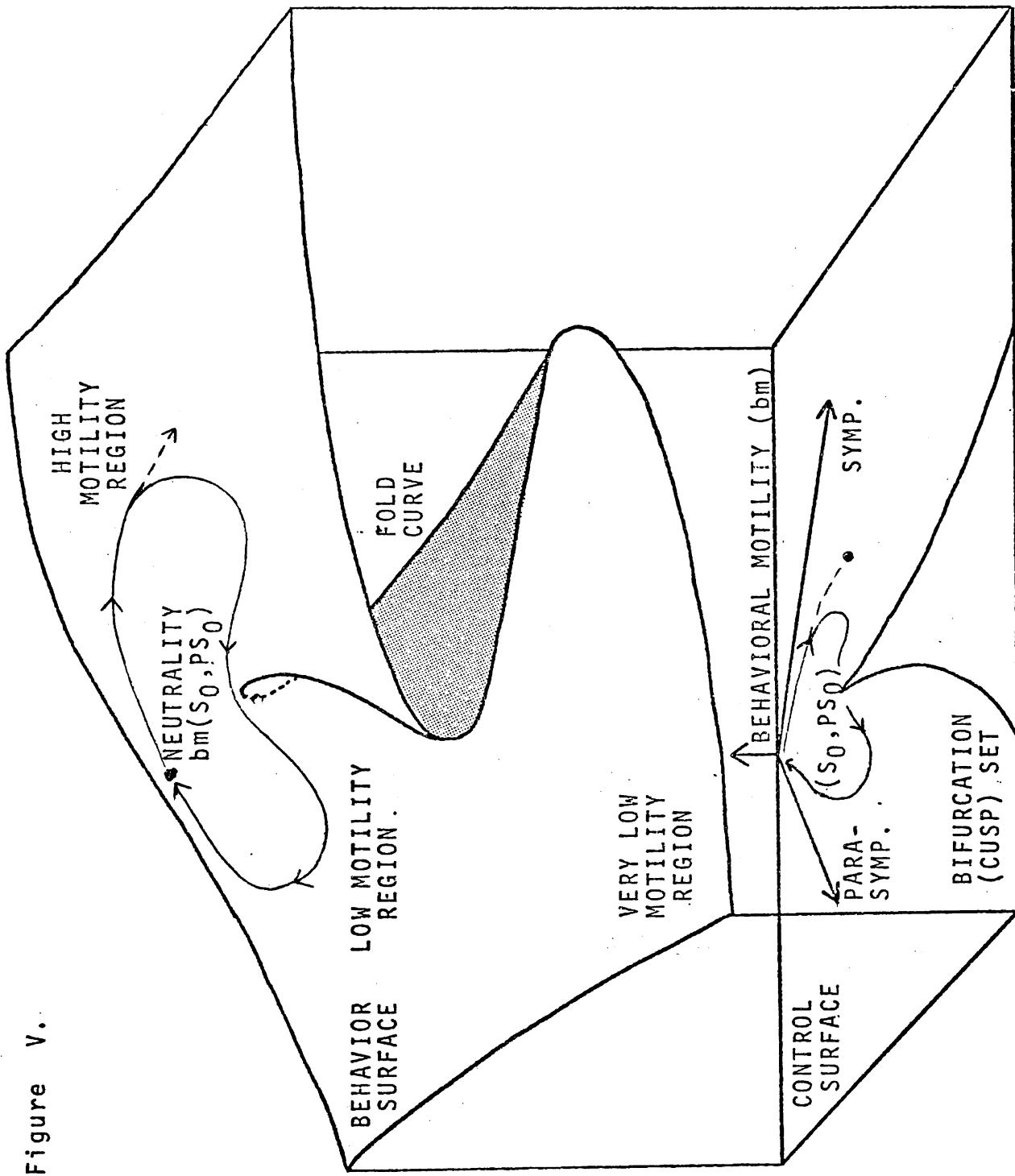
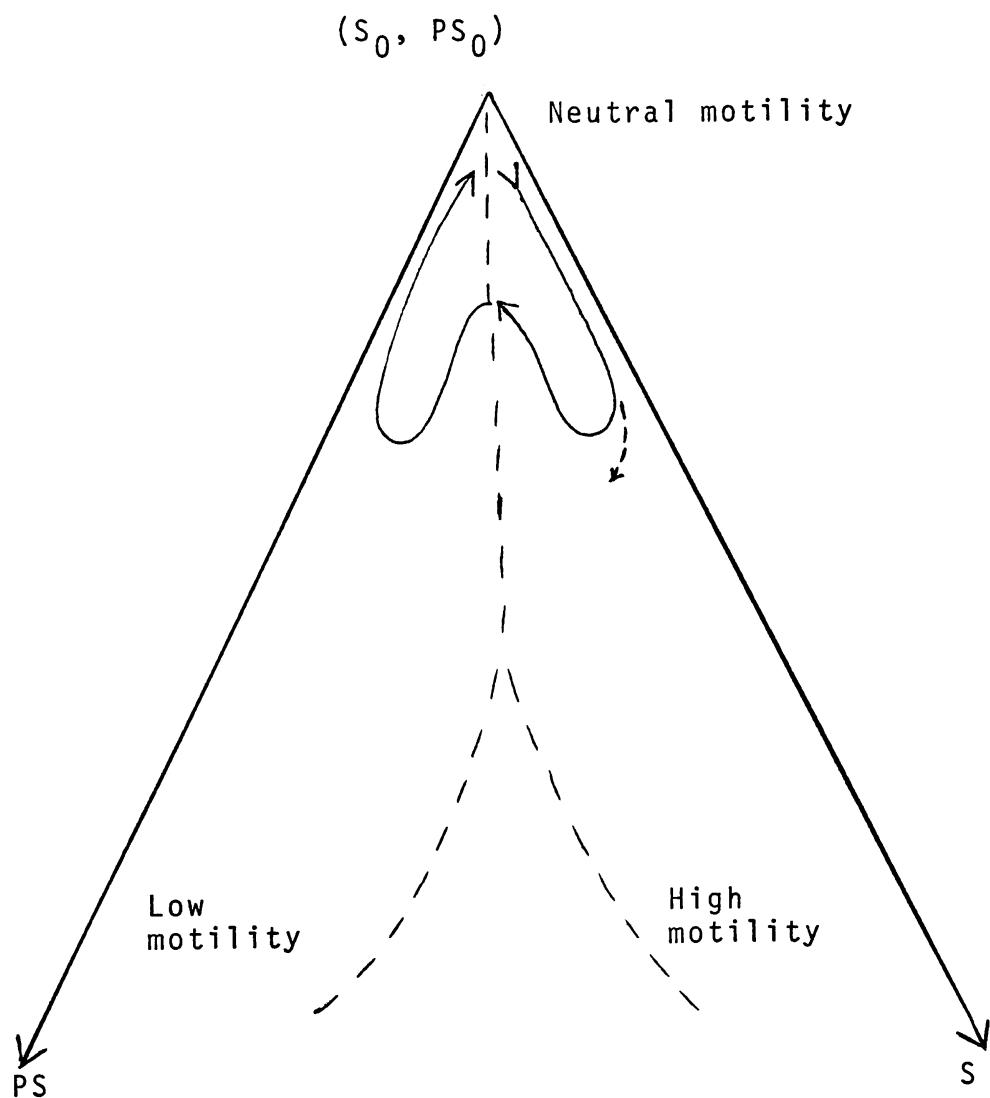


FIGURE VI  
Projection of behavior path  
onto control surface



arousal. The behavioral motility (bm) for both of these curves follows a path which peaks, then subsides smoothly to a low level of motility (lower than the initial pre-stimulus state) and then returns to that value, re-establishing homeostasis. This entire process is carried out continuously and reversibly.

If, however, the cycle of charge into discharge is prevented from completion, then the path, on the behavior surface, is seen to terminate in a region of higher than baseline motility. (Dotted line in figures V and VI.) These curves are essentially a re-presentation of Gellhorn's findings that with rebound from sympathetic excitation, homeostasis is maintained while in the case of afterdischarge it is not.<sup>1</sup>

More interesting behavior, though, begins to emerge as the level of activation increases to higher levels. Gellhorn has demonstrated that for these levels, in addition to reciprocity and rebound, a third property of the autonomic system exists: that at increasing levels of sympathetic arousal, as typified in the response to prolonged asphyxia, a "spillover" occurs of sympathetic activation into the parasympathetic branch. Once an accumulation has occurred in a region outside the neutral origin,<sup>2</sup> then the

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<sup>1</sup>The degree of fixity of those accumulations is really unknown. Experiments on "autonomic learning" by Miller and associates (1964), along with Gellhorn's observations on tuning, suggest that these charges can indeed become fixed.

<sup>2</sup>In Catastrophe space each accumulation becomes the new equilibrium value of the system: The behavior plane, recall, is generated from the set of all the possible equilibrium points (i.e., is the energy equilibrium surface).

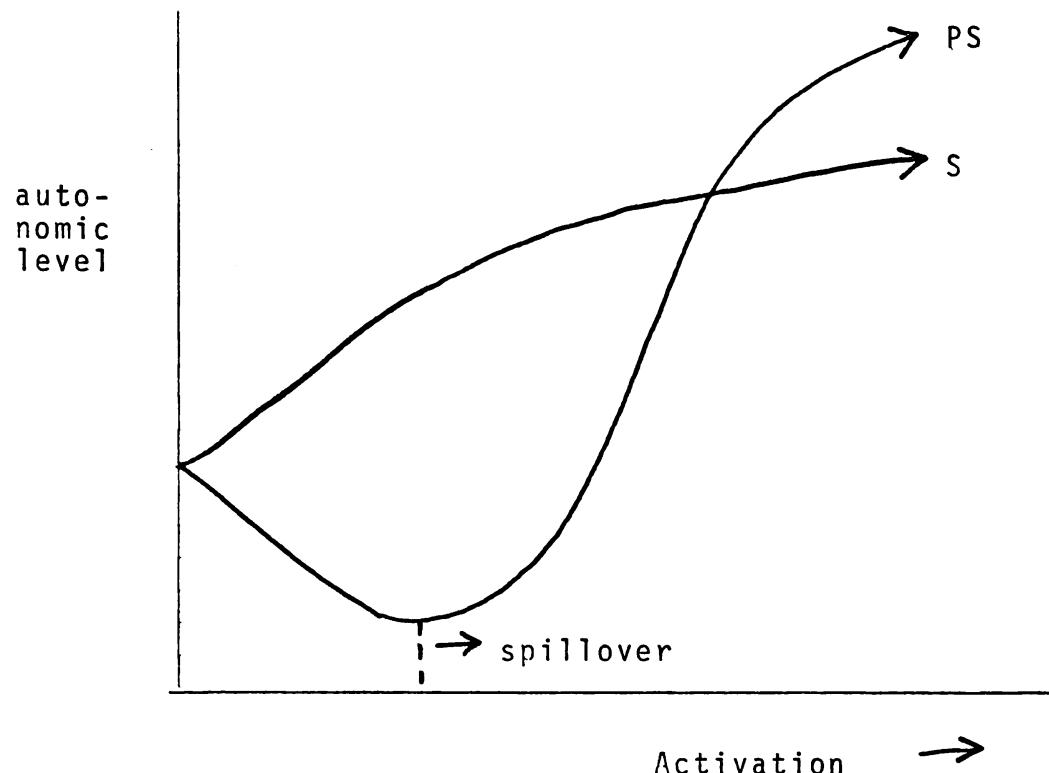
probability for another accumulation is, for the following reason, enhanced. Gellhorn's experiments (see I, B) show that if the sympathetic baseline is maintained at an elevated level, the likelihood of another excitation evoking sympathetic afterdischarge (instead of parasympathetic rebound) is increased. In other words, as the ratio of  $\Delta S/S$  decreases,<sup>1</sup> the probability of resolving that activation also decreases. Thus, with each successive accumulation the probability of the next activation being resolved is diminished. In addition, due to "spillover," the parasympathetic system eventually becomes activated at a greater rate than the sympathetic (see figure VII). This further favors accumulation by "blocking" the potential for mobilization, as follows: Along with a heightened sympathetic tone there is an increase in muscular activity and, therefore, in the likelihood of the organism to respond in patterned movement (the ergotropic syndrome described by Hess). As will be discussed at length in Part III, sections D and E, the muscles send back impulses centrally which activate the ANS. During intense motor activity, then, these brief, high frequency volleys are themselves stimuli to the ANS. And they can trigger a discharge by presenting, in effect, an intense short excitatory stimulus.<sup>2</sup> Thus we see how appropriately phased mobilization increases the likelihood of a stress being

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<sup>1</sup>I.e., the change of sympathetic, relative to its absolute value which an activation stimulus evokes.

<sup>2</sup>The effect of this is to make  $\Delta S/S$  large (and brief) which, from Gellhorn's experiments, will be more likely to evoke a rebound discharge.

Figure VII



resolved (i.e., of charge going into discharge). The normal parasympathetic (T)-reaction, on the other hand, involves an inhibition of somatic tone and responsiveness, thus making a motor response less likely. (Parasympathetic states are usually associated with "internal processes" of restitution, sustenance and maintenance.) Concomitant sympathetic and parasympathetic activation, however, will result (as detailed physiologically in Part III, section D), either meta-stably in a reduced capacity to respond, or in loss altogether of mobilization. A state of high sympathetic tone still exists, but the impulsive trigger stimulus is greatly diminished if not absent. The state of high sympathetic and parasympathetic activation with low motility behavior is termed the stasis.

We see, then, in summary, how stress residue is both accumulative and progressive. And from figure VII the path it takes is readily visualized: Departing, initially, from the neutral equilibrium along the sympathetic control axis, it curves inward towards the cusp (from the high motility side), passes into that region and then eventually takes an obligatory jump to the low motility surface as the control variables exit the cusp. It is important to note that this transition can, when the control point is in the vicinity of the cusp boundary, be precipitated by a minute change in either the sympathetic or parasympathetic control variables.

The development of Catastrophe theory, along the lines of the preceding sections, suggests a number of insights into

possible mechanisms for the accumulation of stress. It also points to the progressive loss in adaptive potential capacity and to the emergence of discontinuous organismic behaviors resulting from chronically unresolved stress. There should be, according to the model, a wide range of baseline activation levels which characterize the underlying form of the stress diseases. It should not be so much the specific symptoms which characterize a disease, but the levels of sympathetic and parasympathetic activation at which that organism has become fixed (within the cusp region); and whether it is in a state of high or low motility. Further, once an organism has become fixed at one of these levels, the likelihood of progressive accumulation and the difficulty of resolving the accumulation are, according to the model, both increased.

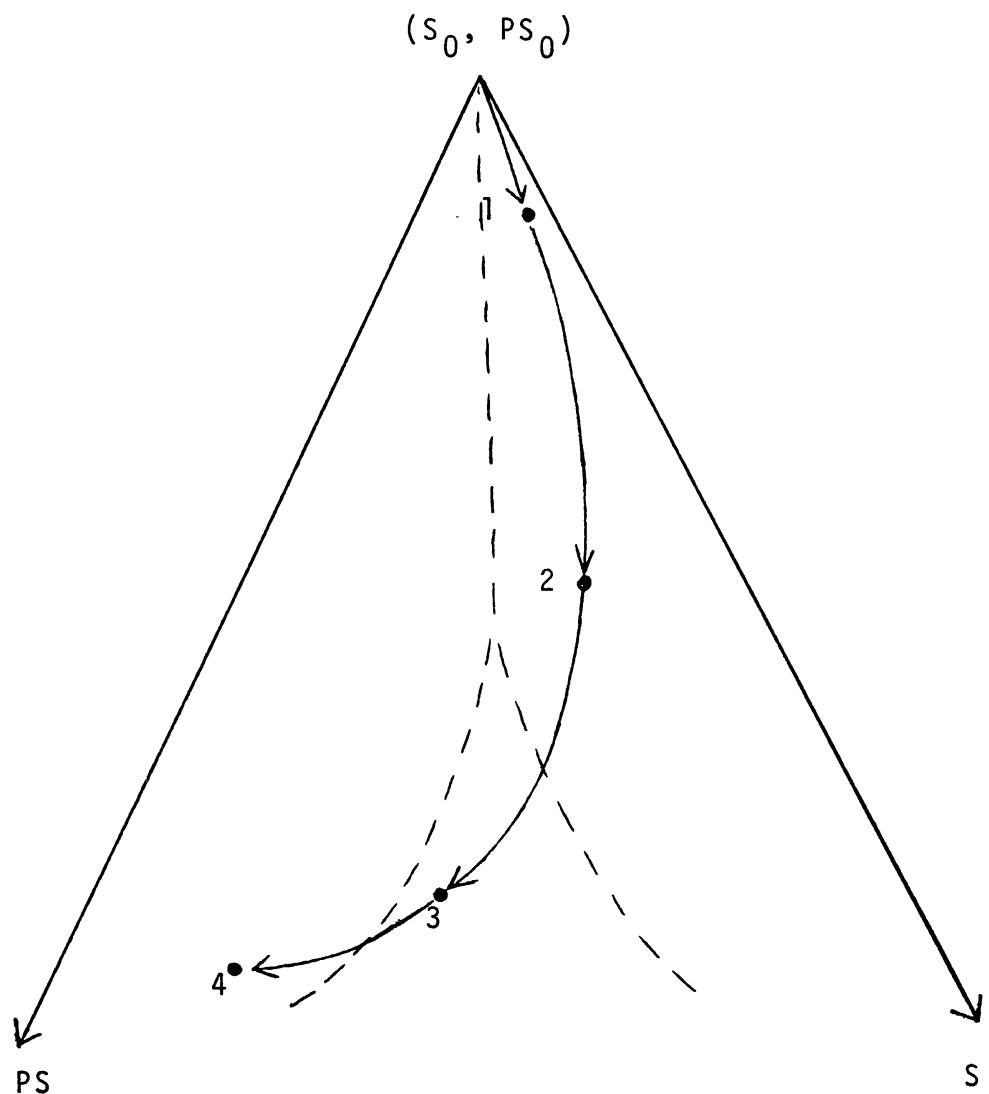
In summary, then, once an organism has been unable to resolve a major stress it is, according to the model, vulnerable to a progressive deterioration in performance: the baselines of motility, fixed at a high level, limit the potential range of response behavior and decrease the probability of returning to homeostasis equilibrium. In addition, the sympathetic and parasympathetic systems are operating, not in mutual reciprocity (as is required for the efficient regulation of energy metabolism) but against each other at high levels of activity like brake and accelerator. As stress continues to accumulate, eventual parasympathetic dominance causes an obligatory discontinuous jump to the lower surface.

#### Section D. Predictions of the Model

In order to formulate quantitative predictions it is necessary to assess theoretically, from the catastrophe topologies, the "resolvability" for these progressive levels of accumulation and then to compare them with a population of unhealthy persons. It will be useful, to this end, to look at a few specific situations: The four points labeled (1, 2, 3, 4) in figure VIII represent a progression of stress accumulation, resulting from failure of completion in the charge/discharge cycle. The first point (1) represents the accumulation, essentially of a heightened sympathetic tone, which will, if not resolved, progress eventually to point (2), where a concomitant parasympathetic accumulation is beginning, in line with Gellhorn's "spillover," to (3), an accumulation on the high motility surface of the cusp region for which the parasympathetic component begins to increase at a greater rate than the sympathetic, and finally to point (4), for which the control variables are only slightly greater than in (3), but where there has been a sudden (catastrophic) decrease in the behavioral motility.

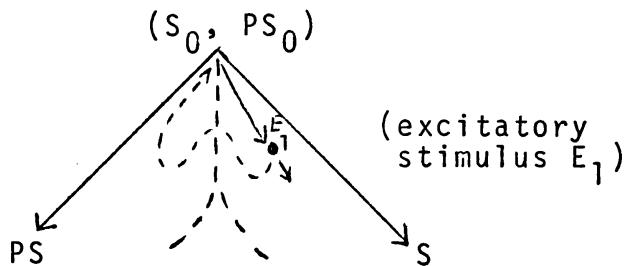
The case (1) topology (from figure VIII) below, suggests a number of ways to bring the behavior point from (1) back towards the neutral equilibrium at  $(S_0, PS_0)$ .

FIGURE VIII



Case 1

(Point 1, figure VIII)



It must be borne in mind first that in an intact responding organism, responses are generated by stimuli which evoke either sympathetic or parasympathetic discharge, and stimuli do not appear to exist which directly and effectively diminish one branch.<sup>1</sup> Thus, ordinarily (in an unstressed--not accumulated--organism), a sympathetically dominated state can most effectively be countered by the introduction of a parasympathetic stimulus and vice-versa.

One "physiologic" possibility, then, would be to evoke a sufficiently intense parasympathetic response, thereby actively inhibiting the sympathetic one. Evoking this type of "relaxation" response<sup>2</sup> is limited, however, in that sympathetic responses tend usually to be much stronger than parasympathetic ones. It may be difficult, then, to evoke a sufficient parasympathetic response if the accumulated sympathetic tone is even moderately high.

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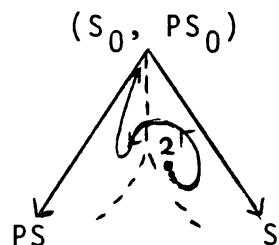
<sup>1</sup>If, of course, an organism is in a situation which evokes a sympathetic reaction, then removing these stimuli (or the organism from the situation) could counter the initial effect.

<sup>2</sup>Parasympathetic stimuli generally tend to be perceived as pleasurable, e.g., touch, warmth, deep muscular pressure, and probably various "internal" meditative procedures.

The other biologic possibility would be, paradoxically, to apply sympathetically acting stimuli to even higher levels so that a rebound into discharge can occur. This is illustrated by the dotted path in the preceding diagram.

For the case of point 2 (figure VIII), it is even less likely that parasympathetic stimuli could be used to draw off the sympathetic charge; and in addition, due to tuning, reversal reactions may occur, causing even a slight increase in sympathetic tone. In this case (2), which has both a higher baseline equilibrium and the beginnings of a simultaneous parasympathetic component than in (1), the timing of the sympathetic stimuli will be slightly more important for resolution to occur. This is visualized below:

Point 2 (figure VIII)

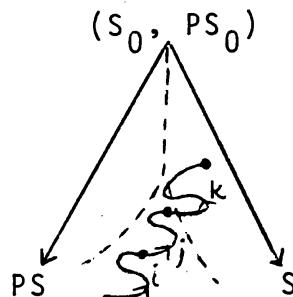


The situation for dealing with accumulation in the region of point (3) becomes more difficult than (1) or (2). This is so, again, for the reasons of the high baseline sympathetic tone and spillover effects; but in addition there is another complication: Further activation will shift the control variables to the right, causing eventually a catastrophic shift onto the low motility surface. This, at first, might not appear so disadvantageous. It is,

however, only the behavioral motility which is much lower here than just before the transition (whereas both the sympathetic and parasympathetic components remain high, increasing only minutely in the transition). This would result in the position of point (4), which will be considered shortly.

What this means, though, in "treating" case (3), is that only small increments of excitation can be used. Otherwise the catastrophic jump may occur to the low motility region, all but "obliterating" the possibility of a mobilizing response. Thus, for an organism operating chronically in this region, (3), successful resolution would be expected only by a series of gradual steps, whereby "just sufficient" sympathetic impulses would be used to successively trigger partial discharges:

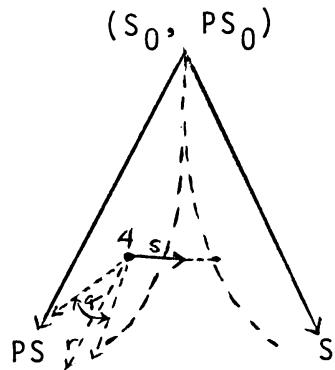
Point 3 (figure VIII)



In the figure the partial resolutions, *i*, *j*, *k*, take the organism approximately towards the region of case (2), which could then be dealt with by progressively larger cycles of charge/discharge.

Case (4), where the catastrophic jump has occurred, represents, unquestionably, the most serious and difficult class of stress accumulations to deal with:

Point 4 (figure VIII)



First of all, the situation involves the concomitant occurrence of low motility behavior with simultaneously high sympathetic/parasympathetic activation, resulting in a very low probability of mobilization. This makes resolution extremely difficult because if an attempt is made to stimulate either autonomic branch directly, then, due to spillover and parasympathetic dominance, movement will be within the vectors shown originating at 0 within the angle  $\alpha$ , e.g., path r. This path is in the direction of further decreasing motility and even higher control (autonomic) coordinates. Thus we see that any attempt to shift balance directly with autonomically acting stimuli will be difficult, as will be shown, and may even worsen the situation (path r). Even if stimuli or physiologic and pharmacologic maneuvers could be applied so as to shift point (4) to the right (path s), behavior would remain on the low motility surface until the

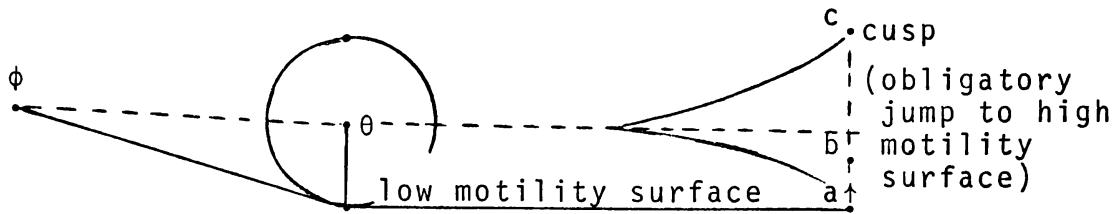
control points were moved all the way through the cusp to the right hand border, where a reverse catastrophe jump would bring the point back to the high motility surface (path s).<sup>1</sup> Since the cusp width (i.e., the distance the control variables must be moved before the reverse jump occurs) increases exponentially along the cusp axis (see figure X), this strategy would be of greater value for accumulations occurring near the origin of the cusp.

The remaining strategy would be to evoke, very briefly, a small autonomic response. This can be expected to initiate a partial charge-discharge cycle (path s above); and then while the control variables, either on the charge or discharge portion, enter towards the right into the cusp region, to impart an "energy of mobilization" to the system, causing it to jump to the high motility surface. This would cause the point to jump, at a region still very close to the left-hand (low motility) border of the cusp and "re-appear" on the high motility surface (at the same control points). Since this point is potentially an equilibrium position, it will remain on the upper (high motility) surface, provided that the right amount of momentum (in the analogy of the Zeeman machine) is imparted to the system. If, on the other hand, too little or even too much momentum is imparted, the point may overshoot the high motility equilibrium and return to the low surface.

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<sup>1</sup>This is an example of the phenomenon of hysteresis (where going up is a longer path than coming down), characteristic of Zeeman's five criteria for cusp behavior.

This process can be visualized nicely in terms of the Zeeman machine analogy as follows:



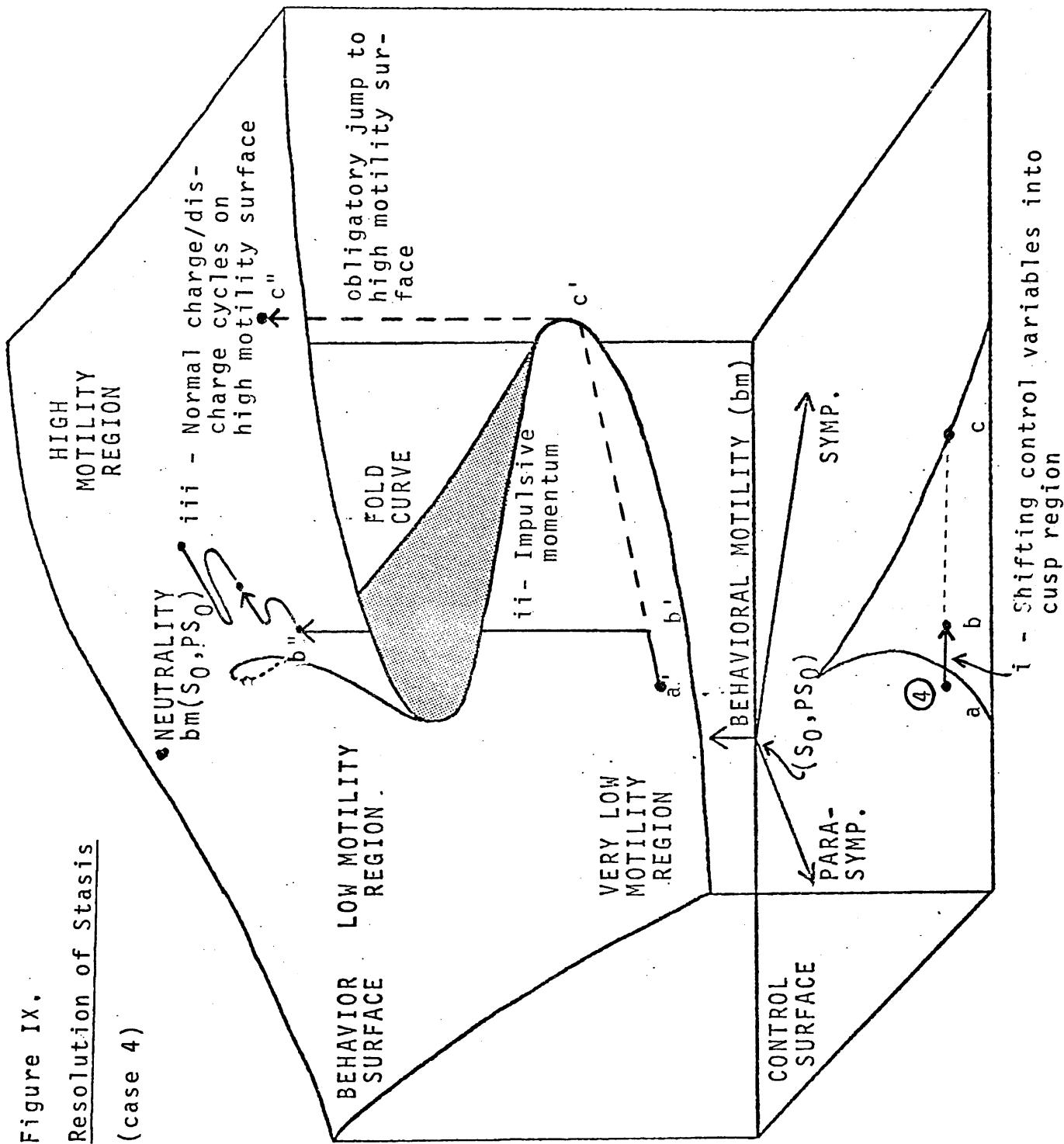
The movable point P is, in case 4, initially at the low motility transition of the cusp (point a on the above diagram). If (as described in the section on Catastrophe theory, IB, and figure II) the control point is moved along the pathway a, b, c (figure IX), the angle  $\theta$  (behavioral motility) does not change until it is moved all the way to c'.

If, on the other hand, the control point P is moved only slightly from position a to b (figure IX), held there, and then the disc is either given a "flick" in the counter-clockwise direction, or rotated in the clockwise direction and released, then the transition between the low and high motility surface can occur directly at b, from b' to b" (on the behavior surface), instead of at c.

What can be said in summary is that what may be crucial to resolving accumulated stress is that the equilibrium state of the system have the potential of being mobilized. In other words, an organism in equilibrium on the high motility surface can be mobilized more readily and is no longer shifted into the progressive cul de sac of lower motility and higher autonomic levels by each activating stimulus; and

Figure IX.  
Resolution of Stasis

(case 4)



has therefore a much larger range of adaptive behavior as well as likelihood of discharge.

The key, then, to dealing with organisms in highly accumulated "stasis" states is the application of finely timed sequences of autonomically acting stimuli coupled with the evocation of appropriate behavior in terms of mobilization (momentum in the Zeeman model analogy). It is this sequential patterning of autonomic and somatic behavior which is central to the resolution of accumulated stress as well as to its regulation in general.<sup>1</sup> This can be seen as occurring in three stages:

- 1) The initiation of small autonomic perturbations (minimal local discharges) so as to shift the control variables into the cusp region.
- 2) Mobilizing appropriate motor discharges so as to force the crucial transition between the low and high motility surfaces.
- 3) Creating a successive charge/discharge pattern on the high motility surface, i.e., re-creating case (3), then (2), (1) and eventually return to neutral equilibrium (homeostasis).<sup>2</sup>

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<sup>1</sup>These patterns of autonomic and somatic function will be discussed in part II, sections D, E, as well as the relation of momentum, in the Zeeman analogy, and somatic mobilization (section III, F).

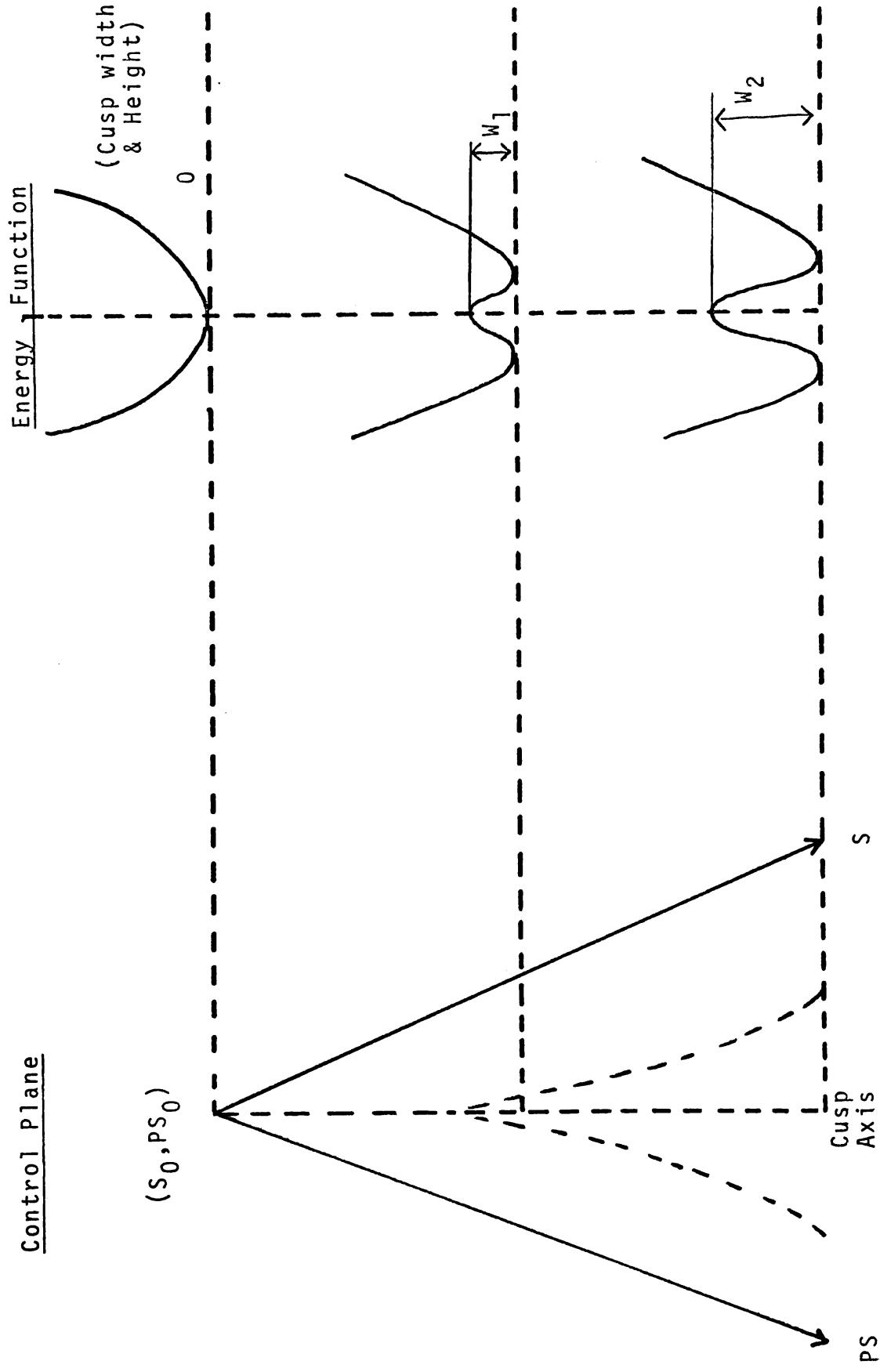
<sup>2</sup>The numbers and magnitude of the steps needed to accomplish this would be a consequence of many factors including not only the number and excitation levels at which stress accumulations occurred, but also the developmental ages at which these stresses had occurred. These developmental etiologies will be discussed in section IV,A.

This is illustrated as paths i, ii, iii in figure IX.

An additional factor in determining the severity of stasis region accumulation is the width and height of the cusp (i.e., the projection, respectively, of the cusp on the control axis and the separation of the two motility surfaces). In the Zeeman analogy, the further along the cusp axis that the accumulation has occurred, the greater the angle that the disc must be moved through, and if the transition is attempted solely by shifting the control variables (towards the right), the greater the distance they must move in order to evoke an obligatory transition to the upper surface. Both of these factors would be expected to increase exponentially along the distance of the cusp axis (see figure X).

In summary, then, the expected response (in terms of the possibility of re-establishing the charge/discharge cycle), to excitatory stimuli in the four instances just described (figure IX) follow: For case (1) (point 1), almost any relatively brief sufficiently excitatory stimulus would be expected to trigger a discharge rebound to a lower level of autonomic (sympathetic) tone and associated motility. Case (2) would be similar, but a chance now exists of moving that point towards the cusp region. Cases (3) and (4), on the other hand, because of their topologic position, represent a more difficult situation. In (4) the system (organism) is already in a low motility state but 'controlled' by high simultaneous autonomic levels, while in (3) the probability of a large excitation "pushing" the organism

FIGURE X



into the "stasis" configuration of (4) is almost assured. Thus, it is not the distance from the origin (of neutral homeostatic equilibrium) which should correlate with the severity ("non-resolvability") of a stress syndrome, but the shifting to the cusp region and to the low motility border where catastrophic transitions occur that determines the "stuckness" of the situation.

The next section presents an attempt to test these predictions directly before they are extended more generally as a basis of the various stress diseases.

#### Section E. Test of Model by Hospitalized Population

In order to test these hypotheses it would be necessary to find an unhealthy population with a high chance of its members falling in a substantial range of accumulation levels, and for whom a prognosis of improvement (either spontaneously or due to a standard treatment) is known. And (importantly) there must exist, in addition, some method to measure, independently, their sympathetic and parasympathetic components of autonomic activity before (and preferably also after) treatment, as well as changes in the behavior of their individual disease processes.

Unfortunately, however, it has not been possible to measure directly (i.e., independently) autonomic response in human subjects, but only their net result expressed on the effector organ level, e.g., Galvanic Skin Response (GSR), skin conductance, heart rate (HR), blood pressure (BP),

pupillary response (which does give a measure of some independence, since the pupil is enervated only by adrenergic fibers). In most of these responses there is usually an inverse "u" relationship to arousal, indicating that in physiologic situations both branches act together (e.g., Malmo, 1959).

Since the components cannot be differentiated directly,  
the strategy taken here will be to separate them by use of  
a systems analytic model.<sup>1</sup>

It is necessary, of course, to choose an output intimately involved in the regulation of "stress behavior." It must then be possible to derive from that peripheral measure (which represents the composite action of both autonomic branches) the underlying individual sympathetic and parasympathetic component functions. It is also desirable that the measure be simple and readily accessible from large populations of persons.

A most appropriate choice is the cardiovascular system. Besides providing experimental access, from two easily measured parameters (Heart Rate--HR--and Blood Pressure--BP), there is relatively substantial analytical knowledge for most of the individual elements involved in this system. Further, the role of the cardiovascular system as the primary global effector system involved with regulating metabolic adjustments, in defensive as well as alerting, orienting and

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<sup>1</sup>This model is described in Part V.

vigilance behavior, is well known and documented (e.g., Lisander, 1970).

Primary reflex control of blood pressure occurs at nuclei within the medulla, whereas defensive stress behavior is integrated primarily by the hypothalamus. The relationship of the hypothalamic, autonomic stress response and basic medullary patterns thus becomes a central issue. Medullary control has been well studied for decades and recently has been successfully analyzed by the systems approach.

This analysis considers the cardio-vascular system as a closed loop, the base level, or constant setpoint, which is maintained by baro- (blood pressure) receptors feeding back to depressor areas in the medulla.

That the hypothalamus can affect medullary BP control has been known for over half a century (Karplus & Kreidle, 1901, 1927), though the details and mechanisms are still largely unknown. Data is now also available which allows additional elements, such as the effect of circulating adrenaline and blood gas saturation levels, to be incorporated into the basic system. What is not available are the effects hypothalamic inputs may have on altering the basic medullary control system response and set point. It is known that the cardiovascular changes evoked, even by gross artificial hypothalamic stimulation (and which lead to global involvement), are indistinguishable from those occurring in behaviorally evoked defensive stress actions. For this

reason, it seems highly probable that the accumulation of autonomic stress would directly alter cardiovascular response.

The peripheral cardiovascular response is readily obtained, quantifiable and of relatively small variance, and its components have been studied as well or better, at an analytical level, than any other system. In addition, heart rate (HR) and blood pressure (BP) can be easily measured without disrupting patients unduly, and these parameters normally respond quite uniformly to standard physical perturbations.

Funkenstein and his co-workers introduced an autonomic test based on the return to baseline blood pressure after the administration of a peripheral hypotensive or hypertensive agent. Meholyl (a long lasting analogue of acetylcholine, which has been administered to thousands of patients without ill effects) is injected into the arm muscle while blood pressure and heart rate are recorded at intervals of 20 seconds to 1 minute for 15 or 25 minutes. The effect of the drug is to lower peripheral blood pressure, thereby diminishing baroreceptor activity and its normal inhibitory influence on sympathetic centers in the medulla. This reflexive release from a major component of inhibition disturbs the balance, evoking a compensatory sympathetic discharge (initiation of pressor action). Conversely, a pharmacological agent which induced peripheral vasoconstriction (noradrenaline) and therefore an initial rise in BP, would stimulate a parasympathetic and vasodepressor response.

On the basis of these tests Funkenstein was able to sort a hospitalized population ("mental patients") plus control group into seven response categories (figure XI, groups 1-7).

In part V (section B) of this paper, independent sympathetic and parasympathetic variables are derived from a control system analysis of cardio-vascular response to peripherally induced perturbations, using the data of Funkenstein<sup>1</sup> (on hyper- and hypotensive drug induced changes). The results of this simulation will now be analyzed in terms of behavior on the surfaces of catastrophe space: The sympathetic and parasympathetic levels characteristic of the major Funkenstein patient groups are plotted on control surface (figure XII).<sup>2</sup>

<sup>1</sup>The treatment used in Funkenstein's study was electro-shock treatment (ect). The long term benefit of such a modality is controversial if not possibly negative. There is little doubt, though, that one of its many effects is an ergotropic activation; and it is this which presumably is responsible for its short term effects on behavioral motility. See Gellhorn (1957).

<sup>2</sup>These data are derived from the control systems analysis of the clinical data, i.e., the cardiovascular response to hyper- and hypotensive perturbations. By this method an independent measure of sympathetic and parasympathetic activity is extracted from the clinical blood pressure data.

The system simulation parameters, pressor setpoint, vagal gain, depressor gain and level of adrenal medullary discharge, are combined as follows:

Sympathetic level = pressor level + adrenal medullary discharge.

Parasympathetic level = depressor gain + vagal gain.

In order to establish a scaling factor, the average sympathetic and parasympathetic levels for groups II and III (which comprise over 90% of the "normal controls") are set at  $S_0=0.0$ ;  $PS_0=0.0$ . This is done by applying a subtractive scaling factor of 0.2 to the simulated sympathetic data; while

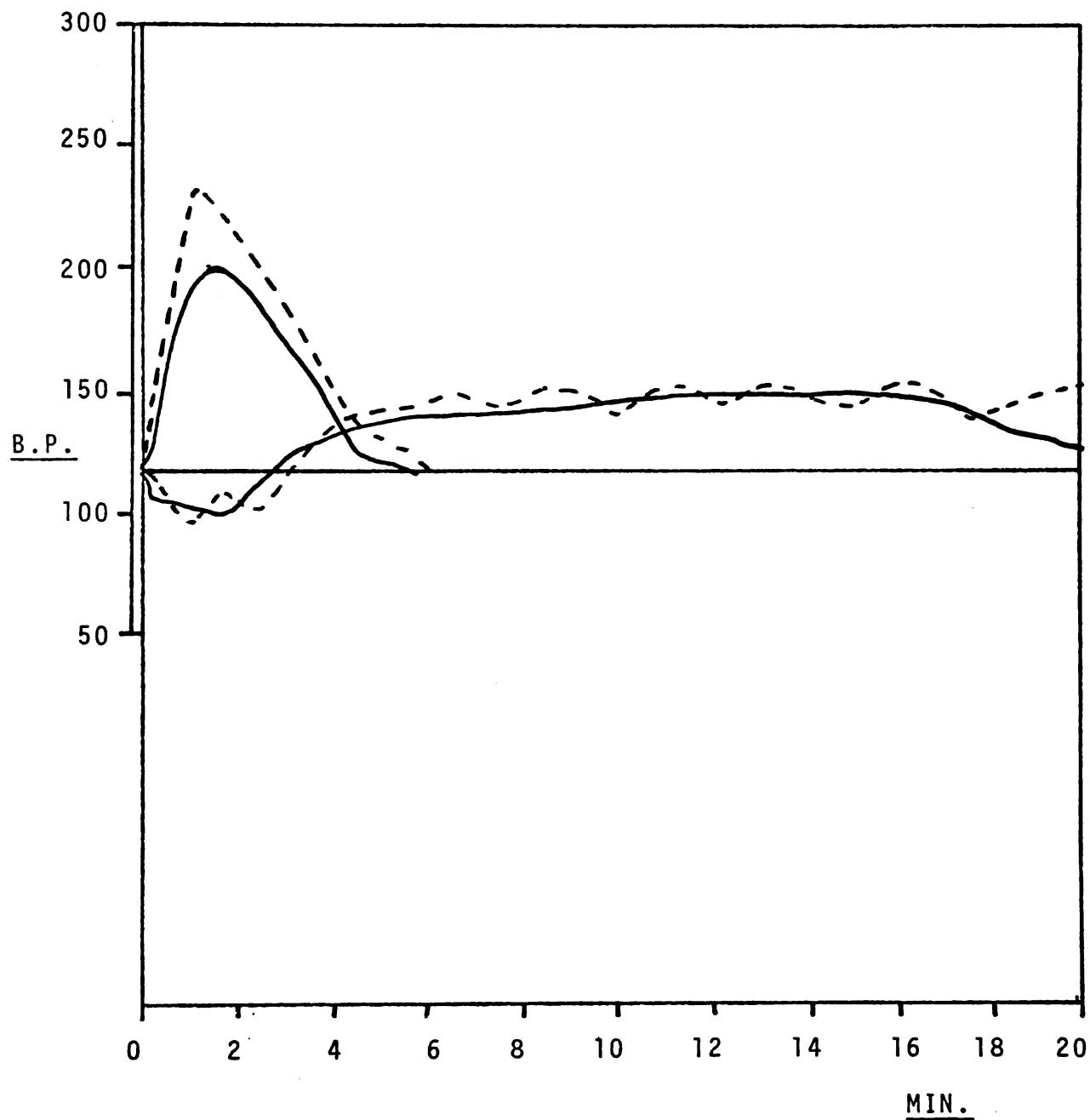
Figure XI: Groups 1-7

Blood Pressure Response Curves

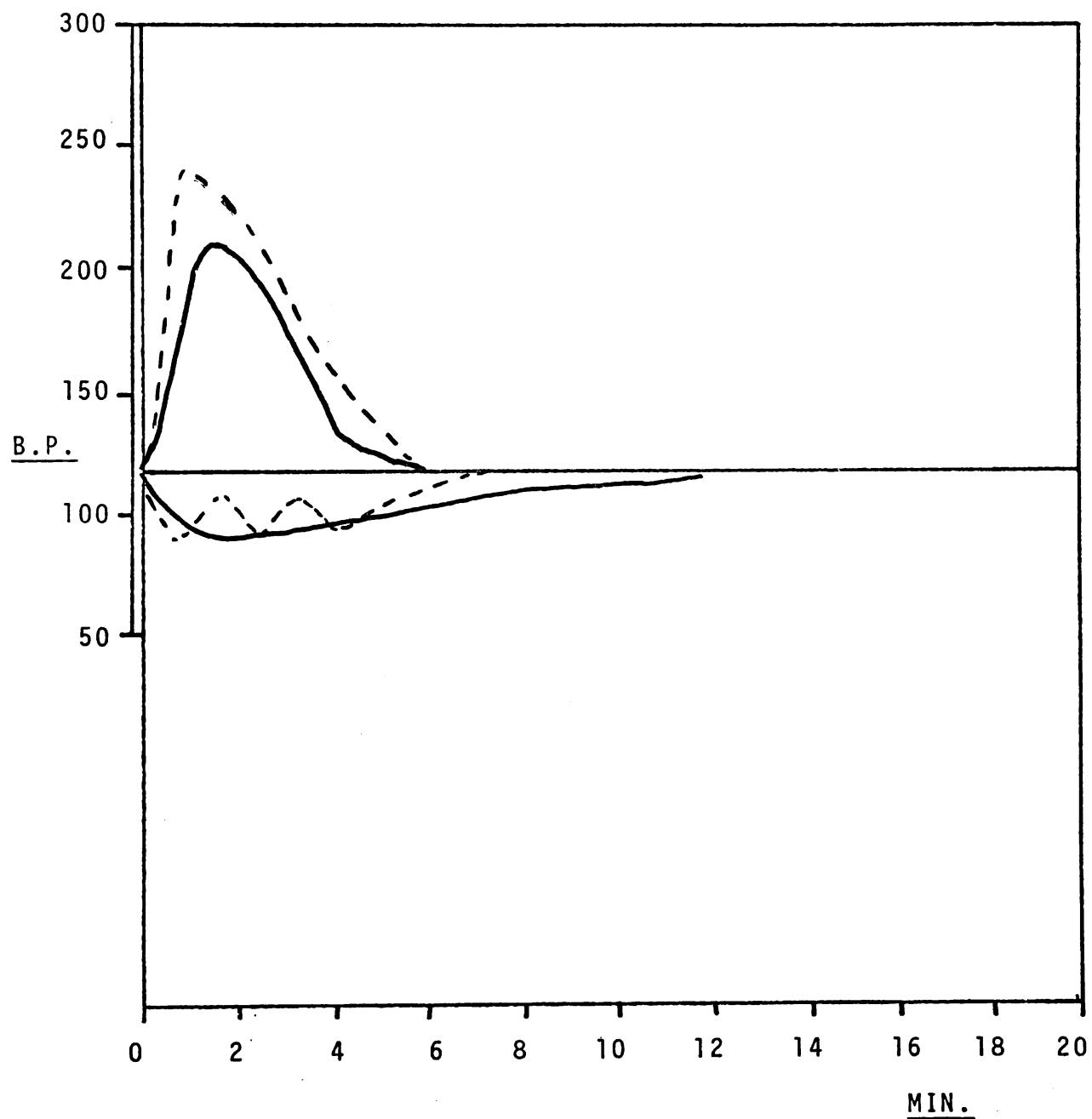
Dotted: Funkenstein Mecholy1 (bottom) and Noradrenaline (top) data from hospitalized population.

Solid: Derived from computer simulation of cardiovascular system as a function of sympathetic and parasympathetic setpoint and gains. (See part V.)

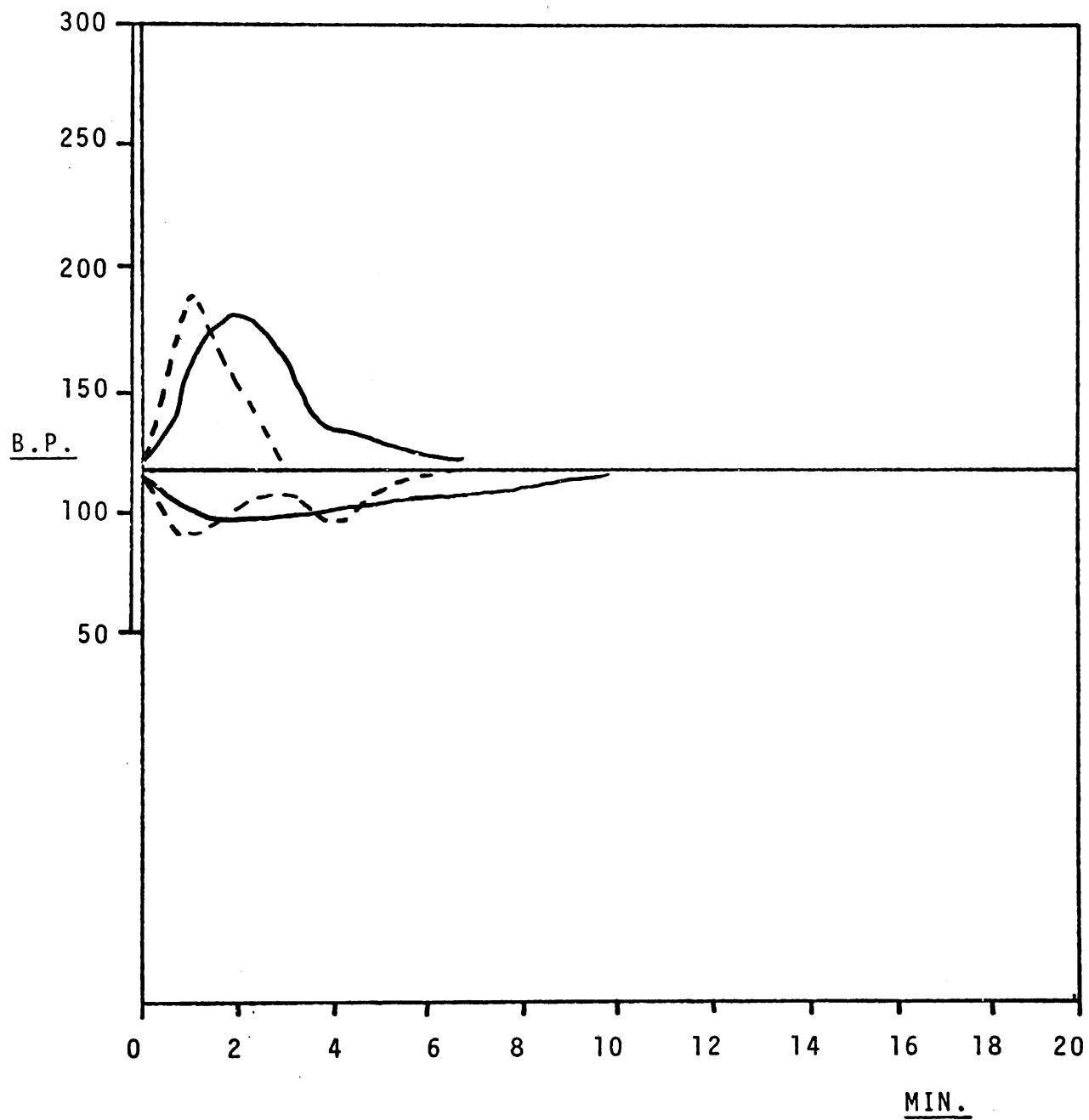
## GROUP 1



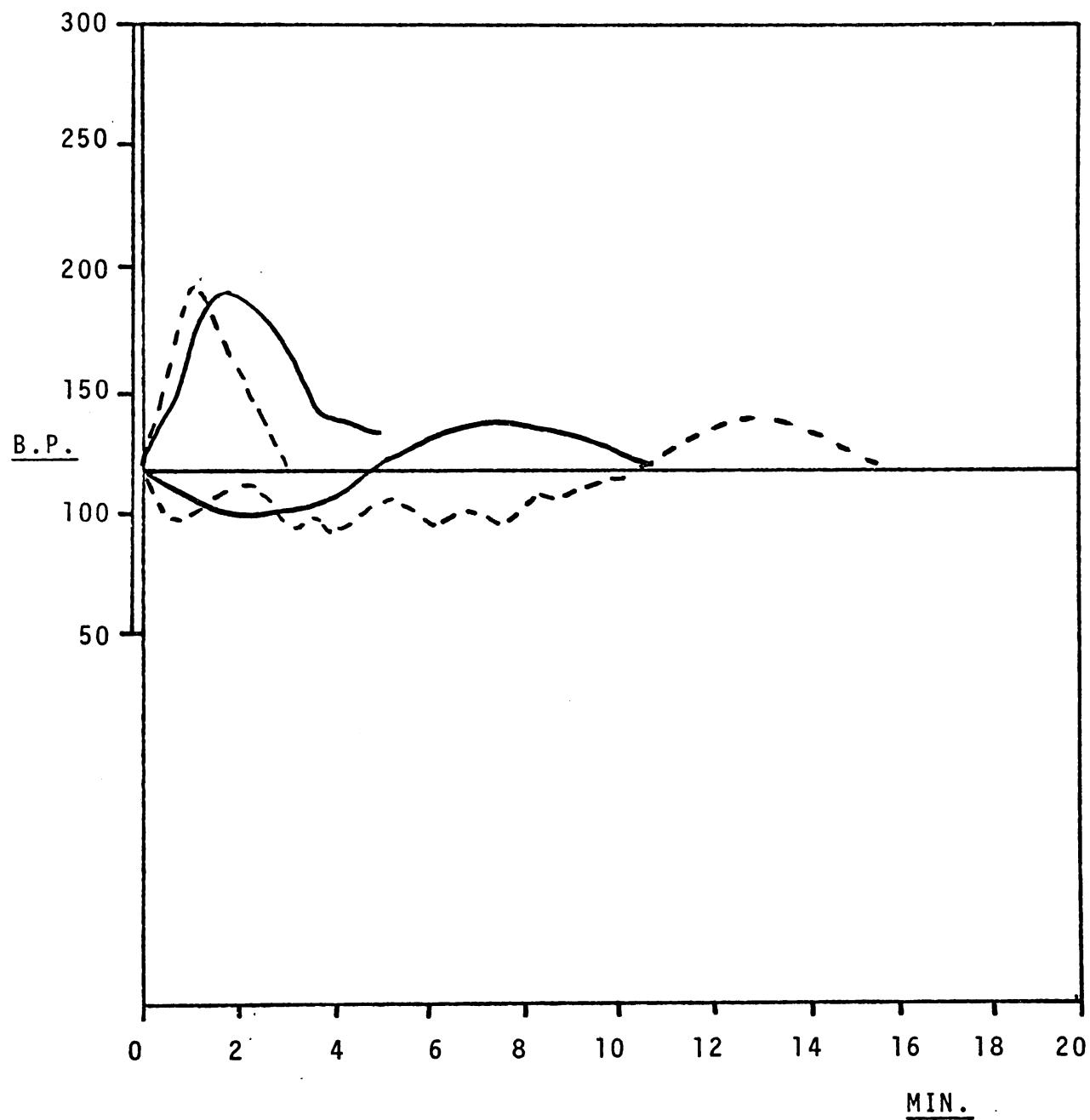
## GROUP 2



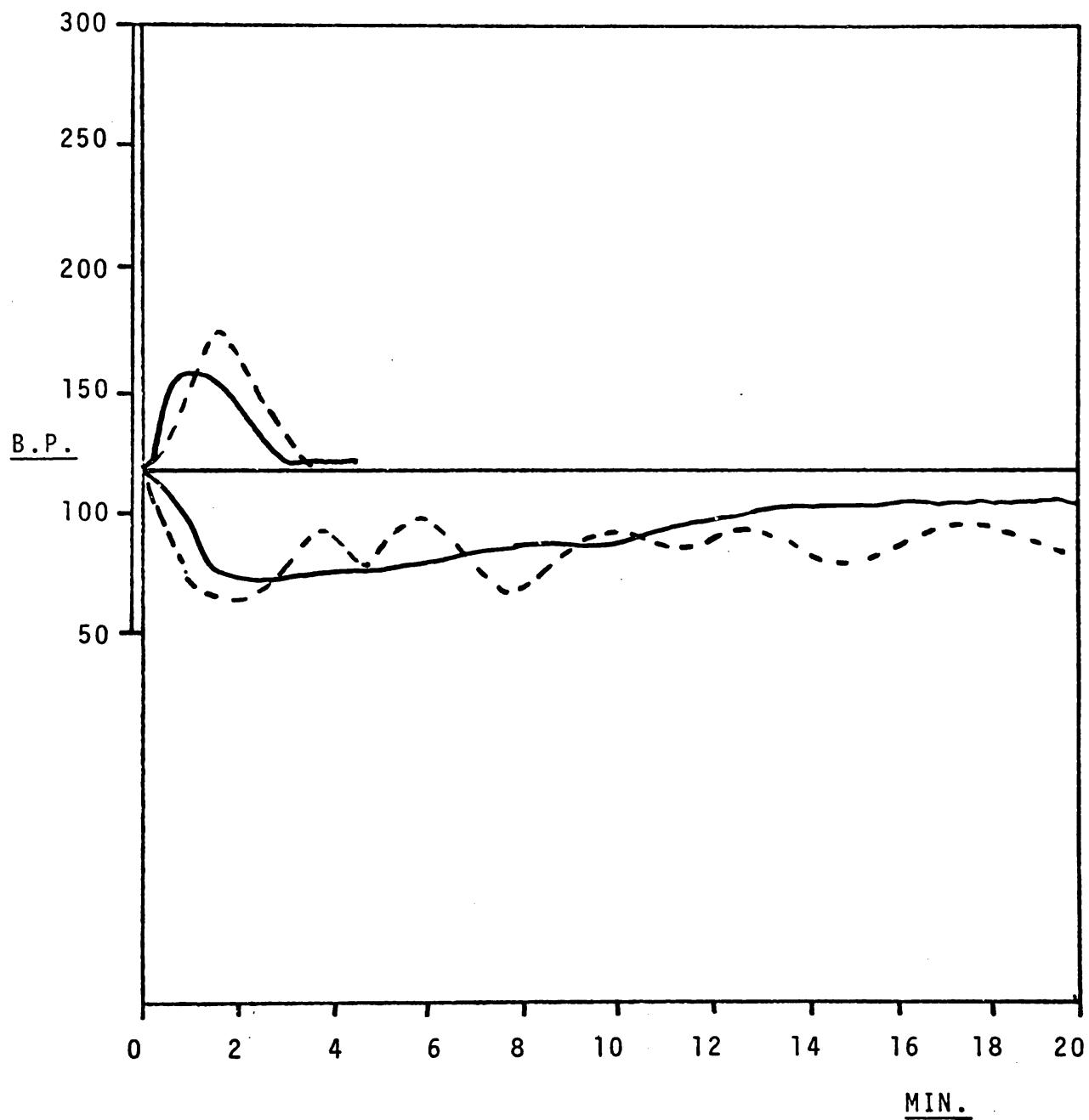
## GROUP 3



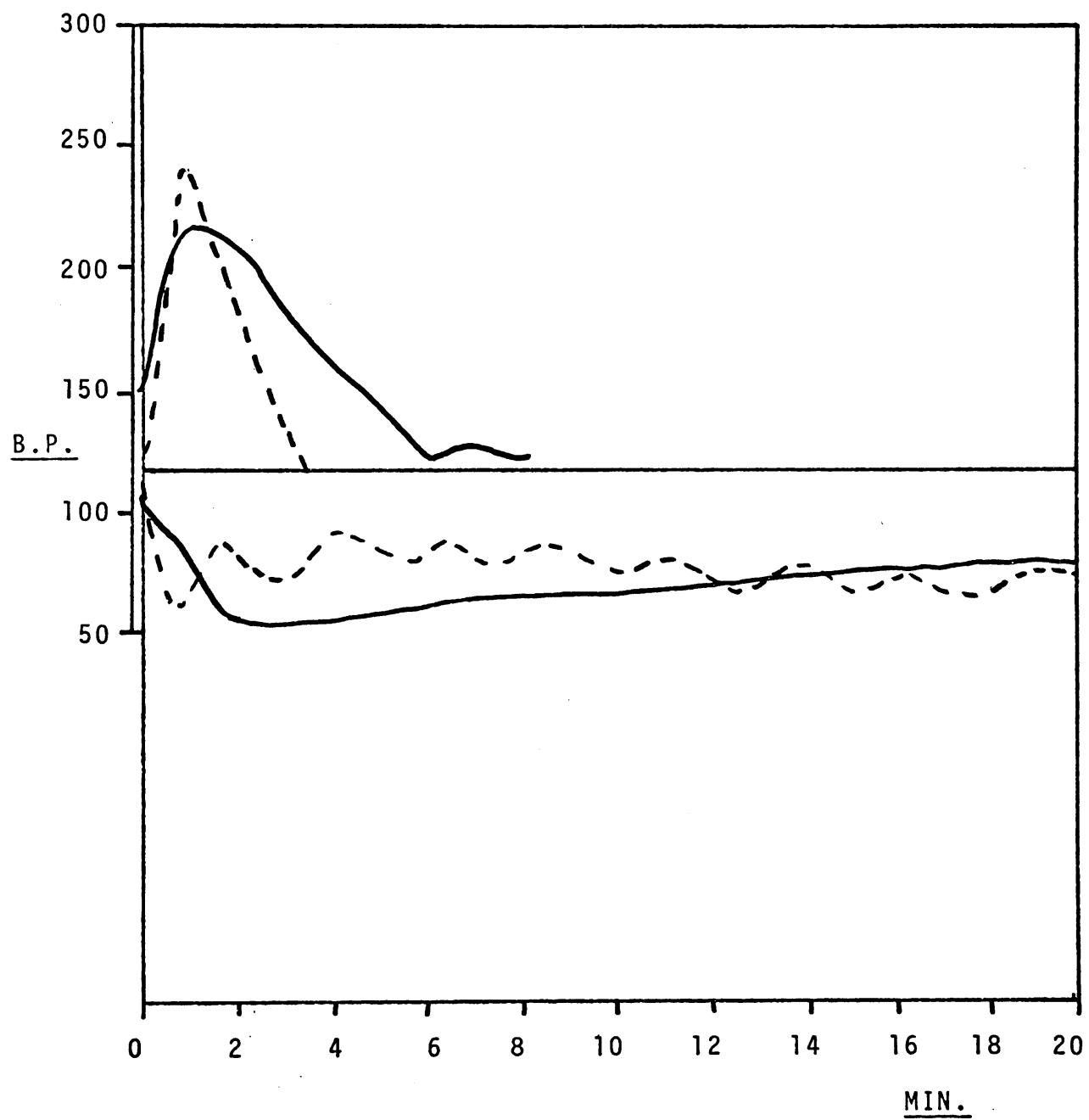
## GROUP 4



## GROUP 5



## GROUP 6



## GROUP 7

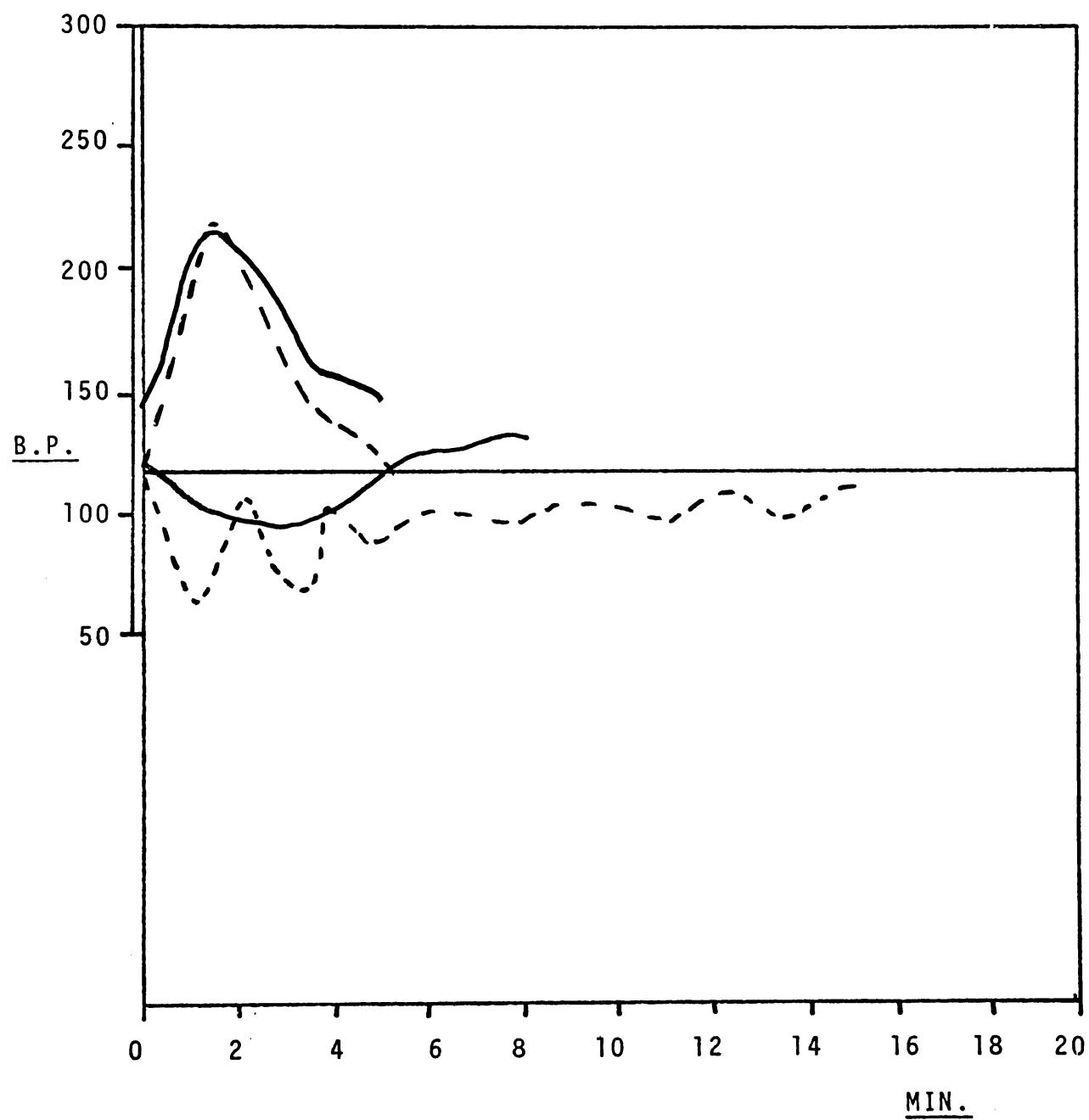
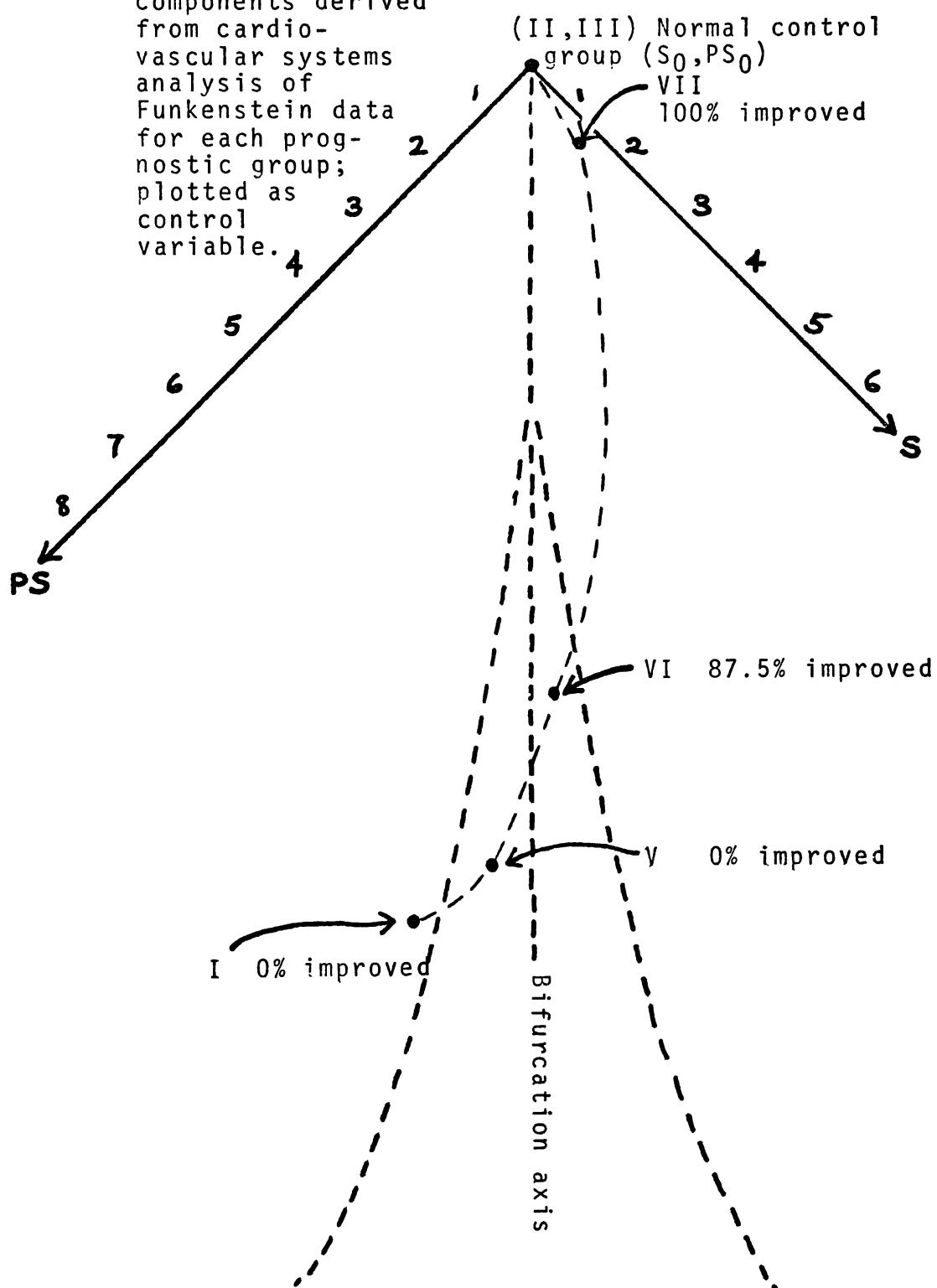


Figure XII: Sympathetic and parasympathetic components derived from cardio-vascular systems analysis of Funkenstein data for each prognostic group; plotted as control variable.



We see that, as predicted, group 7, characterized by autonomic points prior to the bifurcation cusp and origin, has the best prognosis: 100% (11/11) improvement from the treatment. Group 6, considerably further along the axis, is 87.5% improved (14/16), while groups 5 and 1 show no improvement (0/5). Note that the distance on the control surface between groups 7 and 6 is considerably greater than between 6 and 1, while the drop in improvement is from 12.5% to 87.5%. This is predicted by the exponential increase in width of the cusp (see figure X, p.52).

An interesting phenomenon is observed when comparing groups 5 and 1 (both of which do not improve with treatment). The fact that the sympathetic component for group I is negative is at least consistent with the model in that there has been a central reversal of dominance from sympathetic to parasympathetic. This is seen in figure VII, page 38, as a crossover in the plot of component activities as a function of activation.

Group 1 appears, then, to be the low motility "stasis" state predicted by the catastrophe model. It seems reasonable to suppose that group 1 derives obligatorily from group 5 as the consequence of a slight shift in autonomic

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for the parasympathetic ones a factor of 2.0 is subtracted and then multiplied by 10.0 to equalize the disparity in decimals. (Since the units are arbitrary, any constant scaling factor is valid.) See table IIa, b for a summary of the clinical and simulated data.

activation. This is confirmed by the fact that, in the simulation, group 5 is characterized by a high level of adrenal discharge (3.3) while group 1 has an adrenal factor of 0.0, implying that, despite their proximity on the control surface, group 1 is parasympathetically dominated and of low motility, while 5 is still sympathetic and in a state of agitated motility.<sup>1</sup>

While, according to Funkenstein, there is little correlation between clinical classification and blood pressure groupings, it is interesting, from the standpoint of the model, that nine out of ten manic depressive psychoses are in groups 6 and 7, indicating clearly the potential of high motility behavior. It would be most interesting to test these persons both during agitated and depressive stages. Also, the majority of the schizophrenics (15/19) fall into groups 1, 5, and 3. Groups 1 and 5 are, according to the model, in the region of highest accumulation.

Paradoxically, 20% of the patients who do not respond favorably to shock are in groups 2 and 3, which are the groups comprising most of the normal controls.<sup>1</sup>

In summary, it was possible, on the basis of a systems simulation of the cardiovascular blood pressure regulation (detailed in V,B) to obtain a set of curves which fit the

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<sup>1</sup>It is beyond the scope of this dissertation to discuss this apparent contradiction; it is not impossible that in these patients a functional dissociation between autonomic, central and somatic behavior exists and should be looked for, or even that these persons are "normal" but that their behavior is somehow socially unacceptable (e.g., Szasz, 1974).

seven function groups remarkably well (figure XI, 1-7). This by itself is not the most significant fact. But, when those sympathetic and parasympathetic parameters derived from the model (which permitted the experimental curves to be fitted) were plotted on catastrophe space, it was then possible to predict accurately the prognosis of each of these groups to electroshock therapy. This could not be done, a priori, on the basis of the raw data. Thus, at the very least, the model has been able to prognosticate, with surprising accuracy, the response to treatment of a population suffering from so-called "mental" illness, while, on the basis of the raw data, the authors were unable to make any a priori predictions. The relation of progressive autonomic imbalance as a primary, if not the primary factor in these diseases is suggested. This argument is extended in parts III and IV of this paper.

In following sections additional discussion and evidence for these phenomena and for the potential diversity of symptoms will be explored. Inferences will also be drawn from clinical and experimental observation of behavior (section IV A).

## PART II. APPLICATIONS OF THE MODEL

### Section A. The Treatment of Accumulated Stress

In the previous sections the theme was developed that, at least in one particular population, the accumulation of stress gives rise to a spectrum of diverse symptomalogies, the prognosis of which can be ascertained, not on the basis of the symptoms, but by analyzing underlying autonomic response levels and re-presenting them topologically in catastrophe space.

The treatment of "stress disease" is notoriously unsuccessful and unpredictable. One would hope that the theory derived in part I would be of use in this crucial area by suggesting some different approaches.

Gellhorn (1957), in the epilogue of his book on the hypothalamus, talking about the psycho-physical relation in stress disease, states that "Such disorders (stress disease) require a therapy through which, by physiologic or pharmacological means, brain functions are altered and ultimately restored." He goes on to add that "The so-called shock therapies<sup>1</sup> fulfill this postulate, at least to a certain degree, ... and are appropriate in that they increase central sympathetic activity for a period of time."<sup>2</sup>

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<sup>1</sup>Recall that this was the treatment for the Funkenstein hospitalized population.

<sup>2</sup>It is Gellhorn's belief that these diseases are characterized (and caused) by a diminished sympathetic excitability. It seems, however, from the predictions of the

He tempers this by saying (of shock treatment) that "These procedures are distinguished in principle from an ideal form of therapy (even if the curative effect were far greater than it is) in that convulsions and coma affect the whole brain and are not specifically directed toward those structural functions which--at least in the theory presented in this monograph--are responsible for the therapeutic effects." (i.e., the hypothalamus)

On the basis of the data presented in his book, Gellhorn proposes that "a physiologic (pharmacologic) therapy... can be envisaged...that should be directed toward a restitution of autonomic balance."

Gellhorn makes here a tacit assumption which needs to be examined: The parallelism he assumes between the clinical recovery and the Funkenstein test suggests that "autonomic hypothalamic disturbances are not a byproduct but cause the behavioral disturbance." But it does not follow, as he implies, that organismic function will be, of necessity, restored by adding excitation to, or sedating, hypothalamic autonomic centers. What must be realized is that the autonomic balance has the function of maintaining homeostasis and

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Catastrophe systems simulation, that is, is not a simple case of low ergotropic levels but of simultaneous E and T activation where the parasympathetic mode is dominant, resulting in low behavioral motility--immobilization. In section IV, A, a discussion of various clinical syndromes will be made to further differentiate these ideas.

<sup>1</sup> It is this capacity for organized response that has been lost in disease and which must be restored. It is a pattern, in health, vs. the relatively entropic disarray in the disease process which characterizes the difference.

the preparedness for emergency through the charging and discharging of the ergotropic and trophotropic systems in appropriate patterns of activity (i.e., changes in motility).

Autonomic balance is only a static phase of this response when considered in isolation.

In terms of the analysis in catastrophe space of the four accumulations, (figure VIII in the previous section of part I, p. 42), it is clear that merely altering the autonomic variables, by itself, does not necessarily evoke an appropriate shift in the function of behavioral motility (towards re-establishing neutral equilibrium).<sup>1</sup>

In general, strong stimulation to an already stressed organism will evoke some shift--the symptoms exhibited by this organism would be different--but function could certainly not be claimed to have been restored. The point is that in order to resolve accumulated stress one must restore the function of completing the cycle of activation → charge → discharge, by appropriate maneuvers. Further, that while no claim can be made that the catastrophe cusp formulation (presented in part I) is the appropriate representation, it

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<sup>1</sup> As control variables are changed, for example, behavior follows discontinuously while exhibiting hysteresis and divergence. So an organism in equilibrium within the high motility (sympathetically dominated) region of the cusp, if stimulated parasympathetically (or even sympathetically if already sufficiently far along the cusp axis where spillover occurs) may very well jump to the low motility surface. In order to return, it would require now a shift, an enormously larger and more difficult shift, in control variables or the imparting of appropriately timed sequences of small shifts, impulses and charge/discharge cycles (see figure IX, part I, p. 49).

unquestionably does point to the need for a more integrated view of the relation of accumulated stress in biological and social behaviors and in the treatment of the disease process. And that merely stimulating, ergotropically, or attempting to sedate (trophotropic) may well change the behavior of the organism, but that this will restore basic function and a return to homeostasis is not likely. (It may even diminish it.)

To initiate this restorative change in function, again, requires appropriate perturbations of precise magnitude and timing so as to initiate the process of charging to such a degree that it results in discharge with its somatic expression.<sup>1</sup> In this light the use of "shock therapies" may well, in the balance, prove more harmful than beneficial, and should be considered more of a last resort and commentary on our lack of understanding of the substrata of stress than as appropriate treatment.

A truly integrative approach, then, has to understand the "laws" governing the complex behavior of many systems as well as their interactions. One can, from the utter complexity of this, appreciate the desire to isolate a single localized causative factor in the stress diseases (otherwise it would seem a hopeless and entangled maze), as well as to

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<sup>1</sup>It is interesting in this regard that an incidental response to the Funkenstein tests, which indicated a good prognosis, was a shivering reaction from Mecholyl. This indicates, in terms of the model, a pre-existing capacity, in these patients, for somatic discharge.

better appreciate and give more tolerance to certain "unconventional systems" with seemingly less rigorous theoretical basis and practical methodologies. As Gellhorn (1957) remarks, "Man can solve his important problems through action long before he can understand the underlying mechanisms." In any case the need for a basically different approach to the problem does seem necessary.

The results of the previous sections suggest that the susceptibility to stress disease may be caused, not by a reaction to a specific external or internal agent, but primarily to a reduction in the capacity of the organism to shift between states of emergency and ongoing internal homeostasis. And the transition from states of health (ease) to those of stress dis-ease are viewed as a gradual diminution in this capacity.

In the next section the theory developed here will be used to outline and orient various approaches which, it is proposed, attempt to prevent and reverse the buildup of stress with its associated loss in reserve capacity and eventual patho-symptomalogies.

#### Section B. Holistic Approaches to Integrative Medicine

The areas of modern medicine divide into large numbers of specialties and subspecialties; one has to look no further than at the directory of a hospital or medical building to know this. Yet what percentage of these medical persons display the shingle, "Preventative Medicine," even though it

is a recognized specialty (Index of Medical Specialties).

If one looks outside the medical establishment one finds a number of alternative systems that are health and prevention oriented. Some of these are systems which have evolved in the past few decades, usually predicated on the work of a few pioneers; others date back to the origins of civilization. The oldest, most established of these is the Chinese system of healing, the grandfather of the holistic approaches--holistic, because instead of looking toward molecular events as foci, they also look toward more abstract explanations and universals. Of the most recent developments, only those which have been scrutinized by some initial scientific investigation will be discussed. Also, the subject of meditation will not be dealt with because it already has an extensive bibliography of its own.

Acupuncture as the archeoprototype of the holistic approaches will be reviewed first; then the two approaches, those of F.M. Alexander and Ida P. Rolf, which deal with the structure and use of the human body, will be looked at and certain preliminary findings discussed; finally, the work of Dr. Wilhelm Reich will be viewed as an explicit therapeutic approach to the resolution of stress by the mechanisms of charge "containment" and discharge.

In contrast to the pathologic orientation of Western medicine is the rule of the traditional Chinese physician, who was paid by his client only so long as the client remained in good health. If he became sick while under the care of

his physician, payment ceased, and resumed after the patient was restored to good health. The doctor under this system certainly did all he could to maintain the health of his patient. Compare this to our system where (the yearly or bi routine notwithstanding) a person seeks his physician upon the occurrence of more or less striking symptoms or probably more often after debilitation has occurred.

While it is not implied that archaic forms of Oriental medicine are "superior" (the demands and stress of modern occidental living certainly place their unique demands on health and survival), one cannot, at the very least, help being curious about the theory, methods and results of these systems.

### i) Acupuncture Therapy

While the system of acupuncture, with a history of some four to six thousand years of treatment and development, is not based upon the physiology of the ANS, it is fascinating that the basic principle which underlies its theory and application is the concept of two oppositional forms of energy (Yin and Yang). It is the "flow" between Yin and Yang which, in the Chinese cosmogony, generates all observable forms of phenomena. When this flow is "balanced" within the transitional rules of the "five elements," (e.g. Palos 1971) then "harmony" and health exist. When, however, the energy force (Ki) is blocked or diverted in these transformations,

disease will follow unless the energy flow and balance can be reestablished.

Historically, acupuncture (and various other aspects of Chinese medicine: herbology, respiration therapy, etc.) were employed in a preventative context. Diagnosis was made mainly on the basis of 26 or 28 different qualities in 12 radial pulses, taken at different wrist positions and depths of pressure, as well as a host of subtly observable signs including eyes, tongue, ear, skin, posture, gait, odors, behavior, dietary, seasonal and color preferences, and so on. These supply redundant information and are used for the purpose of cross-checking.

There exist, for the flow of energy, essentially twelve meridians or channels corresponding (in name) to several Western organs, though not synonymous with them. These traverse specific pathways, many of which lie along the surface of the skin and comprise over 600 points. There may be excesses or deficits of either Yang (corresponding to attributes of activity, aggression, etc.) or Yin (passive, receptive) in each of these meridians.<sup>1</sup> It is the task of the physician to diagnose this situation and implement a treatment, in accordance with the laws of the five elements, to "transfer energy" appropriately between the various meridians so as to effect a proper balance. This is done by

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<sup>1</sup>More complex situations exist where there may be, in a single organ system, Yang excesses within Yin excesses and so on. These are generally much more difficult to treat. Their possible relation to simultaneous autonomic excitation is an interesting question.

stimulating<sup>1</sup> appropriate points, at various penetration depths, along the meridian lines.

In appendix i, research on the mechanisms of acupuncture is reviewed and discussed. One of the most germane findings is that needle stimulation of certain acupuncture points results in a normalization<sup>2</sup> of fibronolytic activity, which at least one author considers an autonomically mediated system (T. Craciun, et al., 1973). Since abrupt cutaneous stimulation is most probably sympathetically stimulating, if one thinks in algebraic terms of augmenting sympathetic (or parasympathetic) activity, results like this make no sense.

In the context, however, of the catastrophe equilibrium space and charge/discharge cycles, these results are exactly what would be expected: Assuming that the needling treatment activates afferent sympathetic pathways,<sup>3</sup> then the impulsive force would conceivably "lift" the behavior point out of its excess or deficient equilibrium point to a region where completion of the charge/discharge cycle could occur (in complete or partial steps).

It would be premature to mistake this illustration for

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<sup>1</sup>This is done with thin needles of various lengths and recently also with small electric currents.

<sup>2</sup>If the activity is initially above baseline it decreases; if below before stimulation it increases. Stimulation of the same point thus evokes either a sympathetic or parasympathetic reaction.

<sup>3</sup>Noiceptive stimuli characteristically do just this.

an explanation. What can be captioned, though, is the general idea that the treatment works, not at the level of alleviating symptoms, but by provoking a homeostatic return to baseline, and that this is made possible by the existence of a fundamental biologic phenomenon whereby oppositional systems are maintained in balance by a law of "charge and discharge" (charge and rebound).<sup>1</sup>

### ii. The Alexander Work: Structural Body Approaches

Another system which will undoubtedly be considered seminal in the development of a holistic approach is the method devised by F.M. Alexander (1910, 1934), the second example given by Tinbergen in his Nobel address (see III,C,i).

The story of how Alexander's loss of voice (his profession was acting) led him to the general discovery of how man uses and misuses his body is a fascinating one in the use, from ground zero, of the observational method: After consulting every doctor and specialist on the Continent he "took matters into his own hands" and started observing himself, in front of a mirror, as he spoke. He began to notice that his voice was worst when his posture was, as it seemed to him, most comfortable. For years after this he worked at improving the use of his body musculature in varied postures and movements.

The development of his method Tinbergen (1974)

<sup>1</sup>The work of Sherrington and Gellhorn would be seen as special (though broad) instances of this more general principle of integration.

considers to be "one of the true epics of medical research and practice." He compares it with the "breakthroughs in orientation" of Jenner's discovery that milkmaids did not contract smallpox or Fleming's "wondering" about empty areas around the penicillium in his cultures.

As a result of these observations and the process which began to emerge from them, Alexander not only recovered his voice but spent the rest of his life observing people all over the world and developing a series of "lessons" by which he could "teach" the method to others. He found that the majority of modern Western persons use their bodies in as inefficient a way as his own. At the same time many of his students were reporting "miraculous cures": diverse chronic conditions of long duration (both physical and mental) would often become improved remarkably along with and after the treatments.<sup>1</sup> Persons began to come for specific complaints such as rheumatoid arthritis and were surprised, along with their physicians, when chronic hypertension would be relieved as well (sometimes by as much as 20 to 50 mm Hg).

Barlow (1973) in the only complete book since Alexander's some four decades prior, describes the work and results of Alexander's students since that time. Some of the claims in this book seemed so extraordinary that the skeptical Tinbergen and his family underwent the treatment/lessons. Due, both to the wide range of benefits they all perceived in themselves and each other, as well as what he

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<sup>1</sup>Alexander himself had no medical training.

felt to be the inadequacy of the "physiologic explanation" (and "hero-worship") in Barlow's book, Tinbergen suggests some observations and explanations of his own.

He mentions first the concept of reafference introduced by Von Holst and Mittelstadt (1950). In this view feedback from many levels (single muscle units to complex behaviors) are compared with an expectation or "target value" (Sollwert). It is only when the expected and actual feedback match that the brain ceases corrective commands. What Tinbergen feels Alexander has discovered beyond this is that "a lifelong misuse of the body muscles...can make the entire system go wrong." I.e., the target, or setpoint values, become altered in such a way that "all is correct" messages are received by the brain, when in fact all is not correct.

Along with Alexander and Barlow, the modern ethologist sees ineffective posture as phenotypic rather than genetic and therefore amenable to "snapping back" in a short series of half-hour sessions even after 40 or 50 years of extreme misuse. Tinbergen concludes that "misuse, with all its psychosomatic, or rather somatopsychic consequences<sup>1</sup> must therefore be considered a result of modern living conditions of a culturally determined stress."

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<sup>1</sup>One could perhaps dispense with both terms and call them instead consequences of "mis-integration." Tinbergen himself seems to call for this abolition: "Too rigid a distinction between mind and body is of only limited use to medical science...it...in fact can be a hindrance to its advance."

A crucial question is why changes in body posture and use should have such a great effect on internal conditions, such as cardiovascular, many gastrointestinal disorders, various gynecologic conditions, sexual failures, migraines, depressions, etc., if, as Tinbergen says, "There can be no doubt that it often does have profound and beneficial effects ...both in the mental and somatic sphere."

Towards formulating this question it need be realized that posture, while connoting a static state, is more accurately an "equipoise,"<sup>1</sup> i.e., an equilibrium position from which action is initiated and returns within a potential field of movement.

From this standpoint we now look at the effects of autonomic stress on "posture." It is well known that autonomic sympathetic effects are associated with flexor reflexes in the legs and rigid contraction of the abdominal muscles, both in man and animals:<sup>2</sup> Eble (1960), McPherson (1961), and Youmans (1963). Further, it will be shown later that maintained levels of central excitation lead also to simultaneous (non-reciprocal) activation of agonist-antagonist (e.g., flexor-extensor) pairs. The consequence of this is, as previously discussed, that autonomic discharge is blocked, assuring a further feedback of high frequency volleys, which in the absence of mobilization would lead to

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<sup>1</sup>A term suggested by Dr. Julian Silverman--personal communication.

<sup>2</sup>As well, of course, its primary effect is on the functioning of the internal organs via the smooth musculature.

further accumulation of autonomic stress, making the probability of subsequent resolution even less likely.

The skeletal pattern to stress is made graphic in the startle response in which contraction of the abdominal and leg flexors, along with a shortening of the neck muscles and curvature of the spine thrusts the head forward and rotates the pelvic girdle so that the lumbar spine becomes excessively anterior. If this attitude, for whatever reason, becomes chronic, such as if the autonomic stress is not resolved, then an additional factor, gravity, compounds the situation for the vertical biped. Dr. Ida Rolf (1973) points out, in her system of manipulative work, that a progressive strain pattern becomes fixed within the myofascial system of the person experiencing stress. The basic tenets of her theory are deceptively simple. The "ideal body" is seen as made up of segments: head, thorax, abdomen, pelvis, thighs, and legs, which are balanced one upon the other and organized about a gravitational vertical--an imaginary plumb line passing through ear lobe, shoulder, hip joint, and anklebone. Any chronic deviation from this optimal state is seen to spread stress over the entire body by an infinite sequence of compensation until none of the segments are in proper balance. This situation is progressive. It can do nothing but further distort the imbalance. Muscles must now be constantly tightened with a wasteful expenditure of energy to maintain this unstable configuration. The individual is in a constant stress situation, fatiguing more rapidly. Tired, the person lets

his or her head drop even further forward, causing the lower back to arch in compensation and the abdomen to protrude outward. The segments, now further out of alignment, require more muscular energy to keep the body from collapsing. Thus, the effect snowballs into excessive inefficiency and fatigue. (As an example, imagine carrying for even a day a fifteen pound weight--the weight of the head--a few inches in front of one.)

Some consequences of these distortions, as well as their treatment by "structural integration" (SI), are summarized by Dr. Rolf (1973):

Stresses, aches, and pains are the body's language to express the strained imbalance between the field of gravity and the body integrals--weight masses of head, thorax, pelvis, legs. Such a body is unbalanced; we call it random. Return to balance is possible. Manipulation to reposition the soft tissue will give greater freedom to the muscles. This can be combined with a patterning of freer movement to achieve more appropriate balance. The mechanism for achieving improved function is perfectly logical. Within the body as a whole, the relation of individual structural units (head, thorax, pelvis, legs) is brought toward a vertical line in a position of standing rest. Logically, vertical alignment of units must give a structure capable of retaining its form within the disorganizing pulls of gravity on individual segmental units. Structural

Integration has shown that it is possible to create such an alignment. The result is a man of different mechanical and psychological qualities.

Strain between body segments alters patterns of movement. In a random body, any given movement evokes response not only from the muscle primarily concerned (and its antagonist), but from a chorus of other units as well. Some of this accompanying group may interfere with, or limit, the movement, rather than support it. The resulting aberrated flow may, in fact, be an inversion of the movement demanded. It is a jangle of response, altering or even inverting the movement intended. Originally, these compensatory restrictions may well have been an effort at support on the part of the body, an attempt at 'splinting' or 'relieving' an injured part. But at the present time, they are barriers to movement; circumventing their restriction demands exhausting outpourings of energy.

Fascia ensheathes muscles and organs. Control of the position of the weight blocks in space is through these fascial sheaths. The one appropriate, but now outmoded, response reflects interference in the smooth sliding adjustment of fascial planes necessary to free, economical movement. Compensatory mechanisms originate in, and operate under, the laws of mechanics. Accident, habitual posture, or the dramatization of an emotional attitude can distort the vertical alignment

of weight blocks. Then it is the total enwrapping envelope of the superficial fascia which must adjust to keep the weight blocks from literally falling apart. There is, of course, always a point of originating localized fascial strain. But to make acute restrictions subjectively more tolerable, the body adjusts by spreading the strain to more distant points through the medium of the network of fascial planes. Often, reinforcement is through thickening of the fascia; this thickening usually becomes permanent, and the restriction is then chronic. In doing this, the body has adjusted throughout. In the fascia, particularly the superficial fascia, this thickening and displacement is visible in the contours of the body. But such visual cues are usually ignored because their significance is not understood.

There are many patterns of disintegration. Fascial shortening may cause a slight displacement of body parts. Or fascial envelopes may attach to neighboring myofascial units, consolidating several of these elastic sheaths into a single unit of less resilient, less mobile tissue. Or the problem may focus on restricted movement at the joints, where tendons shorten or become displaced. Once started, patterns of disintegration are automatically progressive. As shortening and thickening of fascia proceeds, body cavities become smaller and distorted; visceral crowding ensues. Subjectively and

objectively, the picture is one of consistently lowered energy and lessened vital well-being."

The point is that as a consequence of unresolved autonomic stress, or of improper use of the body musculature, as in poor habits (Alexander) or by chronic immobilization of the myofascial network (Rolf), the probability of a given autonomic stress being resolved is diminished. The accumulation of stress, again, is expressed motorically as a further loss in this capacity by flexor rigidity and then concurrent agonist-antagonist "paralysis."

Hence, in terms of the preceding models and arguments, one major avenue (and probably the most accessible one) to deal with (modify) the mechanisms of stress accumulation is directly at the muscular level, i.e., to affect the autonomic via its somatic connections.

The effect of this should be able to be monitored both at the muscular and autonomic effector outputs. This has been done, to an extent, with the technique of Structural Integration developed by Dr. Rolf. Dr. V. Hunt, in the studies outlined in section III,C, has shown that, as a consequence of "processing" by this method (SI), the pattern of agonist-antagonist firing (emg) tends toward a more efficient "undulating" one. Thus it seems possible that a restructuring and patterning<sup>1</sup> of the functional elements

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<sup>1</sup>This work involves, in addition to myo-fascial manipulation, the evocation of specific movement patterns while certain groups of tissue are prevented from motion. The idea here is to demand "appropriate and efficient action of smaller, more specific groups" in lieu of more general or

which determine the upright relation to gravity can fundamentally reorganize the capacity for discharge of accumulated stress. That autonomic variables are simultaneously affected is suggested by some preliminary observations of Levine and Jackson & Levine. Thermographic measurements<sup>1</sup> were made on body segments before, after and during each of the ten processing hours. Most usually profound thermic changes occurred not only in local regions which were being manipulated (as might be expected from the post-ischemic hyperemia induced by deep pressure), but in distant sites as well. The digits of the hands, for example, which reflect autonomic state particularly well, routinely change 4-12 degrees as a result of the processing series. In addition, many of the local and general changes occurred specifically and only after movement considered "appropriate" for that particular segment-session was evoked. Thus it seemed that the autonomic changes occurred simultaneously with the re-establishment of efficient reciprocal movement patterns. In addition, blood pressure measurements were taken in a few subjects before and after processing and were found generally to normalize towards 120/70, as well as to become more balanced on the right and left sides of the body. That the method affects central nervous and endocrine changes as well, has

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"gross" movements. The study of these patterns has also been greatly extended and advanced by Judith Aston, M.A., in a system called "Structural Patterning."

<sup>1</sup>By using calibrated sheets of liquid crystal.

been demonstrated in an extensive series of computer evoked potential micro-bioassays by Dr. Julian Silverman et al., (1973).<sup>1</sup>

It could be argued that the autonomic system changes were caused directly by the nature of the deep and sometimes painful manipulation of the method.<sup>2</sup> Indeed, this point cannot be dismissed. It undoubtedly affects the results, but the thermographic data indicates that the evocation of appropriate movement seems to be primary. Furthermore, the manipulations used in the Alexander work are by and large extremely gentle and involve neither pain nor deep muscle pressure: "It consists in essence of no more than a very gentle, first exploratory, and then corrective manipulation of the entire muscular system." In addition, Tinbergen observes that "Whenever a gentle pressure is used to make a slight change in leg posture, the neck muscles react. Conversely, when the therapist helps one to release the neck muscles it is amazing to see quite pronounced movements, for instance of the toes, even when one is lying on the couch."

These phenomena, demonstrating "that the innumerable muscles of the body are continuously operating as an intricately linked web," seem also to be an underlying theme in

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<sup>1</sup>These tests include various changes which, Silverman argues, are associated with an enhanced tolerance of stress.

<sup>2</sup>Pain eliciting sympathetic, while deep pressures are trophotropic stimuli; e.g., see Gellhorn (1967), pp. 6-7.

the variously somatically oriented holistic approaches.<sup>1</sup> Thus, there is a basis for arguing that the autonomic changes do occur when this "web" is appropriately altered towards more balanced functioning. It would be most useful to measure autonomic changes concurrent with these manipulations, particularly during and after somatic discharge, e.g., the spontaneous, often rhythmic, subtle movements in one area resulting from the release of another, or from an increase in overall charge. In another form of therapy, to be described next, Dr. Gerald Frank has made a striking color motion picture of body surface temperatures by means of a Barnes thermographic apparatus (personal communication) during charge/discharge cycles. One can observe propagated patterns of autonomic (vasomotor) change which can be predicted from the therapist's assessment of the chronic muscular sets and tensions. (Unfortunately, again, in this case, concurrent somatic changes were not recorded electromyographically,

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<sup>1</sup>Some rather classic observations of Weber (1914) bear an interesting relation to this. He found that if a single muscle (say, the left biceps) is contracted it leads to a vasodilation of the right arm and both legs. After general fatigue such as from vigorous running or swimming the same test contraction causes a vasoconstriction. In addition, if only the single biceps muscle is contracted to fatigue, then the same reversal reaction occurs in all extremities in response to contraction of the fatigued muscle. (The normal vasodilator response, however, is retained if another un-fatigued muscle is contracted, even if the record is taken from the fatigued arm.) Further, Gellhorn & Lewin (1913) had shown that "mental fatigue" produced a similar reversal reaction. Thus, gross physical and mental exertion as well as local muscular fatigue have the effect of profoundly influencing global autonomic behavior, a fact that is taken for granted and applied by holistic avenues in a practical way.

which would have been useful, both to objectify the diagnosis as well as to compare their dynamics with those of the autonomic measurements.)

iii. Respiratory Vegeto-Therapy: Wilhelm Reich, M.D.

The German physician Wilhelm Reich, independently, though slightly later than Alexander, noticed also that many difficulties, both "physical" and "psychological" (indeed, the neurosis itself, he contended) were directly linked to chronic muscular tension patterns and spasticities. He made the discovery that many of these tensions had their roots, not so much in the habitual improper use of the musculature (Alexander's premise), but in preventing the expression of certain instinctive drives.<sup>1</sup>

He found that after a certain degree of loosening these muscular rigidities, which he graphically called armor, spontaneous movement and feelings of "well being" began to occur,<sup>2</sup> along with a free, spontaneous function of respiration.<sup>3</sup> Reich came to realize that these involuntary convulsive discharges served to maintain or to regulate the "energy

<sup>1</sup>Both his work and life are summarized in Wilhelm Reich--His Life and Work by David Boadella (1973).

<sup>2</sup>These feelings, he found, usually heralded an improvement of the patient's symptoms to the point where they neither recurred nor were replaced by others.

<sup>3</sup>This he called the "breakthrough into the vegetative" to underscore its non-volitional autonomic nature.

economy" (his term) of the organism and were one of the principal biological functions of a full (and deeply meaningful), uninhibited sexual union (which he found lacking in all of his patients).<sup>1</sup>

In terms of the ideas here, the great interest in Reich's work is his explicit formulation of the relation of the charge/discharge function and chronic muscular rigidities to the regulation of "bio-energy" (his terms), i.e., in the regulation of accumulated stress. As a consequence of this understanding, Reich and some of his later followers (e.g., Dr. Philip Curcuruto) found that specialized techniques of continuous work on a person's respiratory pattern, employing certain aspects of "hyperventilation,"<sup>2</sup> could be utilized in order to build up an appropriately controlled sympathetic charge concomitant with intensification of the "somatic armor."<sup>3</sup>

The paradigm of a typical session in vegetative therapy, as practiced by Dr. Phillip Curcuruto,<sup>4</sup> is gradually, by

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<sup>1</sup>This capacity was always absent in the patients when they entered treatment with him, even if their reported "performance" was adequate. (There has been much dispute over the primacy he attached to the orgasm, as well as its causal relation to impaired psychosomatic function. These issues are entirely outside the scope of this work.

<sup>2</sup>See appendix ii.

<sup>3</sup>This could be interpreted as a consequence of the hyperventilation, but, as mentioned in appendix ii, these effects disappear as the blocks become dissolved, which cannot be explained by the strict medical model.

<sup>4</sup>Personal communication.

means of various specialized respiratory patterns and responses, to build a sympathetic charge<sup>1</sup> to the point where a discharge either occurs spontaneously or can be provoked by appropriately manipulating certain muscles so as to evoke, centrally, a mobilization reaction, triggering the discharge phase.<sup>2</sup>

One of the reasons for utilizing the respiratory function, and not just stimulating by manipulating the muscles, is that a goal of the process is to build a capacity for the "containment" of charge so that the discharge phase begins to occur spontaneously as a consequence of the excitatory buildup.

The sessions can be looked upon, in a sense, as an "autonomic learning" situation whereby the process of building charge into discharge is repeated, the client becoming less anxious<sup>3</sup> and more at home after each successive cycle; the fear of being stuck diminishes as they are able, biologically, to resolve that buildup and even begin to experience it pleasurable. This capacity, which they bring, involuntarily, according to Dr. Curcuruto, into their life situations, increases their ability to tolerate and to resolve ongoing

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<sup>1</sup>See appendix ii, on Hyperventilation.

<sup>2</sup>These manipulatives probably have similar autonomic effects to those of acupuncture stimulations.

<sup>3</sup>The process, at least initially, can be quite anxiety producing. It is, recall, the "life or death" emergency response which is being evoked.

stresses spontaneously, as they occur.

One cannot help but be struck by the correspondence of this work to the topologic re-presentation of the previous sections. The progressive building of charge and, in particular, the need initially for mobilization followed by charge/discharge cycles is what is predicted for the resolution of accumulated stress.<sup>1</sup> See figures IX and VIII (pages 49 and 42), which show the need for mobilization in low motility cusp regions as well as a progressively decreased resolvability. Contrast Reich's therapy to the effect of the global "neurologic assault" of electroshock treatment; the resolution of accumulated stress is not simply a matter of introducing a "random" excitation, but a "re-negotiation" process which involves a critically timed buildup of excitation and appropriate trigger into discharges. Otherwise, the level of accumulated stress could well become "hooked" at a higher autonomic level, with lower probability of subsequent resolution. In the actual work it is the ability of the teacher/therapist to assess the range and limitation of that person, at any given time, and to work appropriately within it, that gradually expands their perimeters.

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<sup>1</sup>This depends on the developmental and life history; the course of sessions is to some degree unique for each individual.

### PART III. ORGANISMIC EFFECTS OF ACCUMULATED STRESS

#### Section A. The Hypothalamic Hub

In the introductory section stress was defined in terms of autonomic activation and accumulation. A model of organismic behavior was then derived by applying the topological theory of Catastrophe to the interaction of sympathetic and parasympathetic components. Only the most basic physiological principles (as worked out by Gellhorn and his associates) were used. A control theory analysis of cardiovascular dynamics, incorporating extra-medullary (hypothalamic) influences was then applied to separate the peripheral autonomic response of a hospitalized population into independent sympathetic and parasympathetic components. It was possible, in this way, to predict accurately a prognosis to a standard form of treatment.

In this section we want to look further at possible physiological mechanisms for the accumulation of stress within the ANS, as well as at its more global expression, through various other systems. As a starting point, the hypothalamus,<sup>1</sup> which is linked directly to visceral-

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<sup>1</sup>The central role of the hypothalamus and autonomic nervous system is summarized succinctly in Mountcastle's (1972) Edition of Medical Physiology, VII, by Koizumi & Brooks, Chapters 30 & 31: "It is improper to think of the hypothalamus as an independent entity; neither should it be associated exclusively with the autonomic or endocrine systems because it plays an equally important part in the control of somatic reactions. The hypothalamus is unique in that it confers on animals the ability to maintain

autonomic,<sup>1</sup> as well as to endocrine and somato-motor systems, will be characterized as the central hub of the stress reaction. In addition, the accumulation of autonomic activation will be viewed as not merely one expression of stress, but as the core matrix upon which dysfunction and symptoms at many levels are centered.

While Hess (1948), with his stimulation and ablation experiments, must be credited with proving the central role

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essential body states, to react to conditions of stress, and to carry out certain specific components of functions such as reproduction, locomotion, and postural adjustment. It is involved in the process of sleep and awakening, maintenance of body water and weight balance, and regulation of body temperature. The function of virtually no organ system can be adequately discussed without mention of this complex structure identified as the hypothalamus. It is an entity but also a way station that affects those regions of the nervous system lying caudal to it and those that lie above and laterally.

<sup>2</sup>The autonomic nervous system (my italics) is a part of the CNS, not a distinct entity as the term might suggest. It is an efferent outflow, a complex of efferent neurons innervating the visceral organs. Although afferent nerves are included in autonomic nerve trunks, these afferents serve the somatic as well as the autonomic system, except in a few cases to be discussed later.

The autonomic outflow is segmental and parallels to some degree the somatic motor outflow to skeletal muscles of the body. Directives from the brain and reflex responses initiated by general and specific stimuli course out these two motor pathways to affect visceral organs and other body parts as reactions appropriate to the occasion are organized and executed. Neither autonomic nor somatic reactions occur in isolation, and it can be said that the autonomic nervous system organizes the visceral support of somatic behavior. The CNS integrates the activities of the body through these two complexes.

of the hypothalamus in integrating autonomic and somatic components into complete behavioral action, Cannon (1929) was certainly aware that the sympathetic division created favorable (catabolic) conditions for maximal performance of the somatic nervous system by cardiovascular adjustments, increased blood sugar and delay in fatigue, among others. The parasympathetic, on the other hand, he concluded, enhanced the restitution of cellular functions through anabolic processes. This involved reduction in activity as well as increased circulation and gastrointestinal motility.<sup>1</sup>

Associated with these syndromes, which ranged from states of violent aggression to adymia and sleep, were highly characteristic alterations in the synchronicity and amplitude of cortical and subcortical activity. Hess pointed out that (in Gellhorn's words) "even the most complex functions of the brain which underlie the psychic process are thus altered. This has been validated by the finding that hypothalamic excitation changes cortical potentials and psychic behavior. Gellhorn (196~~7~~) on the basis of reviewing over one thousand references, stated "that it cannot be doubted that a hierarchy exists within them (organs, organ systems and subsystems) with respect to responsibility and authority. Near the apex stand the hypothalamus and the limbic and reticular systems. The neocortex with its

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<sup>1</sup>Hess, to underscore unity of action, suggested the terms "ergotropic" (E) and "trophotropic" (T) reactions. (E) activation was characterized by sympathetic discharges in association with increased tone and activity of the skeletal and respiratory muscles, while (T) syndromes consisted of parasympathetic effects coupled with a lessened responsiveness of the somatic nervous system.

detectors, analyzers, computers, and dispatchers is a sine qua non for their efficient operation and their lines of communication with it are abundant." He goes on to add "that the alterations in autonomic balance are not merely reflections of changes in over-all behavior but are causally related to them." As a phylogenetic idea, this was introduced, originally, by Paul Yakovlev and pre-dates the key anatomical and empirical findings of Nauta (1946) and McLean (1962, 1963) which eventually put the concept on a more definite, firm ground:<sup>1</sup>

Yakovlev (1934) proposed that central nervous structure as well as behavior evolved from within outward: The innermost, and evolutionarily most primitive brain structure regulating internal states was through autonomic control of the viscera. And it is this system, he argued, that formed the matrix upon which the remainder of the brain, as well as behavior, evolved. Intermediate was a system in tight connection which provided for posture, locomotion and external expression of the internal visceral states. The outermost development, in his schema, allowed for control, perception and manipulation of the external environment. This was an outgrowth of the middle system and remained closely associated with it in function.

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<sup>1</sup>The following few paragraphs are a summary of some of Yakovlev's ideas. They are not essential for the following arguments but do "anticipate" many of the basic ideas being developed. Hence they will be included in indented form on the next few pages.

Anatomically the innermost system consists of the brain stem reticulum and spinal cord along with the "entopallium" or primitive cortex (intimately related to the olfactory bulb and called the rhinencephalon). The mesopallium surrounds the entopallium and is serially connected, by a number of subcortical nuclei with motoneuron pools, to the skeletal muscles. Finally the ectopallium forms the outermost layer of the cerebrum. It is separated from the mesopallium by white matter consisting of neo-cortical association and projection fibers linking neo- and subcortical nuclei.

In his paper Yakovlev (1948) equated behavior with internal motility. Behavior, in all organisms, he pictured to have evolved in three spheres: (1) internal; (2) external form, which reflects changes in internal states; and (3) external work done on the environment. The first sphere, visceration, he suggested, was the only form of behavior in primitive organisms, but also characterized the earlier embryonic stages of more complex and specialized ones. In its most basic form this "behavior" consisted of cellular metabolism and plasmotic motion characteristic of unicellular organisms. As the diffuse nervous system developed and elaborated, the three spheres differentiated into: (1) visceral movements which included not only intracellular metabolic movements but also respiration, circulation, secretion, excretion..., i.e., visceration,

then, in higher animals; (2) motility of outward expression of internal states, i.e., emotional expression; and (3) "conscious-volitional" activity, which creates material change in the organism's physical and social environment.

Yakovlev emphasizes that the spheres are not independent but are overlapping and integrated parts of the organism's total behavior, and also that visceration is its matrix. It is his contention, in other words, that the second and third spheres of behavior evolved and developed as extensions of visceral function. The appearance of more complex neural apparatus and even the tendency towards encephalization, then, are refinements of the evolutionarily primitive needs of visceral function and not primarily of new and independent processes.<sup>1</sup>

This evolutionary perspective, while less sympathetic to man's emerging ego-consciousness, focuses on integrative survival function as a primary substrate of all neural organization. The matrix, Yakovlev's sphere of visceration, is the reticular formation of the mammalian nervous system. This innermost core, a diffuse, brainstem feltwork of short neurons, or reticulum, provides the basis for integrating intero-extero sensory, paleo- and neo-cortical inputs in forming the

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<sup>1</sup>In contrast, for example, to the view that visceral regulation by "lower" centers frees the "higher" ones for independent conscious activity.

outflow of the sympathetic and parasympathetic effector systems.

MacLean (1955), in a seminal paper, showed that the basic addition to the brain stem, which he aptly termed the "neural chassis," was a "driver of the wheel" to "decide on alternative courses of behavior and to direct the behavior of the organism as a whole." About this "driver" he says, "Its harbinger is found in the hypothalamus and olfactory apparatus of fishes, two structures so closely allied in some primitive forms that they are practically indistinguishable."

The hypothalamus not only directs the neural chassis (Yakovlev's innermost system), but is directly coupled with the intermediate or limbic system. Nauta (1959) sees the hypothalamus as a "nodal point in a vast neural mechanism extending from the medial wall of the cerebral hemisphere caudalward to the lower boundary of the mesencephalon."

Simply, the hypothalamus can be viewed as a "controlling" nodal point linking autonomic outflow at the reticular formation, as well as limbic, paleo- and neo-cortical contributions. Thus, in Yakovlev's concept, the matrix of behavior, visceration, would be formed at the hypothalamus, which then initiates and regulates the paleo- and neo-cortical components enhancing the primary vegetative functions.

The idea of the hypothalamus as a nodal point in the organization of organismic behavior is now firmly based. Table I (from Weil, 1974) summarizes the basic constituents of the hypothalamic-reticular (h-r) limbic system, while figure I illustrates the gross anatomical substratum. In figure II the various pathways connecting the limbic to the h-r system are shown. Table II references these connections. They can be aptly summarized by Weil's statement that "All limbic roads lead to the hypothalamus and reticular formation."

The reticular formation, in turn, projects upward to the cerebral cortex via "non-specific" irradiations (figure III), as well as downward to visceral organs through the sympathetic and parasympathetic nerves of the ANS.<sup>1</sup> Similarly, the skeletal motor system is highly influenced by descending gamma efferent tonics as well as by rhythmic extra pyramidal pathways. To complete the picture, there is the relations of the limbic-hypothalamic circuit to direct control of the pituitary gland. These relationships are portrayed in figure IV.

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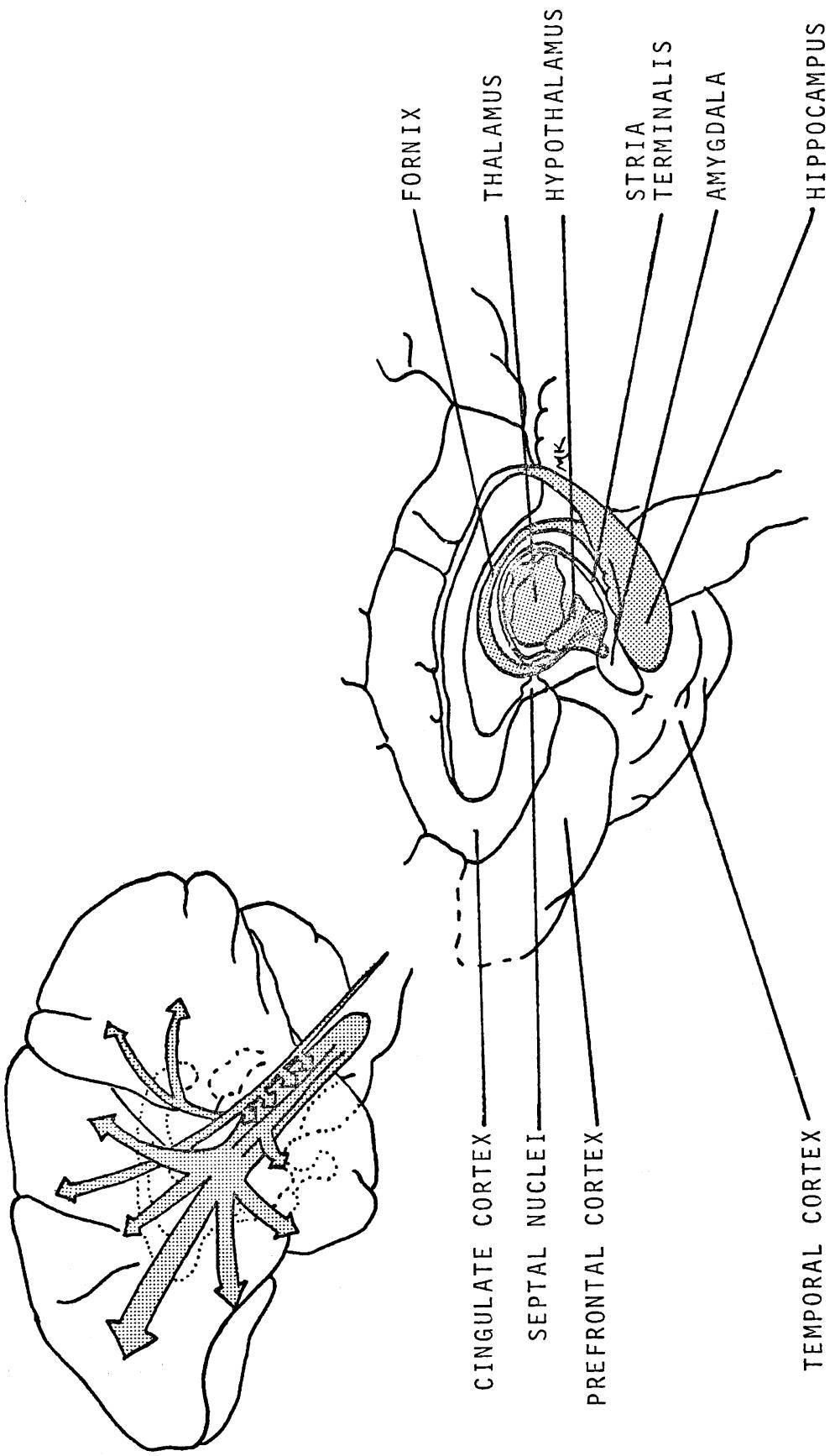
<sup>1</sup>The total of this central integration, in other words, is expressed, in parallel, by three primary effector systems: the neuromuscular, the endocrine, and the autonomic. The former and latter are transmitted by only two competing efferent processes, i.e., extensor/flexor and sympathetic/parasympathetic, respectively. (Thus, in the terminology of Hess, diffuse systems are mobilized, activated and deactivated in accordance with two primary biological processes--ergotropic and trophotropic.)

Table I: The Limbic System

Limbic System Constituent	Position Within the Limbic System	General Structure and Position Within the Central Nervous System
Reticular formation	Lower limbic	An internuncial network within the brainstem, midbrain, and thalamus; contains the tegmental reticular nuclei
Hypothalamus	Central limbic	Diencephalic core of the limbic system
Septal nucleus	Upper limbic	A subcortical component of the limbic system, anterior and superior to the hypothalamus
Amygdaloid nucleus	Upper limbic	A subcortical component of the limbic system embedded within the temporal cortex
Hippocampus	Upper limbic	Primitive ancient " <u>paleo-</u> " ("archi") three-layered cortex which together with the pyriform cortex forms the bulk of the cerebral hemispheres in lower vertebrates
Pyriform, (Entorhinal) cortex	Upper limbic	Primitive ancient " <u>paleo-</u> " three-layered cortex lying on the ventral aspect of the temporal lobe
Cingulate cortex	Upper limbic	" <u>Meso-</u> " four to five-layered newer limbic cortex medially forming an arch above the corpus callosum
Orbito-insular-temporal cortex	Upper limbic	" <u>Meso-</u> " four to five-layered limbic cortex contributing to the formation of the anterior-medial and basal cerebrum
Prefrontal cortex	Upper limbic	Six-layered limbic " <u>neo-</u> " cortex of the anterior cerebrum

From Weil (1974)

Figure I: The Limbic System



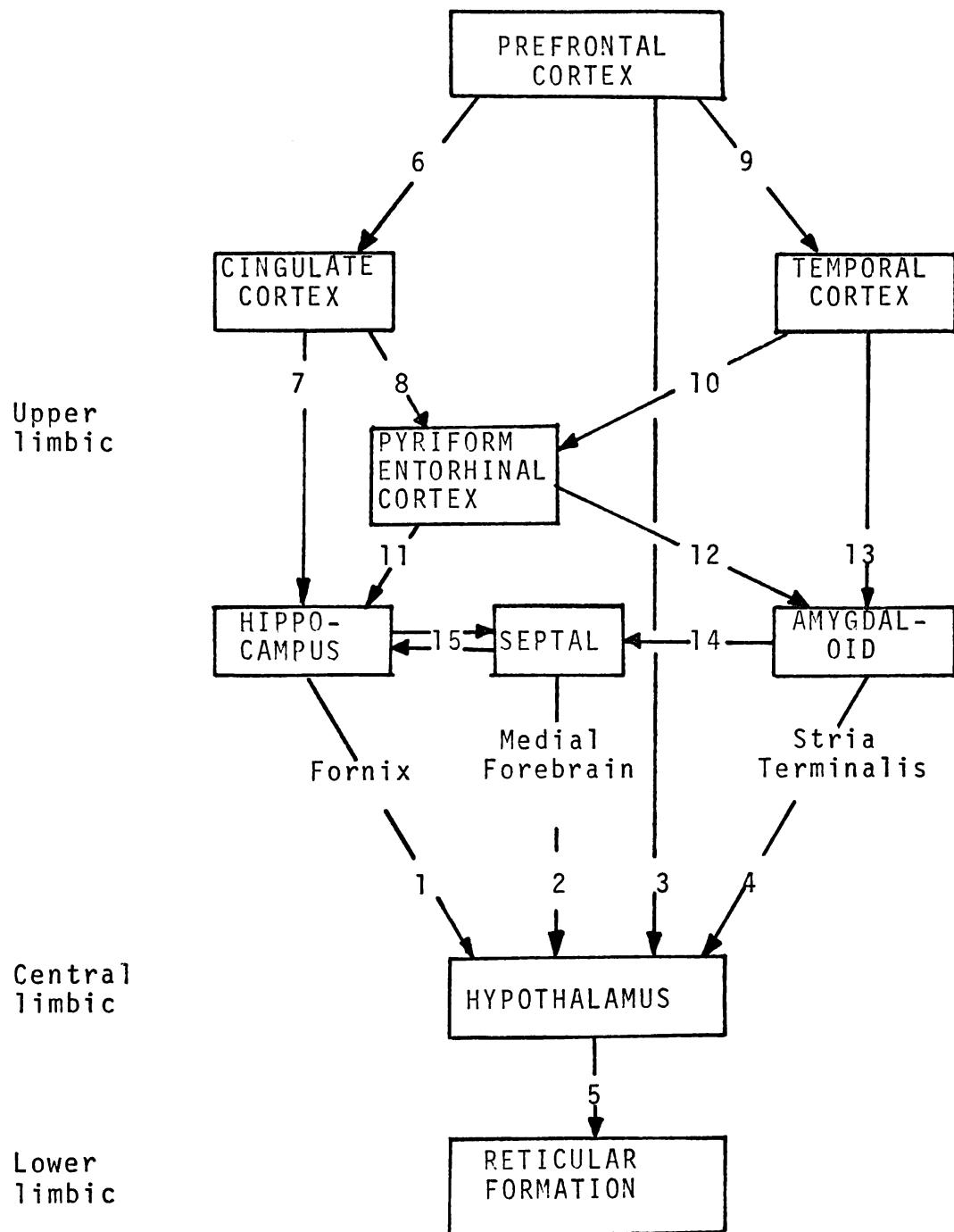
Redrawn from Weil (1974)

Table II  
Anatomical Connections Within the Limbic System

Connection	
1. Hippocampus	→ Hypothalamus
2. Septal Nuclei	→ Hypothalamus
3. Prefrontal Cortex	→ Hypothalamus
4. Amygdala	→ Hypothalamus
5. Hypothalamus	→ Reticular Formation
6. Prefrontal Cortex	→ Cingulate Cortex
7, 8. Cingulate Cortex	→ Hippocampus and Pyriform Cortex
9. Prefrontal Cortex	→ Temporal Cortex
10. Temporal Cortex	→ Pyriform Cortex
11. Pyriform Cortex	→ Hippocampus
12. Pyriform Cortex	→ Amygdala
13. Temporal Cortex	→ Amygdala
14. Amygdala	→ Septal Nuclei
15. Septal Nuclei	→ Hippocampus

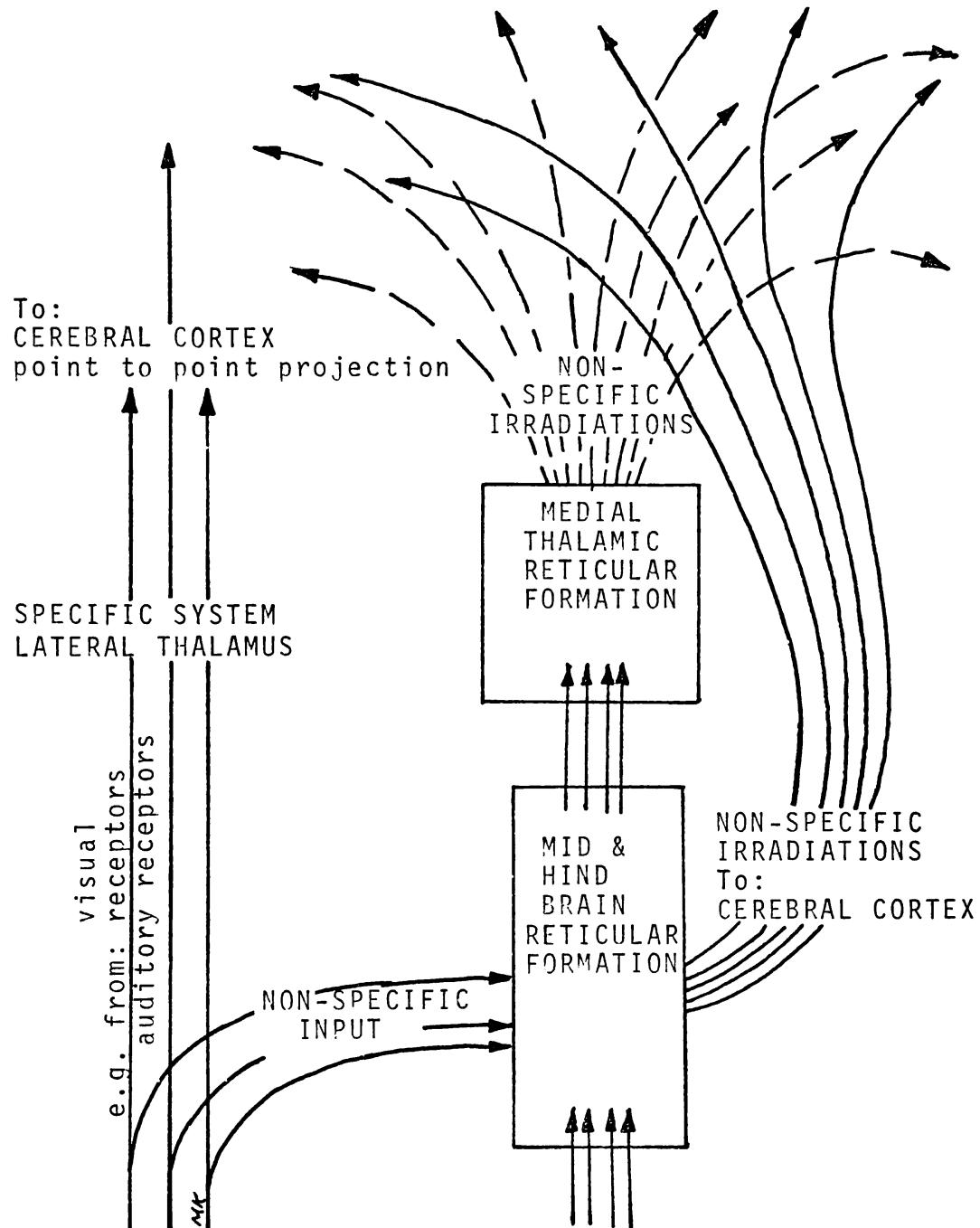
From Weil (1974)

Figure II



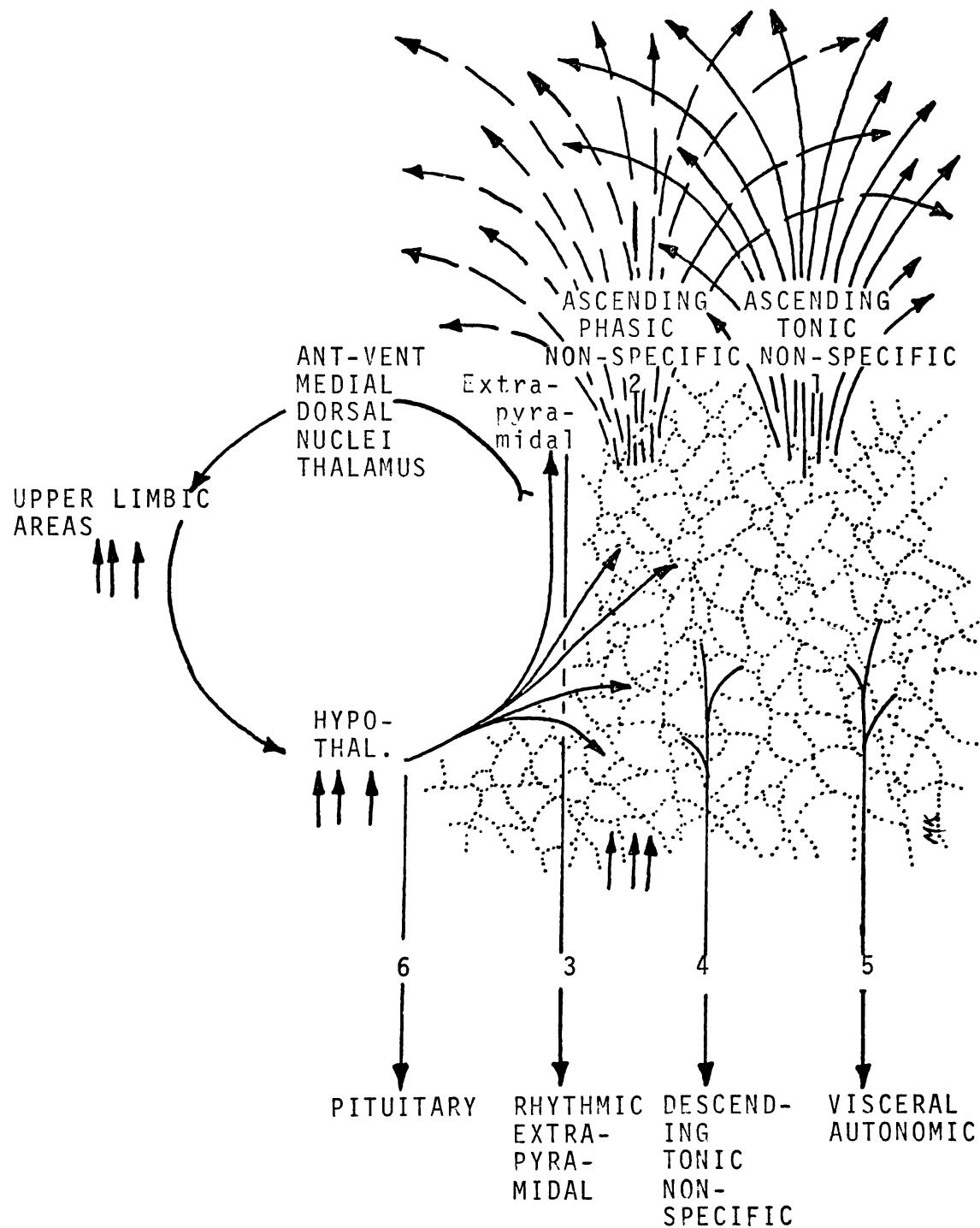
From Weil (1974)

Figure III

Ascending Reticular Non-specific Irradiations to the Cortex

From Weil (1974)

Figure IV



From Weil (1974)

Section B. Autonomic-Endocrine Relationships in Accumulated Stress

On the basis of limbic connections with the hypothalamus and its close association with the autonomic outflow of the reticular formation, as well as with the pituitary gland, it would be expected that the accumulation of autonomic stress (i.e., stress measured in terms of its effect on the ANS) would be associated with varying degrees of endocrine imbalance; and eventually to diseases characterized by glandular imbalances. Guillenin and Burgns (1972) made the somewhat alarming claim that most (my italics) patients (especially younger ones) with "glandular deficiencies," contrary to medical understanding and treatment, have normally functioning glands, since they respond promptly to the administration of synthetic hypothalamic hormones.<sup>1</sup> Their illnesses, then, are due neither to deficiencies in glandular secretion nor to a defect in the master gland, the pituitary. The problem must therefore reside within the CNS, involving the u-h-r circuitry. Let us look, then, at specific functional relations between integration, at the level of the hypothalamus, of autonomic and endocrine function.<sup>2</sup>

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<sup>1</sup> It has only been quite recently that these hypothalamic releasing factors have been identified and synthesized. See Guillenin & Burgns (1972), and Besser (1974).

<sup>2</sup> In appendices iii and iv relevant background on the structure and function of the hypothalamic endocrine system is first presented. A review of various physiologic findings, that the hypothalamus behaves, not like a relay or way station, but through a complexly organized system of convergent and divergent connections.

While it has variously been recognized that, in principle, the ANS would be a prime candidate for measuring the "stress state," as it relates to endocrine disturbance, Mason (1968), for example, points out that this is not possible because the sympathetic and parasympathetic components could not be recorded independently.<sup>1</sup> He has then focused alternatively on the development of highly sophisticated bio-assay techniques to detect changes in minute plasma and urinary endocrine levels. Preliminary results suggest that, in response to "psychologic stress," they appear to fall into two phased components: hormones associated with catabolic and anabolic reactions. These are, interestingly, just those associated with E (sympathetic) and T (parasympathetic) responses also.

In the following paragraphs the remaining output (downward somatic) of the u-h-r will be discussed in terms of autonomic activation.

### Section C. Autonomic Somatic Relationships

The remaining pathways (3, 4 in figure IV) suggest that expression of the accumulation of stress should be looked for also within the somato-muscular system: path 3 represents outflow of the u-h-r into extra-pyramidal motor tracts.

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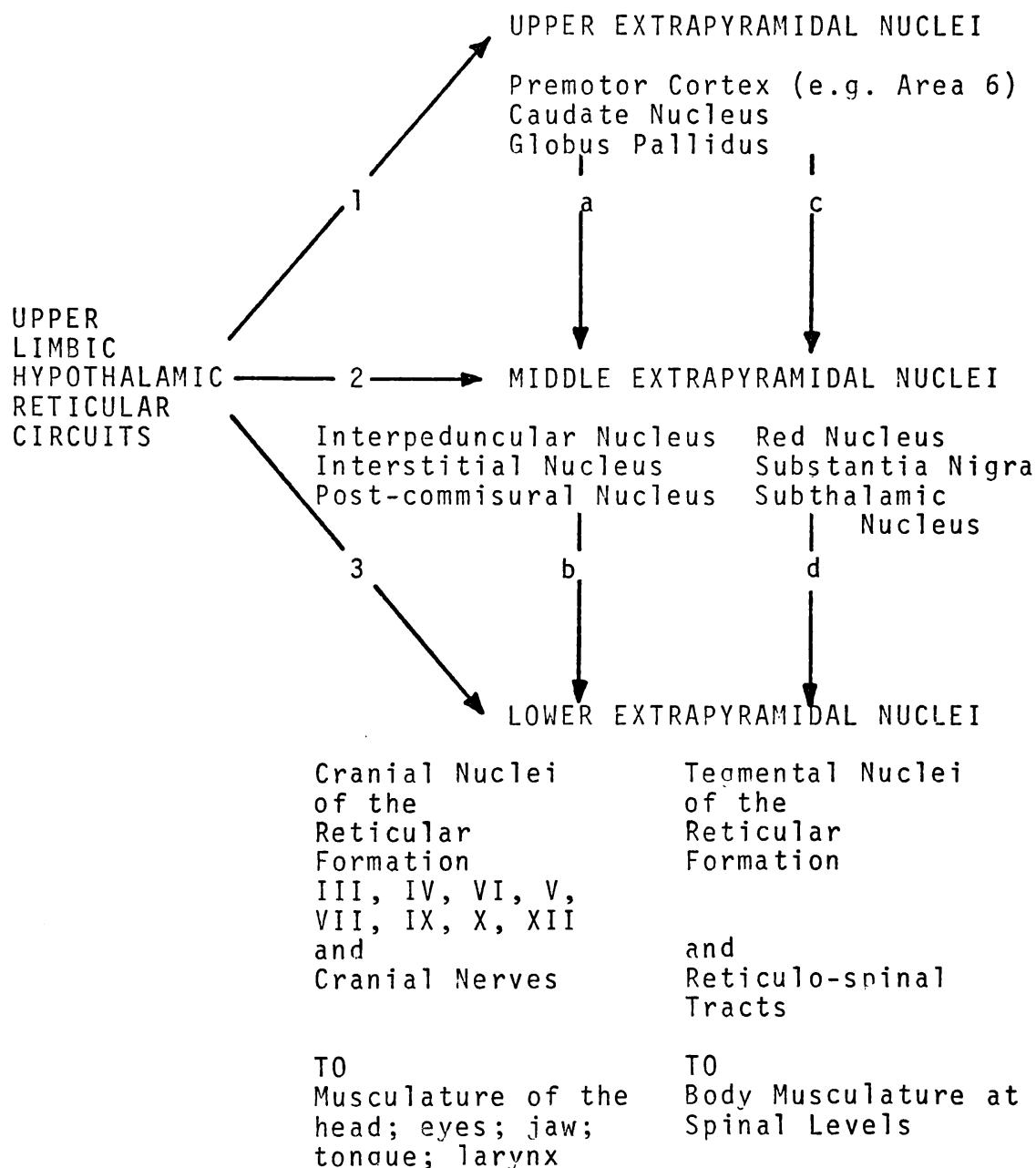
<sup>1</sup> It has been demonstrated here that the sympathetic and parasympathetic components can, however, be separated by application of systems theory, giving a basically new handle to this problem.

These connections, which occur at three levels, are responsible for a wide range of rhythmic movements and postural adjustments. These are summarized in figure V. The remaining pathway (4) is through the descending reticular, non-specific, tonic motor system (gamma efferent). The reticular formation (an internuncial reticulum, as the name implies) is fed by collaterals from all the specific sensory systems, as well as, intrinsically, by the u-h-r circuits.

The reticulated core projects diffusely, not only cortically but also downward, directly to a number of nuclei which become activated en masse: the reticular nuclei for flexion/extension and for right/left turning become activated equally. "The maintenance of such diffuse tonically non-specific activation in turn results in a state of immobilization. For, if flexion, extension and rotation to the left and to the right at spinal and cranial levels are all equally activated, then a rigid, equally balanced state of activation of all the musculature and of all muscular reflexes occurs." (Weil, 1974) Further enmeshed within the reticular formation are inhibitory nuclei for the flexors and extensors as well (Eldred & Fujimori, 1958). Tonic non-specific activation to the total assembly could therefore lead as well to muscular flaccidity or quite possibly to a spasticity characterized by both hyper- and hypotonic components.

In regard, then, to the probable connection of stress to rhythmic movements, rigidities and spasticities, the Nobel

Figure V



From Weil (1974)

speech for Medicine and Physiology<sup>1</sup> delivered by Nikolas Tinbergen is particularly interesting:

I have decided to discuss today two concrete examples of how the old method of watching and wondering about behavior can indeed contribute to the relief of human suffering, in particular to suffering caused by stress.

The first example he discusses is autism, an affliction of young children which involves a total withdrawal from the environment, a failure to acquire, or loss of previously learned overt speech; a serious lack in the acquisition of important skills; obsessive pre-occupation with a limited number of objects; the performance of "senseless" and stereotyped movements; as well as an encephalographic (EEG) pattern indicative of a high degree of central arousal.

Tinbergen's unique contribution as a "naive" observer (i.e., an ethologist and not a medical psychiatrist) is his acute ability to see similarities as well as differences. He observed that there exists some degree of overlap between the autistic and the normal child's behaviors in terms of subtle non-verbal expressions, gestures, and posturings. On that basis, he was able to establish some degree of communication and encourage socializing behavior.

From the standpoint of the Catastrophe model, in addition, the concurrent association of low behavioral expression with states of high central activation is particularly striking. This is the characteristic behavior

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<sup>1</sup>Delivered 12 Dec. 1973, and reprinted in Science, 185:5, (July 1974), as "Etiology of Stress Diseases."

of the "stasis." One would expect, then, loss of spontaneous and rhythmic movements due to diffuse non-specific discharges on paired movers, and also simultaneous sympathetic and parasympathetic activation. A severe and obligatory limitation in the capacity of the autistic child to make any refined or spontaneous (no less appropriate) response would certainly be a limitation in the formation of any behavior.

Plans to implement these predictions of the stress model by establishing a treatment modality for autistic children are presently being made. Ian MacNaughton, at the Fielding Institute, plans to affect behavior in autistic children by influencing the autonomic control variables. This will be done with various somatically oriented, manipulative procedures involving also specialized techniques of neuro-muscular re-patterning.<sup>1</sup> They will be used in the context of catalyzing the process of contact, bonding and socialization by permitting a greater possibility of appropriate responses, as well as by enhancing positively experienced outcomes.

The generality of the relations between autonomic stress and somato-motor behavior may be obscured by the fact that there has often been a lack of consistent correlation

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<sup>1</sup>The idea of affecting the ANS by somatic procedures appears to be a central theme in a number of "non-Western," "non-orthodox healing systems. Section B, part II of this paper discussed briefly the ideas of some of these methods as they relate to the stress model.

between the two (Malmo, 1959). Some provocative possibilities have emerged from rather unusual studies carried out by Valerie Hunt (personal communication), director of the UCLA movement behavior laboratory. Dr. Hunt has measured telemetrically the electromyographic (emg) recordings of various paired muscle groups in unrestrained subjects. She discovered that certain groups of subjects were characterized by particular agonist-antagonist (e.g., flexor/extensor) patterns.

Most (average) subjects exhibited a sustained and partially overlapping pattern of activity from paired muscle groups. Polynesian dancers, young children and a percentage of Negro adults tested exhibited an undulating pattern characterizing a more rhythmic and efficient transfer of muscular energy. Athletes (e.g., baseball players) also had their own unique patterns.

Persons experiencing frustration and older subjects in general exhibited what Dr. Hunt labels a "restrained" pattern. Here the agonist-antagonist muscle pairs fire, not reciprocally, but in sustained co-contraction, one pair cyclically dominating the other in a rather inefficient utilization of muscular energy. In a further study, Dr. Hunt obtained a high degree of correlation between the degree of "restrained contraction" and "psychologic anxiety" measured by scales such as the Taylor Manifest Anxiety. Her work is being extended by computer frequency spectrum analysis, which, in addition to greatly refining her early work, has

been used by Dr. Hunt to study at least one non-conventional healing system<sup>1</sup> with the particularly fascinating finding that treatment (processing) by this modality tends to shift a person's emg patterns (irrespective of their pre-grouping) towards the undulating patterns (those of the Polynesian dancers).

While these and her other results cannot yet be considered more than provocative, they certainly point in the direction of a fundamental and highly significant relation between the accumulation of stress and neuromuscular patterning.

#### Section D. Somatic (Muscular) Mobilization; Mechanisms and Relation to Accumulated Stress

An organism responds to environmental change through a continuous integration of motor response with sensory data (both from inside and outside its boundaries). The response to changes, either in the external environment or internal visceral shifts, requires appropriate action of the neuromuscular skeletal system. Feedback from the effector organs and the external senses not only determines whether a particular action is "successful" or not, but is the integral link both in its execution and timing. This is perhaps what Sherrington (1953) means when he states that "the motor act

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<sup>1</sup>The myofascial manipulative system invented by Dr. Ida Rolf, Ph.D.

is the cradle of the mind."

Towards understanding the role played by the external effector organs (muscles) in the regulation of autonomic activation in the resolution or accumulation of stress, we look first at some of the functional connections between the autonomic and somatic NS at the level of a muscle group: each skeletal muscle is composed of many fiber bundles which are aggregates of several thousands of microscopic fibers. It is the parallel development of tension in these extrafusal fibers, stimulated by their spinal alpha neurons, which is responsible for mechanical contraction and movement.<sup>1</sup> There are also small bundles (comprised of about ten fibers) called intrafusals. These fibers are innervated by the gamma efferent motor system.<sup>2,3</sup> Within the intrafusals are two kinds of afferent sensory nerve endings: centrally in the nuclear sac region are the annulospiral receptors, and at either side of these, in the myotubal region, are the flower spray endings (see figure VI). Both of these receptors fire proportionately to degree of stretch. Since the intrafusals are arranged "in parallel" with the working fibers, contraction leading to movement slackens tension on the spindles and decreases their frequency of firing (see figure VII). When,

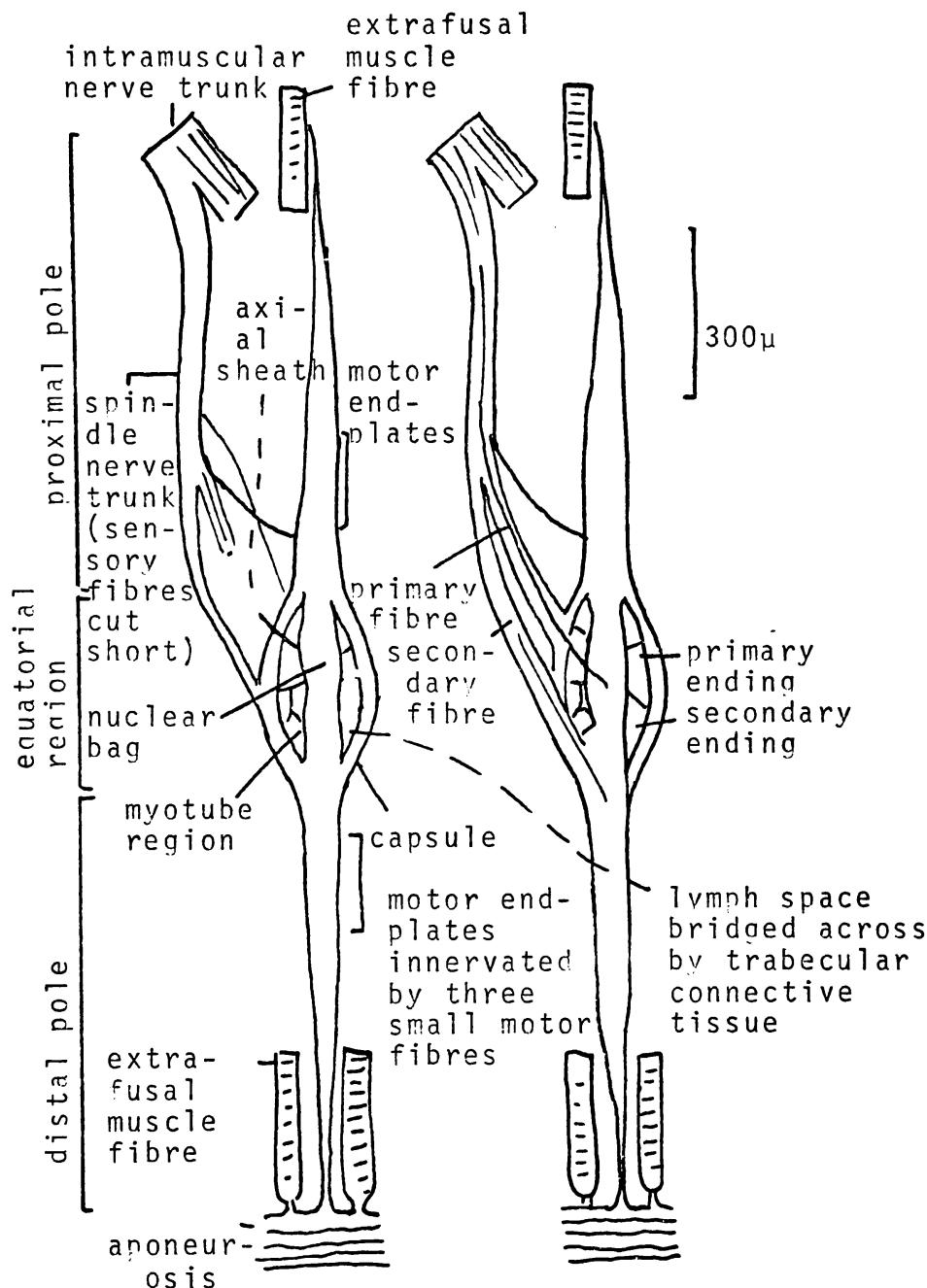
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<sup>1</sup>The alpha neurons are a part of Yakovlev's outer and middle "conscious" neo-cortical sphere.

<sup>2</sup>The gamma efferent system can be stimulated directly from various points in the medulla and brain stem reticular formation and u-h-r circuits (see section D, part III).

<sup>3</sup>In Yakovlev's system they derive more from the middle and inner sphere in close connection with the visceral-autonomic.

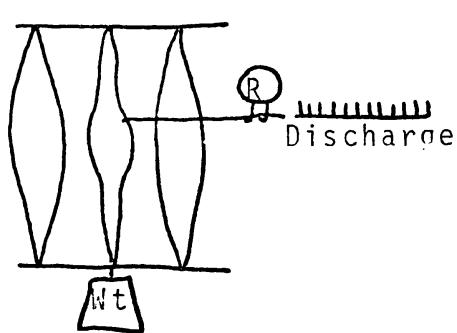
Figure VI.



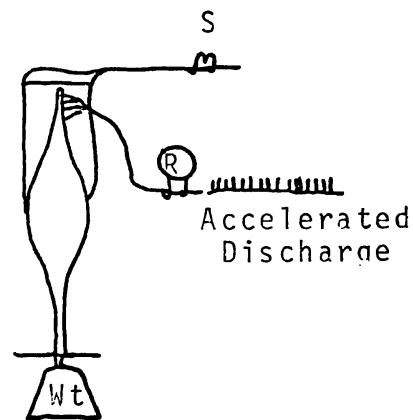
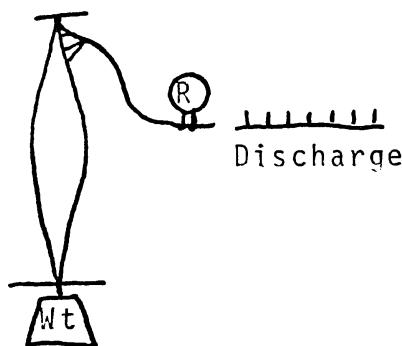
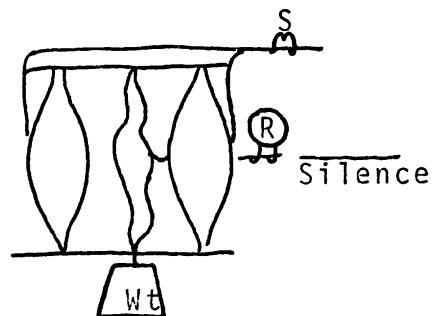
From Ruch, Patton, Woodbury & Towe, Neurophysiology (Saunders, 1965)

Figure VII.

MUSCLE STRETCHED



MUSCLE CONTRACTED



From Ruch, Patton, Woodbury & Towe, Neurophysiology  
(Saunders, 1965)

on the other hand, the intrafusals alone are stimulated by their gamma neurons the contraction is not strong enough to cause muscular movement. But this shortening, which in itself has no direct effect on movement, sends back afferent impulses to spinal and supra-spinal centers identical with those as though the entire muscle had been passively stretched. Alpha motorneurons are then stimulated so as to "restore" the muscle to its original position (even though no stretching actually took place).<sup>1</sup> See figure VIII.

With these relations in mind, we look first at a hypothetical example of a simple reflect withdrawal to a "localized stress" stimulus: irritation. The initial response, muscle activation and withdrawal of the appropriate body part (e.g., the reflex withdrawal of an arm upon touching a hot object), will, if successful, eliminate the provoking stimulus. The appropriate muscle is then released ("discharged").<sup>2</sup> If, on the other hand, the reflex action was not successful (e.g., the strong pinch of a crab on one's finger), the noxious focus would not be eliminated and a more intense or integrated response would be required.

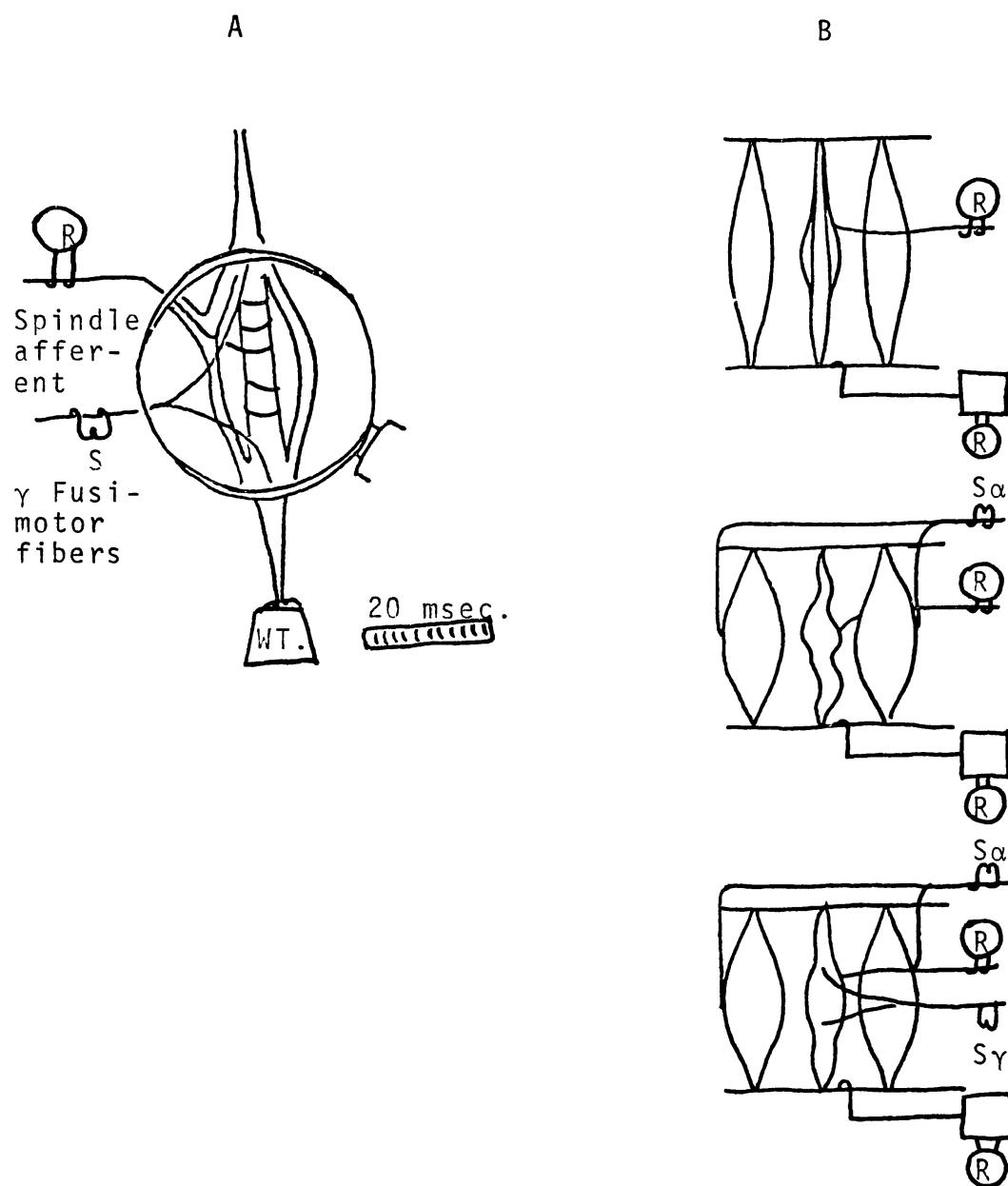
We see how, under prolonged or intense noxious stimulation, somatic and autonomic systems might be integrated to

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<sup>1</sup>This type of mechanism is the basis of the many anti-gravity reflexes whereby a change in weight is countered by increased muscle tension in maintaining constant position. (The knee jerk elicited by the physician with his hammer.) The same reflex prevents the knee from collapse under changing loads.

<sup>2</sup>Again the basic charge/discharge rhythm.

Figure VIII.



From Ruch, Patton, Woodbury & Towe, Neurophysiology  
(Saunders, 1965)

act synergistically in removing the source of irritation: the somatic response to nociceptive stimuli (e.g., pain) is a reflex contraction of appropriate muscles. Nociceptive agents also act directly upon central sympathetic areas, evoking gamma efferent impulses, which in turn cause contraction of the intrafusals. Under these conditions the muscles shorten even more, by reflex activation of their alpha motorneurons. In this way the autonomic indirectly reinforces somatic protective action and the movement, when successful, both eliminating the original cause of the withdrawal and allowing the muscles to return to their previous state. This decreases impulses from the afferent spindles, removing a potential source of reactivation to the sympathetic centers, and allows a parasympathetic rebound discharge to re-establish the autonomic balance. The fact of somatic (muscular) discharge is crucial because most somatic afferents at high frequencies augment central sympathetic activity (see Gellhorn, 1967).

But consider another example of persistent noxious stimulation, this time, though, where the appropriate response is restrained by blocking reflex movement, i.e., preventing appropriately phased mobilization. As in the above case, the initial response is muscular activation. The contraction, however, will be isometric and the spindle receptors will not decrease their firing. The gamma efferent discharge associated with the sympathetic response will shorten the intrafusals, thus causing the spindle to fire at

a higher rate. The flower spray neurons (since they are group II fibers) stimulate sympathetic response (Laporte et al., 1957). This will lead to a further increase in gamma firing, causing the intrafusals to contract more and the spindle receptors to fire at an even higher rate. A positive feedback loop is thus formed, progressively stimulating sympathetic activity; and the main (extrafusal) muscle fibers continue to tighten against the restriction until they develop enough strength either to overcome the restraint, or eventually to stretch the tendonous connective tissue sufficiently to cause golgi receptor neurons to fire, causing collapse.<sup>1</sup>

The enormous significance of this buildup sequence to autonomic activation derives from Gellhorn's experimental data on the hypothalamus. He has shown, as already mentioned, that while brief periods of sympathetic activation evoke a compensatory parasympathetic rebound, stimulation which lasts for over ten to fifteen seconds is followed by reinforcement of the sympathetic response which may persist for extended time intervals. Thus we have here, in the absence of appropriately phased somatic discharge, as the response to autonomic activation, an important physiologic mechanism in the accumulation of stress.

Situations, whereby an organism is physically

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<sup>1</sup>This "jack knife" reflex releases the extrafusals via spinal inhibitory pathways, keeping the muscle from rupturing.

restrained, probably do not happen all that often in nature. Even if the articular segments are not physically immobilized, however, the action of the gamma system in diffuse activation is such that, in contradiction to the law of mutual reciprocity, flexor-extensor, agonist-antagonist tonus are both augmented simultaneously (see section F, part III). This push and pull will cause a partial immobilization of the joint, thus limiting the capacity to move: the longer the "irritating" or noxious stress situation persists, the greater the sympathetic tone that will be developed, the "somatic power" that will be contained, and the motor discharge that will be required to "reset" the autonomic imbalance created.

It is not necessary that the hypothetical sequeli of local reflex irritation to organismic immobility occur exactly as outlined in the preceding paragraphs. If the "noxious agent" is compelling enough it would be eliminated by one of a number of mechanisms long before immobilization. If the noxious agent is more subtle, however, it is not unlikely that one or more body segments within the background of a more global activation (of the sympathetic system) may remain undischarged, and thus contribute prolonged afference to the posterior hypothalamus preventing a parasympathetic discharge.<sup>1</sup>

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<sup>1</sup>As an anecdotal illustration, Percy Knauth, chairman of the National Association for Mental Health, relates his battle for survival against a severe depression (a state which, it will be shown later, is probably typified by

These autonomic-somatic, change-discharge relations can be considered in terms of the activation systems discovered by Cannon and Hess: Cannon, as mentioned previously, proposed that the response of the sympathetic nervous system with its concomitant adjustments in cardiovascular performance, rise in blood sugar, increased activity of the skeletal and respiratory muscles, etc., prepared the organism for fight and flight. Under normal conditions a particular evoking stimulus (e.g., a predator) would be dealt with by appropriate motor response: i.e., fight or flight; or if the danger passed, by a more or less smooth gradual shift back to the pre-stimulus condition. Now if some aspect of the innate motor response is prevented, or the evocative stimulus is so overwhelming that its autonomic effects cannot be integrated into appropriate motor action on account of diffuse activation resulting in, at least, partial paralysis, then the potential for mobilization is lessened and the stage is set for the accumulation of stress.

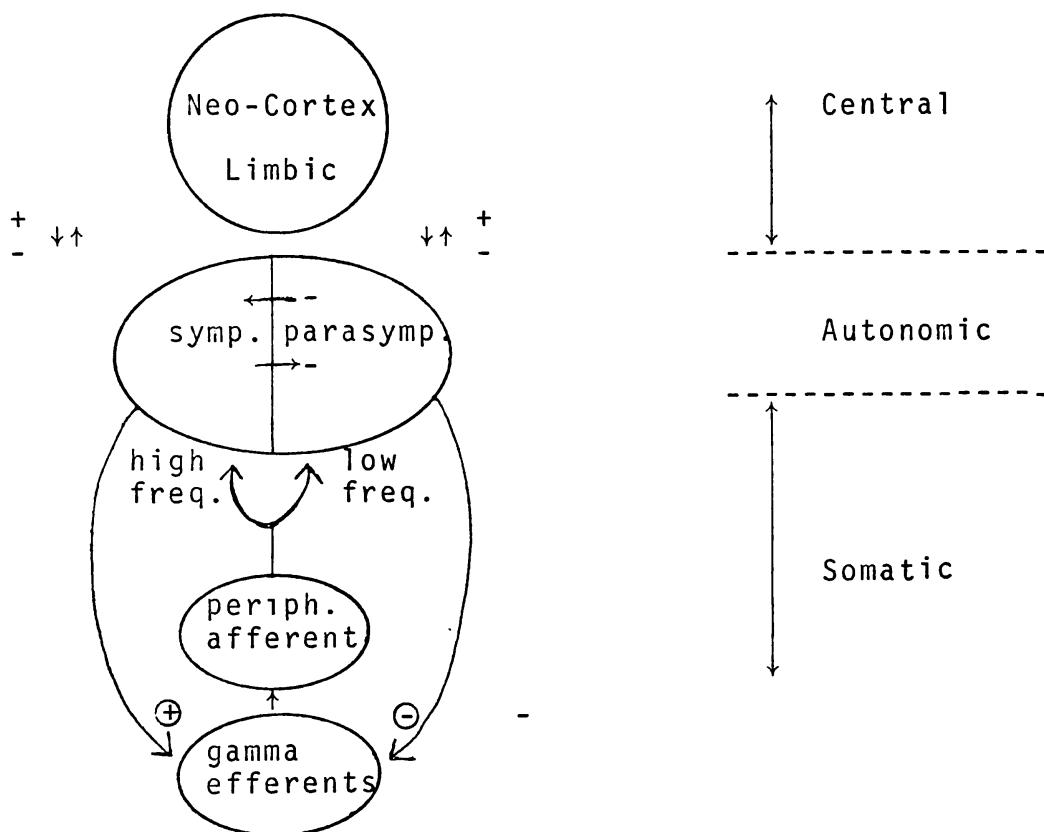
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simultaneous sympathetic and parasympathetic activity). To the question of what actually triggered his 18-month siege with suicidal depression, he replied:

"As I was swimming, a piece of seaweed brushed my leg and I snatched myself away in alarm...I was suddenly flooded by an icy fear...After several desperate panicky tries, I finally pulled my body over the gunwale...I had pulled a muscle in my left leg." (my italics)

Certainly this could be coincidence, and is not presented in scientific evidence; but the two crucial elements--extreme stress and partial immobilization--are certainly there. Again, in an individual of greater adaptive resource such a reaction might not occur. But we are dealing with a progressive situation both before and after any given specific "precipitating factor."

In summary, then, in a healthy organism (high reserve capacity), stimulation to either the sympathetic or parasympathetic hypothalamic centers (from below or above) will tend to shift (tune) the balance to that side. Upon cessation of mild or moderate stimuli, mechanisms within the hypothalamus (brain stem) as well as motor feedback will discharge in a compensatory rebound towards the other side. These rebound phenomena serve the function of autonomic homeostasis.



On the other hand, if stimuli are too intense or prolonged, then these internally-timed mechanisms apparently are unable to rebound and shift back to a balanced state. The autonomic centers will, then, through successive tuning induction, begin to shift, usually, in a sympathetic

direction. The autonomic/somatic state will tend towards a set of chronic arousal and limited, a-rhythmic and rigid movement.

If this state persists (i.e., is not resolved), it may eventually devolve to a situation where both sympathetic and parasympathetic are simultaneously active. As this simultaneous autonomic activity becomes an established pattern, a new "meta-stable" state will be created, where the spiralling sympathetic excitation finally is kept in check by central parasympathetic inhibition, and in the periphery by inhibiting of the gamma system. The runaway sympathetic situation has been limited, but so has the potential for discharge: further arousal stimulates both sympathetic and parasympathetic activity but without concurrent increase in muscle tone (in fact a decrease), as the parasympathetic begins to dominate the already heightened sympathetic. The cyclic stimuli leading to appropriate motor discharge are no longer present.

## PART IV. STRESS DISEASE

### Section A. Compendium of Stress Diseases

#### i. Nomenclature

While almost no one would argue basically against a multifactorial view of disease (incorporating stress, infectious agents, and other epidemiologic considerations); and since, as Selye (1976) points out, "increased corticoid production has been demonstrated in "virtually every pathologic condition of any importance, a certain relationship between stress and the most dissimilar diseases has been suspected."

Which diseases, though, are primarily stress-induced is not as clear, and if stress is a predominant factor in so many diseases, why they often exhibit such a wide range of varied symptoms and pathogenic sites is by no means apparent.

Reasons for this are undoubtedly extremely complex, involving an intermeshing of specific and non-specific factors. Nevertheless, certain diseases, because of correlated clinical and experimental data, are almost universally accepted to be primarily stress related (notwithstanding that the definition of stress may vary from situation to situation, if even defined at all).

Various nomenclature has been proposed to classify the stress diseases, for example, a list by Dr. B. Haynes,

from his book Autonomic Dyspraxia (1958).<sup>1</sup>

<sup>1</sup> Central Nervous System

Anxiety A.D. (Anxiety neurosis)  
 Obsessional A.D. (Obsessional neurosis)  
 Traumatic A.D. (Traumatic neurosis)  
 Shock A.D.  
 Exhaustion A.D.  
 Psychotic A.D. (various psychoses)  
 Epileptic A.D. (Epilepsy)  
 Migrainous A.D. (Migraine)

Endocrinial

Thyrotoxic A.D., with or without adenomata (Primary and secondary thyrotoxicosis)  
 Diabetic A.D. (Diabetes mellitus)  
 Climacteric A.D. (Menopausal syndrome)

Respiratory

Rhinotic A.D. (Hay fever)  
 Asthmatic A.D. (Asthma)

Circulatory

Hypertensive A.D. benign (Essential hypertension)  
 " " cardiac (Hypertensive heart disease)  
 " " renal (Chronic nephritis, Nephrosclerosis)  
 " " malignant (Malignant hypertension,  
     Chronic interstitial nephritis)  
 Acute rheumatic A.D. (Rheumatic fever)  
 Acute renal A.D. (Glomerular nephritis)  
 Coronary A.D. (Angina pectoris)  
 " " with infarction (Coronary occlusion, Coronary thrombosis)  
 Cerebral A.D. with or without hypertension  
 " " with hypertensive encephalopathy (Hypertensive encephalopathy)  
 " " with supervening thrombosis (Cerebral thrombosis)  
 " " with supervening haemorrhage (Cerebral haemorrhage)  
 Arterial A.D. (Raynaud's disease)  
 " " with degenerative arterial disease (Intermittent claudication)

Alimentary

Oesophageal A.D. (Achalasia cardia, cardiospasm)  
 Gastric A.D. with or without ulceration (Gastritis, Gastric ulcer)  
 Duodenal A.D. with or without ulceration (Duodenitis, Duodenal ulcer)  
 Ileal A.D. (Regional ileitis, Crohn's disease)

Appendiceal A.D. with or without infarction (Catarrhal appendicitis) and gangrene (Gangrenous appendicitis)  
 Colonic A.D. with or without ulceration (Mucous, Spastic and ulcerative colitis)  
 Rectal A.D. (Proctalgia)  
 Biliary A.D. with or without cholelithiasis (Biliary colic)  
 Pancreatic A.D. with or without infarction (Chronic and Acute haemorrhagic pancreatitis)

#### Genito-Urinary

Catamenial A.D. (Menopause)  
 Leucorrhoeal A.D. (Leukorrhoea)  
 Fallopian A.D. (Intermenstrual pain, Ectopic pregnancy)  
 Coital A.D. (Impotence, E. praecox, Frigidity, etc.)  
 Vesical A.D. with or without ulceration (Frequency, Chronic interstitial cystitis)  
 Nephritic A.D. (Nephritides)

#### Dermatological

Macular A.D. (Macular rashes)  
 Papular A.D. (Papular rashes)  
 Urticular A.D. (Urticaria)  
 Angioneurotic A.D. (Giant urticaria)  
 Purpuric A.D. (Various purpuras)  
 Dermatitic A.D. (Neuro-dermatitis)  
 Psoriatic A.D. (Psoriasis)

#### Locomotor

Cervical A.D. (Torticollis)  
 Lumbar A.D. (Fibrositis, Myositis, Lumbago, Fibromyositis, etc.)  
 Shoulder girdle A.D. (Shoulder syndrome, Shoulder-hand syndrome, Subscapularis, etc.)  
 Supinator A.D. (Tennis elbow)  
 Acute rheumatic A.D. (Rheumatic fever, Acute rheumatism)  
 Rheumatoid A.D. (Rheumatoid arthritis, Atrophic arthritis)  
 Podagra A.D. (Gout, Podagra)  
 Hydrarthrotic A.D. (Intermittent hydrarthrosis)

All of these diseases are diagnosed as "autonomic dyspraxia" on the basis of the following symptoms (in addition to the primary presenting complaints), any two of which, he submits, proports a very good chance of primary autonomic dysfunction.<sup>1</sup>

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<sup>1</sup>These symptoms "occur so exclusively in patients suffering from a gross autonomic dyspraxia, that I have no hesitation at listing them as reliable evidence of autonomic dyspraxia."

#### Symptoms Suggestive of Autonomic Dyspraxia

Headaches, especially vertical headaches, hemicrania, postural headaches, migraine or chronic headaches.  
Chronic tic doloureux.  
Insomnia.  
Disturbances of smell or taste.  
Paroxysmal rhinorrhoea (hay fever). Asthma.  
Flatulence and flatus.  
Indigestion.  
Hot flushes.  
Muscae volitantes.  
Sensation of falling or jumping when nearly asleep.  
Globus hystericus.  
Paraesthesia of limbs, especially of upper limbs.  
Frequency of micturition associated with emotion. Enteric diarrhoea.  
Collapsing knee.  
Dizzy attacks and black-outs to flaccid unconsciousness.  
Vertiginous attacks with or without tinnitus, and vice versa.  
Paradoxical postural pain.  
Dysphonia and Hysterical aphonia.  
Pruritus ani and/or vulvae.  
Amnesia.  
Inability to concentrate, restlessness.  
Live-flesh, live-blood or myokimia.  
Dysmenorrhoea and Dyspareunia.

#### Clinical Signs of Autonomic Dyspraxia

Abnormal sweating	Abnormal nasal secretion
Abnormal lacrimation	Abnormal salivation
Abnormal sensory findings:	
Spiral fields of vision	Site tenderness
Abnormal palate sensation	Glove and stocking
Abnormal smell and taste	anaesthesia

For example:

Globus hystericus (difficulty in swallowing) is possibly one of the most common symptoms, as are headache, flatulence, flatus and indigestion (even in the case of diaphragmatic hernia he contends that the symptoms are invariably due to a concomitant autonomic dyspraxia).

In the case of headaches persisting over a period of months he quips that "the vast numbers of aspirin preparations consumed daily makes the sum total of all 'organic cases' at our hospitals... truly microscopic in comparison." Nevertheless he does feel that "the first step in diagnosis is still to exclude this small but most important group." This, he says, "is possible in the first or second consultation, mainly by clinical methods. In the great majority of cases, multiple tests, and X ray procedures à la Mayo, are not only unnecessary but definitely contraindicated." (Haynes (1958)

Hans Selye (1976), on the basis of an extensive (massive) review of the clinical and experimental literature, presents an even longer list of stress related disease categories. It would serve no useful purpose to review these areas again; discussion is limited to a few cases, as they relate to the concepts derived in this paper.

Eppinger and Hess (1910), in their classic (if not somewhat horrifying) clinical studies on psychosomatic medicine, divided psychosomatic disorders into two broad categories: those associated with sympathetic predominance (sympathetonia) and those with parasympathetic dominance (vagatonia). Various authors, e.g., Gellhorn (1965) have

Abnormal muscular activity:

Hippus	Chorea
Unequal pupils	Tic
Tremor	Aerophagy and belching
Myoedema	Borborygmus
Fibrillary twitching	Certain cardiac arrhythmias

Abnormal reflex activity:

Light reactive hippus	Hypersensitive reflexes
Myotonic irritability	Absent palate reflex

followed this line in classifying stress diseases with an associated dominant or "tuned" autonomic branch.

ii. Hypertension

This dichotomy appears to make sense, for example in the case of essential hypertension, where Folkow and Rubenstein (1966) were able to produce, in rats, sustained heightened blood pressure by daily stimulation, for several months, of the postero-lateral hypothalamus.

This showed that chronic ergotropic (sympathetic) activation is capable of inducing hypertension along with degenerative cardiovascular and renal lesions (Henry, 1967). In addition, pressor responses can be conditioned in man and animals with hypertensives conditioning much more readily (Miasnikof, 1962).

While these and similar observations cannot by themselves be considered proof that the various clinical hypertensive syndromes have, as their basis, prolonged sympathetic tone, they must be considered highly relevant to these pathologies.

Thus the prolonged accumulation of sympathetic cardiovascular stress is at least contributory in a wide range of very serious tissue pathologies.<sup>1</sup>

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<sup>1</sup>Hypertension, with its many probable expressions, e.g., the infarct, thrombosis, certain renal failures, arteriosclerosis, etc., might best be considered as a primary predisposing factor for these pathologies rather than a disease in itself.

According to the model, "simple" sympathetic accumulation is an initial stage in the progressive accumulation of autonomic stress. Further accumulation, while perhaps having no more dramatic consequences than those of this initial stage, would be expected to exhibit more complex, varied and divergent behaviors and symptoms. This is because, according to the model, parasympathetic components begin to enter into the accumulation, progressively, at higher levels, resulting in cusp region catastrophe behavior.

### iii. The Ulcer

The duodenal ulcer is a disease often ascribed to a trophotropic imbalance since hypersecretion of hydrochloric acid is associated with vagal activity. (It is even sometimes treated surgically by partial vagotomy.) In addition, ulcer patients are also often known to exhibit such signs and symptoms as low blood pressure and easy fatiguability, indicating a trophotropic pattern. Thus, as Gellhorn (1965) argues, it makes sense to consider the ulcer as a case of parasympathetic tuning. Nonetheless, Simeons (1962) points out that high concentration of hydrochloric acid does not per se cause ulcers, implying vasoconstriction as a necessary factor, too. This would presumably be due to a concurrent sympathetic activation. Also, while many ulcer patients exhibit hypotension and other symptoms of vagotonia they are often (against their doctors' admonitions) involved in highly driven and aggressive behaviors which are more

characteristic of the ergotropic syndrome. So while trophotropic signs and symptoms appear to predominate, it would be well worth looking for "masked" sympathetic tonus also in these individuals,<sup>1</sup> as well as discontinuous shifts in their behavior and matrices of symptoms.

#### iv. Vasodepressor Syncope

In this "fainting" syndrome the probability of dual autonomic activation seems somewhat clearer. Vasodepressor syncope is usually precipitated by pain and fear of injury; and as Engle (1962) points out, it is evoked "in a situation where the general circulatory preparation for flight (i.e., the ergotropic syndrome) takes place but for some (italics mine) reason flight is impossible." This "some" reason is reflected in a loss of tone in the skeletal muscles and is quite probably due to parasympathetic inhibition of the gamma efferents.<sup>2</sup>

Thus it seems that the simultaneous activation of both autonomic components leads to the maladaptive response of, so to speak, "being overwhelmed." If, though, the individual, at the moment of fainting, tenses his muscles, the attack can be halted. In terms of Catastrophe topology this would amount to introducing a momentum factor at that critical time,

<sup>1</sup>As by the systems analysis described in part V.

<sup>2</sup>This adds to the tendency of collapse since, in addition to loss in venous return to the heart, loss of proprioceptive impulses tends to tune the parasympathetic tuning further.

causing behavior to jump back to a higher motility surface.  
(See figure IX, page 49.)

v. Anxiety States (General)

Gellhorn (1965), in summarizing a wide variety of physiologic experiments, reports that anxiety states are associated with high degrees of ergotropic activity and simultaneously with "abnormal behaviors," when accompanied also by trophotropic signs. These behaviors appear to often stem from an alternation between opposite extremes of possible action, e.g., attack-retreat, or approach-avoidance. It seems reasonable in studying anxiety experimentally, then, (the experimental neurosis) to look for cusp Catastrophe behavior, and to correlate it with autonomic states. The experimental neurosis, in animals, would provide a unique window in that central sympathetic and parasympathetic activities could be measured directly by electrical recordings.

vi. Anorexia Nervosa

Patients suffering this life threatening illness are characterized by "obsessional" behavior of alternately fasting and gorging themselves with food. The disease has been classified in almost every diagnostic category imaginable: Mecklenburg et al. (1974) have investigated hypothalamic function in patients with this syndrome to test the hypothesis that a lesion (their word) in this region is critical to

the pathophysiology of this "disease."

Their conclusion is that "patients with anorexia have primary hypothalamic disease of unknown etiology." The data they present, however, support equally if not more strongly the Catastrophe formulation that small (functional) shifts in hypothalamic (autonomic) balance can account for the striking behavioral changes evidenced by this disorder. For example, the following data compare the response to acute hypo- and hyperthermia of normals and anorexics (see tables on page 140).

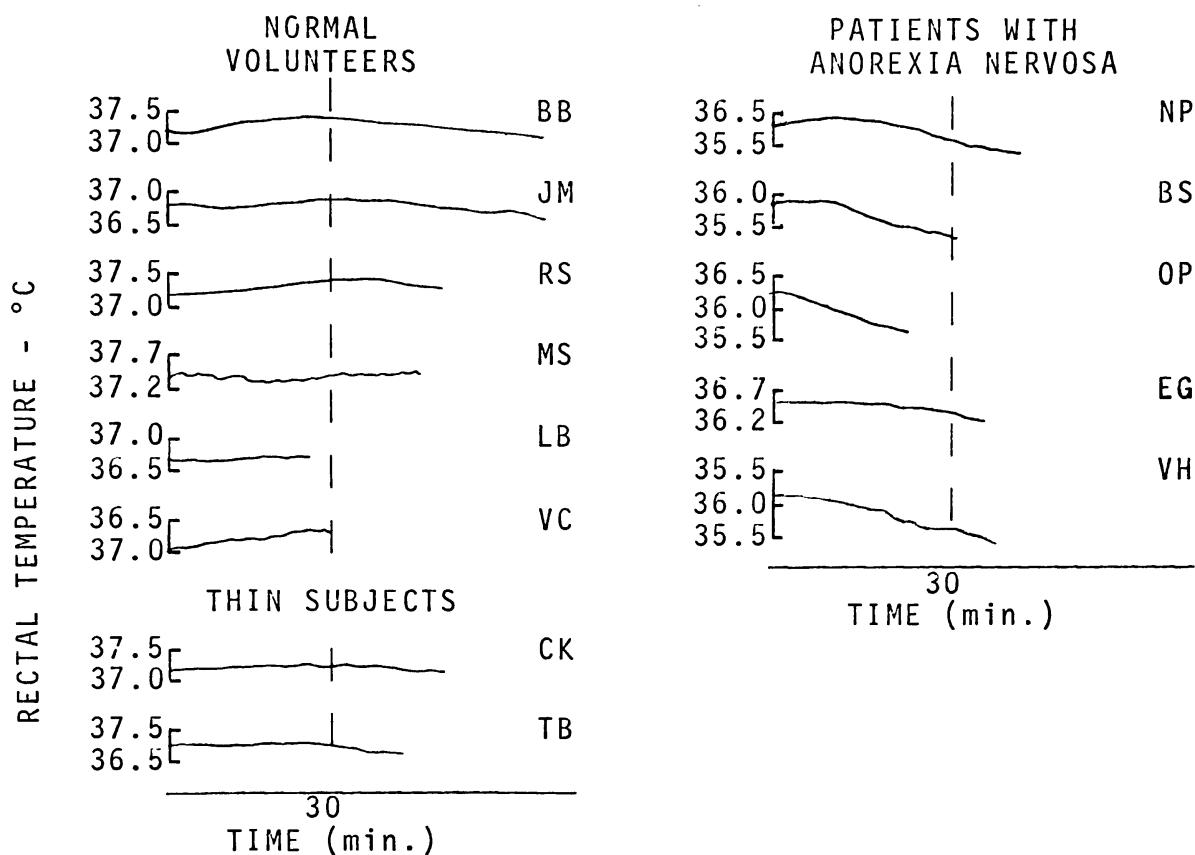
The authors state that "it is possible to clearly separate patients with anorexia nervosa from normal subjects by their responses to heat and cold." Yet clearly, in their response to hypothermia, subjects BB and NP are quite similar, as are EG and RS (more so than most patients within the group, e.g., BP and EG). Similarly, in the response to hyperthermia, normal BB and patient OP are quite alike, as are RS and EG, indicating only small autonomic shifts.

The statement that the pathogenesis is a hypothalamic lesion is supported, the authors claim, by:

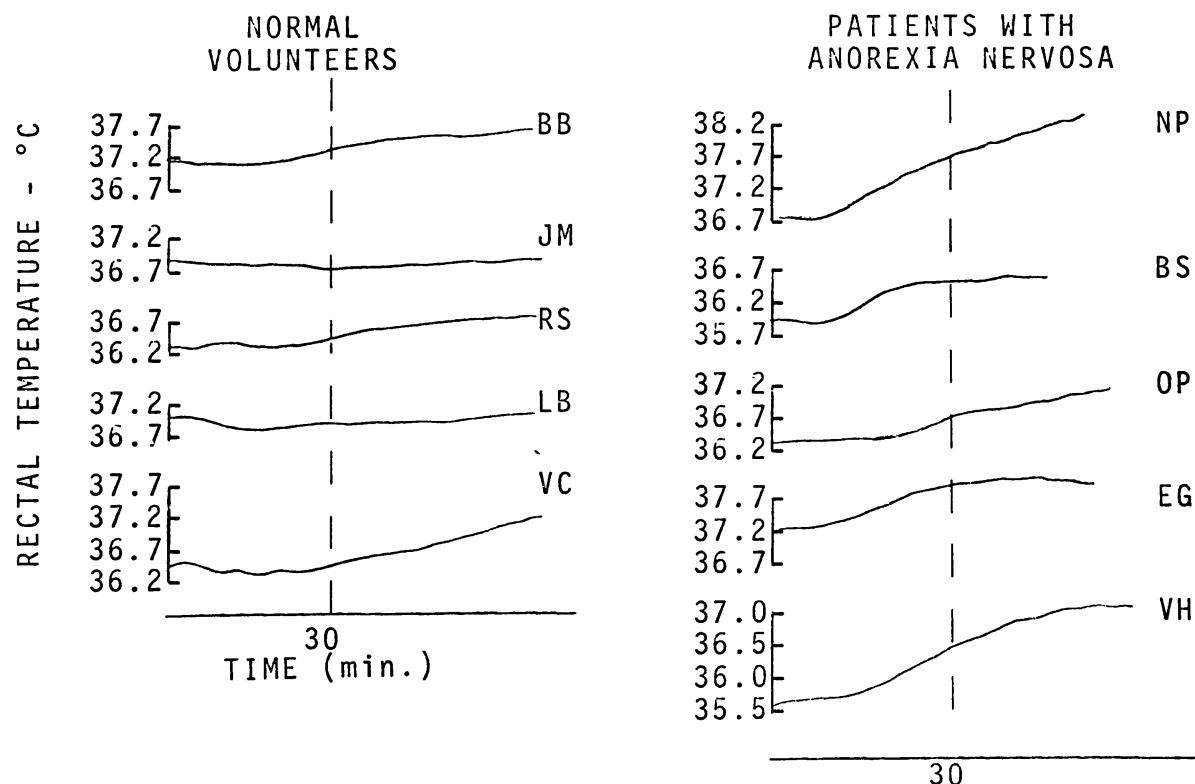
...the observations that emotional and behavioral disorders as well as abnormalities of sleep-wake pattern, water balance, thermoregulation, carbohydrate metabolism, and gonadotropin secretion may follow experimental hypothalamic lesions. Patients with syndromes approximating (italics mine) anorexia nervosa have been reported with tumors in the hypothalamic region or following central nervous system infection.

But all of these effects are equally compatible with the diminished adaptational capacity of autonomic imbalance

Responses to Acute Hypothermia



Responses to Acute Hyperthermia



characteristic of concurrent sympathetic/parasympathetic activation. In addition, Zeeman (1976) reports the work of a hypnotic trance approach which appears possibly to be the most effective form of therapy for this disorder, the only one where a substantial portion (though still small in number) report being cured and regain normal weight. Zeeman has been able to model this form of therapy quite elegantly by Catastrophe theory, suggesting again that the model is a promising choice for stress related disorders.

vii. Role of Stress in Primarily Infectious Diseases

The role of stress as a prominent contributory factor even in diseases of less obscure etiologies (infectious disease) is suggested by a fascinating paper by Akiro Saito (1970) of the Tohoku Medical School, Sendai, Japan.

On the basis of more than 15,000 patients, this author has studied the autonomic/hematopoietic relations in several infectious diseases. He summarizes this extensive work as follows:

Thus, observed from the level of the autonomic nervous system, the auto-adaptation mechanism of the human body consists of 2 major antagonistic systems which are composed of many antagonistic links of 2 nerves of the autonomic nervous system--2 phases of mitosis of the neutropoietic system in the bone marrow--2 defense reactions of the blood--2 fields of the blood defense reactions. These 2 major antagonistic systems...maintain life in a most suitable and purposeful way...The author has found that in a person who has an imbalance of the autonomic nervous system the adaptation of the body to the internal environment loses its suitableness and purposefulness, and an abnormal defense reaction occurs, causing a series of adaptational disturbances from acute to chronic type.

The implications of this are simple and inescapable: The outcome and process initiated by a foreign infective agent are determined perhaps as much by the functioning and dynamic capability of the autonomic system, as by the agent itself.

Some degree of caution, however, is needed, as certain steps in reasoning are not adequately connected in Saito's paper. Nonetheless, what he does offer is the possibility of a rather direct relationship between the accumulation of autonomic stress and the realm of infectious pathogenesis in general.

#### viii. Aging and Stress

In a provocative paper, V.M. Dilman (1971) at the Petrov Research Institute of Oncology in Leningrad proposes that age changes in the self-regulating systems affect the maintenance of a stable internal environment.<sup>1</sup> The key in this process, he argues, is the decrease, in aging, of hypothalamic sensitivity to feedback suppression. In his words, "This gradually leads to the loss of rhythmic functioning of the main homeostatic systems." He makes further the statement that the existence of this hypothalamic phenomenon per se is sufficient for the age related "switching on

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<sup>1</sup>"Gradual disorders of homeostatic stability are observed in man during aging (e.g., increased body-weight and serum-cholesterol, decreased glucose tolerance, and the climacteric). These changes characterize aging as a process of disordered homeostatic stability of internal environment."

and off" of the reproductive cycle, which is "needed for the establishment of relationship between energy and reproductive homeostasis in ontogenesis and to ensure their interaction with external environmental factors; regulating the density of population, and also for the gradual age-related impairment of homeostasis that finally leads to death from the natural onset of diseases of compensation."

In other words, he sees aging as the same process: "loss of hypothalamic sensitivity to feedback-suppression," as that induced by accumulated stress (as in this model), but at a slower time scale (in aging). Thus, behavior which has become restricted to "energetically confined" portions of the space<sup>1</sup> is due to simultaneous sympathetic and parasympathetic activation. This prescribes a "process of disordered homeostatic stability of the internal environment." (See III, B.)

#### ix. Hyperventilation: Syndrome and Clinical Effects

The mechanisms of hyperventilation are discussed in appendix ii. As a clinical entity:

The syndrome of hyperventilation is one of the most common and yet one of the most infrequently recognized medical disorders (italics mine). This functional derangement of breathing, with the sequela it precipitates, is often regarded as a manifestation of nervousness, yet when organic disease is simulated by the syndrome of hyperventilation, serious consequences by unwarranted restrictions may result from an erroneous interpretation of a patient's symptoms.

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<sup>1</sup>Behavior space in this instance would be labeled on an endocrinological/metabolic dimension.

The syndrome of hyperventilation results from excessive loss of alveolar carbon dioxide caused by increased respiration. By reduction of the partial pressure of alveolar carbon dioxide from its usual value of that of 40 mm. of mercury to a value less than half<sup>1</sup> that, respiratory alkalosis is induced in the body.

That the syndrome is a manifestation of "nervousness" is only a part of the story: the sensation resulting from hyperventilation is one of suffocation and illness, evoking then further hyperventilation and thus setting up a vicious cycle.

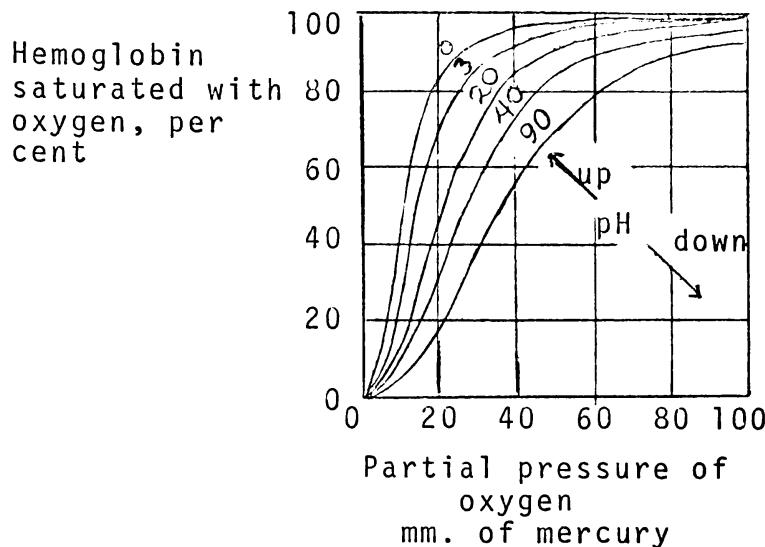
It appears that thoracic stretch receptors are particularly effective in evoking sympathetic discharge which will evoke further hyperventilation, which in turn stimulates the sympathetic via these receptors. (See Koizumi & Brooks, 1972.)

This process cannot go on unchecked, and it is reasonable to assume that eventual spillover onto the parasympathetic (which decreases respiration) will maintain the system in a "meta-stable state," i.e., the low motility, high activation stasis.

The net result is a lowering of the carbon dioxide tension to the tissues, which sets up an anoxic cellular condition. This is due to two factors: firstly, a decrease in transport of oxygen into the tissues due to local vasoconstriction caused by hypocapnia; secondly (and perhaps more significantly, according to the author), a greatly lessened oxygen saturation in the hemoglobin dissociation:

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<sup>1</sup>Staff meetings of the Mayo Clinic, October 1, 1947, Haddon Carryer, M.D., presiding.



In other words, as shown in this graph, the percentage of oxygen available from the hemoglobin for the cells varies greatly with the blood pH (i.e.,  $\text{CO}_2$  pressure).

Thus, the accumulation of autonomic stress must eventually lead, by altering the osmotic gradient, to subtle changes in cellular respiration. Carryer concludes, in fact, "that an important factor in the causation of symptoms by respiratory alkalosis is the effect that such alkalosis has on intracellular exchange of gases." In this regard, the thesis presented by Dr. Otto Warburg<sup>2</sup> (Nobel laureate 1931) for his work on cellular respiration on cancer seems relevant:

Cancer, above all other diseases, has countless secondary causes. Almost anything can cause cancer. But, even for cancer, there is only one prime cause. Summarized in a few words, the prime cause of cancer is the replacement of oxygen in normal body cells by a fermentation of sugar. All normal body cells meet their energy needs by respiration of oxygen, whereas cancer cells meet their energy needs in great part by fermentation. All normal body cells are thus obligate aerobes, whereas all cancer cells are partial

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<sup>1</sup>Second International Seminar on Cancer Prophylaxis and Prevention, Rome, November, 1968.

anaerobes. From the standpoint of the physics and chemistry of life this difference between normal and cancer cells is so great that one can scarcely picture a greater difference. Oxygen gas, the donor of energy in plants and animals, is dethroned in the cancer cells and replaced by an energy yielding reaction of the lowest living forms, namely, a fermentation of glucose.

While this may be "a gross oversimplification," the importance of Warburg's basic idea is certainly worth pursuing as a possible avenue by which chronic stress can lead to degenerative diseases like cancer.

#### x. Childhood Autism

As previously mentioned in section D<sub>i</sub>, part III, Childhood Autism is characterized by an extremely low outward motility but with excessively high internal excitation. Thus this "disease" appears to be similar to the stasis condition described in sections C and D, part I, where behavior is trapped in a cul de sac of low motility, while the autonomic state remains high centrally. This extreme split of behavior and internal set makes for limited and "fixed" modes of emotional expression<sup>1</sup> which characterize these most unfortunate human beings.

The extreme nature of this split between autonomic and behavioral components may well be, as Tinbergen argues, a function of the early developmental age (birth or before) at which major unresolvable stresses have occurred.

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<sup>1</sup>As with Yakovlev, emotion is considered as the outward expression of internal visceral states in the sphere of somatic behavior.

The work of William Windle reported in his book, The Physiology of the Fetus (1971) is particularly disturbing in this regard: Monkey neonates, delivered by various routine hospital procedures, exhibit gross morphologic and histological brain defects due, he argues convincingly, to asphyxia neonatorium, as compared with spontaneous births. This may have its unfortunate parallel in humans, in whom, he argues, Apgar scores correlate inversely to the degree of hospital involvement; see Ch. 15, on mental retardation. Thus, the combined effects of anaesthetics, delivery position, entrapment, etc., may well have profound effects on an organism's potential reserve capacity well beyond the gross damage observed histologically.

Windle states in his introduction that:

To be born undamaged mentally as well as physically is the primary right of every human being. We should inquire from time to time whether all possible provisions are being made to protect this right. The medical scientist has an obligation to seek and evaluate factors that may affect health in utero and well-being after birth. As new knowledge of physiology becomes available, its application to clinical practice needs to be considered. Attention will be directed to some of the factors that can damage the brain, oftentimes quite subtly but permanently.

The effect of stress is, in this regard, certainly one of these obligations. The next sentence after the above quote reads, "First, however, a survey of the normal physiology of the fetal organ systems is in order." Unfortunately this cannot be done in the case of accumulated stress. To understand the mechanisms of stress accumulation and minimize its effects, particularly at crucial developmental periods, is a step towards insuring these primary

rights, spoken of by Windle. If this goal is aided by the efforts of this dissertation, then its many shortcomings and limitations are more than compensated for by its basic validity.

#### B. Pre-symptomatic (Accumulated Stress) Diagnoses

The approach of modern medicine is geared to the appearance of symptoms or debilitation and then--at least in the instance of the "stress diseases"--to the treatment of the pathologic expressions, along with advice to the patient to "relax," to "not worry," to "exercise," to "vacation..." In short, not to accumulate any more stress. But it is just the fact that they are no longer able to discharge or resolve stress sufficiently that underlies such patients' symptoms and pathologies. It is in this direction that the various unconventional systems discussed in section IIB appear to be most concerned. In particular, they view the detection and correction of these imbalances before they become symptomatic (certainly before they become chronic) as the primary focus. It is in this stage that the organism still has the reserve capacity, the resiliency and strength to begin to resolve, successively, these accumulations before they become debilitating. In addition, when chronic conditions are presented, these systems often treat the underlying imbalance independently of the specific symptoms.

This focus on "pre-symptomatic diagnosis" could be one of the most immediately viable aspects of these systems to be

incorporated into modern orthodox diagnostic procedure. (Certainly there can be little doubt that early diagnosis is often related to favorable prognosis.) The problem of diagnostic screening is becoming one of the most complex and alarming issues in medicine today, and radically different inroads certainly seem appropriate. The case of stress disease is painfully obvious. The cure rate of these conditions once they have become established is pathetically low. The cost of administering "care," for example, to the "mentally ill" is alarming financially but primarily in human suffering. Surely no one would argue against the benefits of preventive medicine, yet systematic approaches to the problem simply do not exist. Beyond the adages, "Early to bed, early to rise," "sensible nutrition," and "regular exercise," etc., there is, in Western medicine, no coherent picture of the ways in which an organism's capacity to respond to the "stress of life" is maintained, diminished, measured or treated.

It is the view of this dissertation that sufficient knowledge does exist, in the form of cybernetic analysis of physiologic function (both at the unit and systems level), to provide a basis for an integrative approach to human health--to its assessment and maintenance, as well as to its quantitative measurement. It cannot be overemphasized that this will (and must) involve a multiplicity of factors, from the molecular to social and environmental. This dissertation

deals only with the "tip of a titanic iceberg" of these factors. In the balance, the ideas, derivations, predictions, etc., derived here depend for their validation on the successful evolution of "integrative medicine."

Since these studies must ultimately, for their empirical validation, involve cross-sectional testing of large populations, the question of measurement is paramount. The mecholyl-noradrenaline test, discussed in section E, part I of this paper, has many practical as well as theoretical limitations. Notably, there is a lack of graded sensitivity to subtle autonomic shifts, and awkwardness in administering the test.

The pivotal issue in assessing accumulated stress is the definition of central integrative states on the basis of readily observable peripheral outputs. That this is, in principle, plausible, stems from the fact, discussed throughout this work, that the entire spectrum of central integrative processes is expressed, peripherally, by two opposing systems of output. These outputs in the "unstressed organism" operate in a mutually antagonistic mode, while as stress accumulates, this reciprocity begins to "break down."

This systems view of bipolarly organized adaptive stress behavior was found in several instances to be represented and predicted from the basic principles of Catastrophe theory, and it is expected that this approach would be an excellent one to future studies of the accumulation of stress and its behavioral expression. It should, in

principle, be possible to plot an individual's adaptive range in terms of these typographies, and correlate them with the appearance of eventual "breakdown" in disease, as well as to assess a particular course of treatment.

Perhaps one of the most promising tools in the area of pre-symptomatic diagnosis, based on the findings of this thesis, could be time analysis thermography (section II, B<sub>ii</sub>). This highly sophisticated technologic device, perhaps more than any other, is suited ideally, not only for recording sensitively and graphically a wide range of vasomotor responses over the entire body, but as an integrative bridge between systems-topology viewpoints and the observations and principles of the various "archaic" and holistic approaches presented in section B of part II.

One of the pervasive themes of the holistic approaches is their "energetic perspective." They view behavior as a rhythmic bipolar interplay. When this flow is unimpeded, "harmonious," efficient function will be evident, but when "blocked" or "imbalanced" a disturbance of function (disease) results.

The thermographic motion picture data taken by Frank (Section III B<sub>iii</sub>) offer a direct observation at a physiological level of these autonomically mediated energetic phenomena. From his data on Reichian vegetotherapy, one can discern clearly traveling wavelike patterns of vasomotor changes which are modified in their magnitude and speed and may even be reversed in segments where "muscular blocks"

occur. Further, as these blocks are "dissolved," the wave-like propagations continue, unimpeded, until they reach another, more distal or deeper "block" (and so on).

If it proves that these propagated waves of vasomotor tone can be related predictably to the neuromuscular patterns recorded by Dr. Hunt (section III, C), then not only can the relation between autonomic and somatic components in the charging and discharging process be measured, but the response to any given autonomic stress stimulus can be visualized on the Catastrophe surface. Thus, the specific stress configuration of any individual could, in principle, be determined topographically.

It may not be overenthusiastic to hope that this sort of methodology will open entirely new avenues in an integrative medicine. There is, however, a practical limitation in that both the telemetered computer emg and thermographs require highly specialized and expensive equipment, and to have use of both, in the same laboratory setting, may "take some doing." The actual diagnostic work, however, would eventually be done with the thermographic equipment alone (after the autonomic-somatic relations had been established). And since many hospitals already have computers (or the time shared use of them), the cost of setting up such a facility would not be prohibitive and might even pay for itself in a surprisingly brief period of time.

The cost of not having such a tool for research and medicine, in the opinion of this author, is intolerably

expensive. To quote Tinbergen again, at the risk of sermonizing: "It is stress in the widest sense, the inadequacy of our adjustability, that will become perhaps the most important disruptive influence in our society."

Part V, which follows, details and discusses the systems simulation used to derive the independent sympathetic and parasympathetic autonomic components plotted in figure XII (p. 66), and which allowed the various predictions of section D, part I to be tested in section E, part I.

Thus, part V, which provides the basis for the predictions from Catastrophe theory, of the Funkenstein hospitalized population data has already been summarized; and to allow for better continuity, this part can be skipped, for now, and read after part VI (the epilogue and conclusions).

PART V. THE SERVO ANALYSIS OF CARDIOVASCULAR DYNAMICSSection A. Cardiovascular Control

The cardiovascular (CV) system functions to provide, not only a constant blood pressure, but to regulate the metabolic preparedness for various extra-homeostatic purposes, in particular, in emergency and flight and fight. CV dynamics, therefore, are controlled by multiple information transformed into patterns of autonomic response. The simple regulator function of maintaining a constant pressure occurs mainly at the level of the medulla and pons by a combination of baro and chemo receptor afferents.<sup>1</sup> More generally, though, greater flexibility is insured by more central interaction of these as well as other inputs.

Recently control engineering techniques have been extremely useful in relating a system's "closed loop" behavior to the responses of its individual components (which can be measured independently and in relative isolation).<sup>2</sup> In a typical physical control system the "controlled process" (the output variable being measured) can be distinguished from a "feedback transducer," which provides afferent information to the "controlling system." The latter establishes a "set-point" with which the output of the system is compared. This difference provides an "error" signal which activates

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<sup>1</sup>See appendix vi.

<sup>2</sup>E.g., Korner (1971).

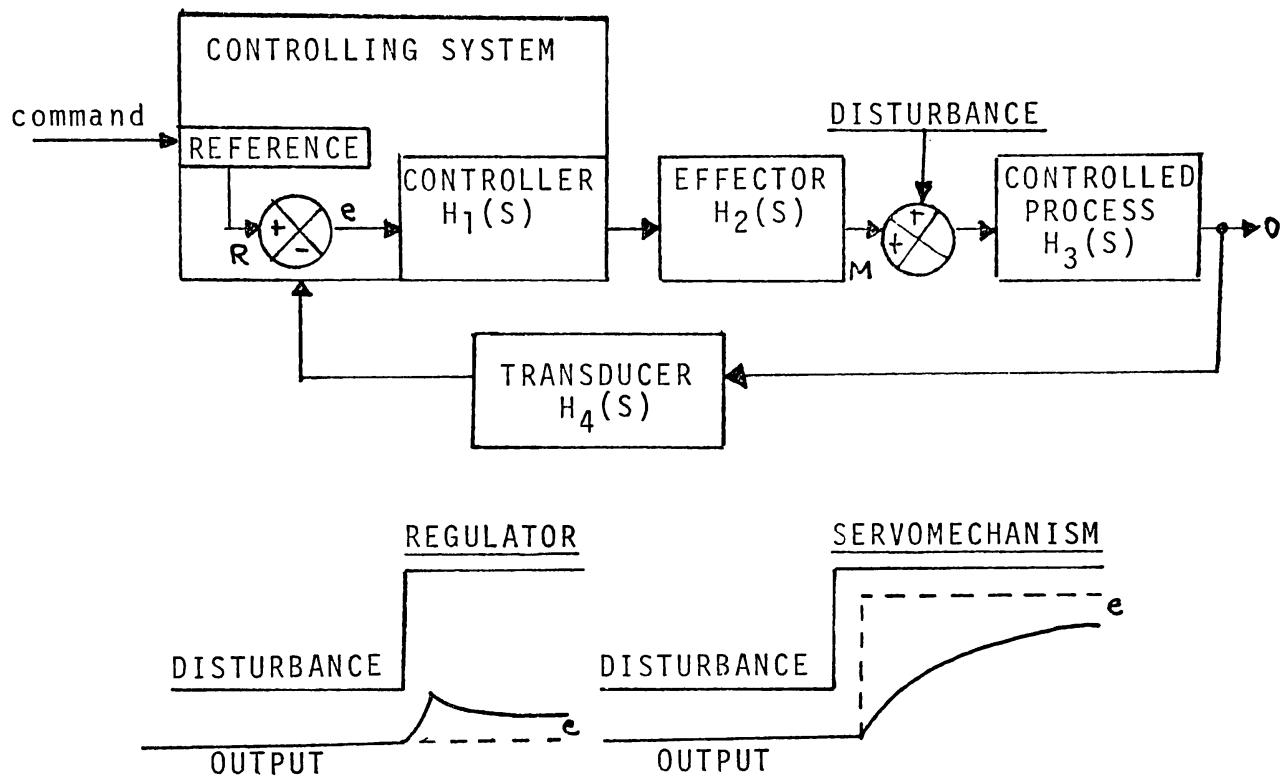
the effector, influencing again the controlled process. The set point is modified usually by an external independent "command system," but inputs may also be provided by the same elements which provide feedback information for the controlling system.

The basic schema of a negative feedback control system is shown in figure I. The output variable  $O$ , of the controlled process, is referenced with  $R$  and the difference function  $e$ ;  $(R-O)$  determines the magnitude of the effector output  $M$ . The transfer functions of the various blocks are  $H_i(S)$ .

The neural circulatory control system can be put in this standard form, as shown in figure II. The output variable arterial blood pressure is controlled by phased movement and tone of cardiac and vascular muscles, respectively. This is accomplished both through a number of local and humoral mechanisms (Johnson, 1964) as well as globally by the sympathetic (heart rate, stroke volume, and vasoconstriction) and parasympathetic (heart rate) branches of the ANS. The system operates at a particular setpoint of arterial pressure and excursions from this value and/or changes in blood chemistry evoke compensatory changes in the autonomic activity (Astron, 1967).

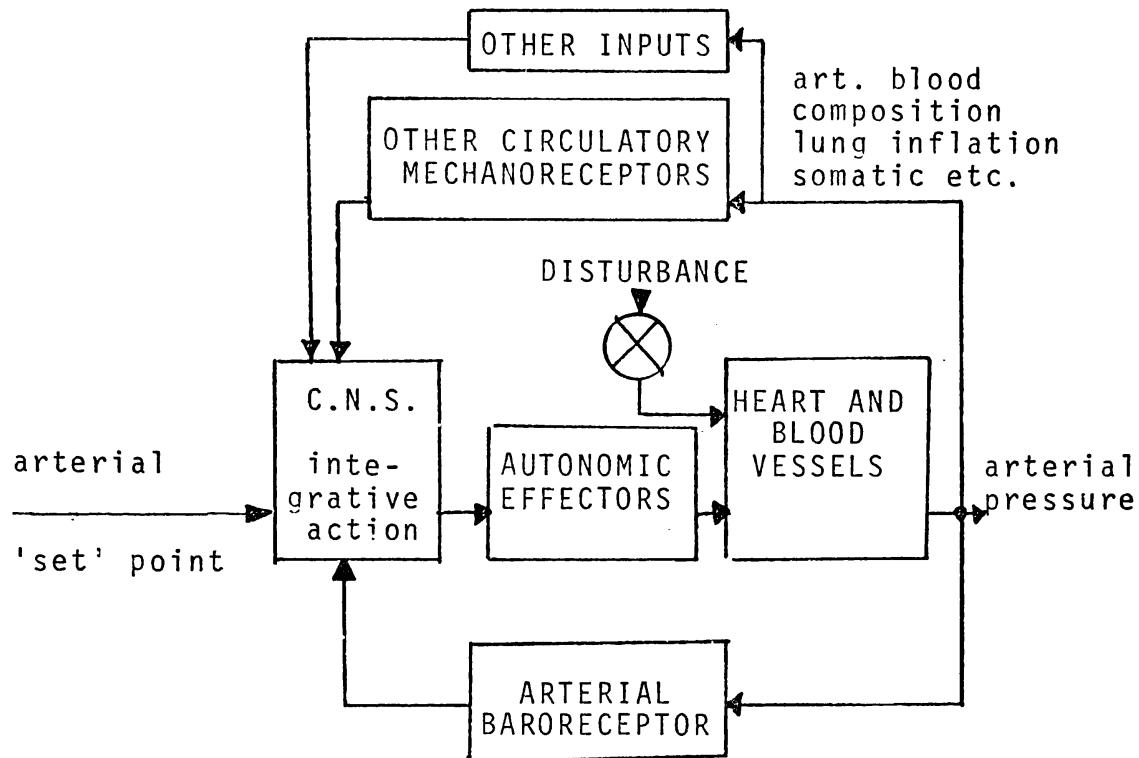
The afferent modalities which transmit information, centrally, during any particular stress depend, of course, upon the specific nature of the stimulus, and are often complex and interrelated. It is the generalized effect of accumulated stress upon the transient response of the

FIGURE I



From Korner (1971).

FIGURE II



Neural circulatory control system, where changes in circulatory state are signaled as changes in intravascular pressures through arterial and other circulatory mechanoreceptors. Other inputs provide collateral information about various body systems. Set point for arterial pressure is the level about which there is reversal in autonomic activity during reciprocal changes in arterial baroreceptor input. Set point is variable due to central effects mediated through other inputs. Modified from Korner (1971).

cardiovascular system (to a single specific variable, changes in blood pressure) that is of interest in the model.

The compensatory response to the drugs used by Funkenstein varies very little in a normal population and is in itself not a stress stimulus. The response can be accounted for solely by the baro receptor regulation of constant blood pressure mediated at the level of the brain stem medulla. Yet the same stimulus, when applied to the hospitalized population, evokes one of seven discernable responses; and the reason for this, we assume, is that stress has been accumulated within the CNS so as to alter the basic medullary response. In systems terms the arterial setpoint, as well as various transfer functions and gains, could be altered, accounting for the Funkenstein groups.

As Korner (1971) points out, until quite recently the function of these higher effects has been considered to be mainly related to specific specialized tasks such as thermo regulation, the autonomic concomitants of exercise, and emotional as well as conditioned autonomic responses. It is now unquestionable, he states, that "these same suprabulbar mechanisms are of the utmost importance in integrative reflex cardiovascular control," and he cites Adams et al. and Korner et al. (1969), but adds that "very little is at present known about central nervous integration" (of cardiorespiratory control).

In studying asphyxia, a prototypic stress stimulus, Uther et al. (1970) summarize the influences upon effector

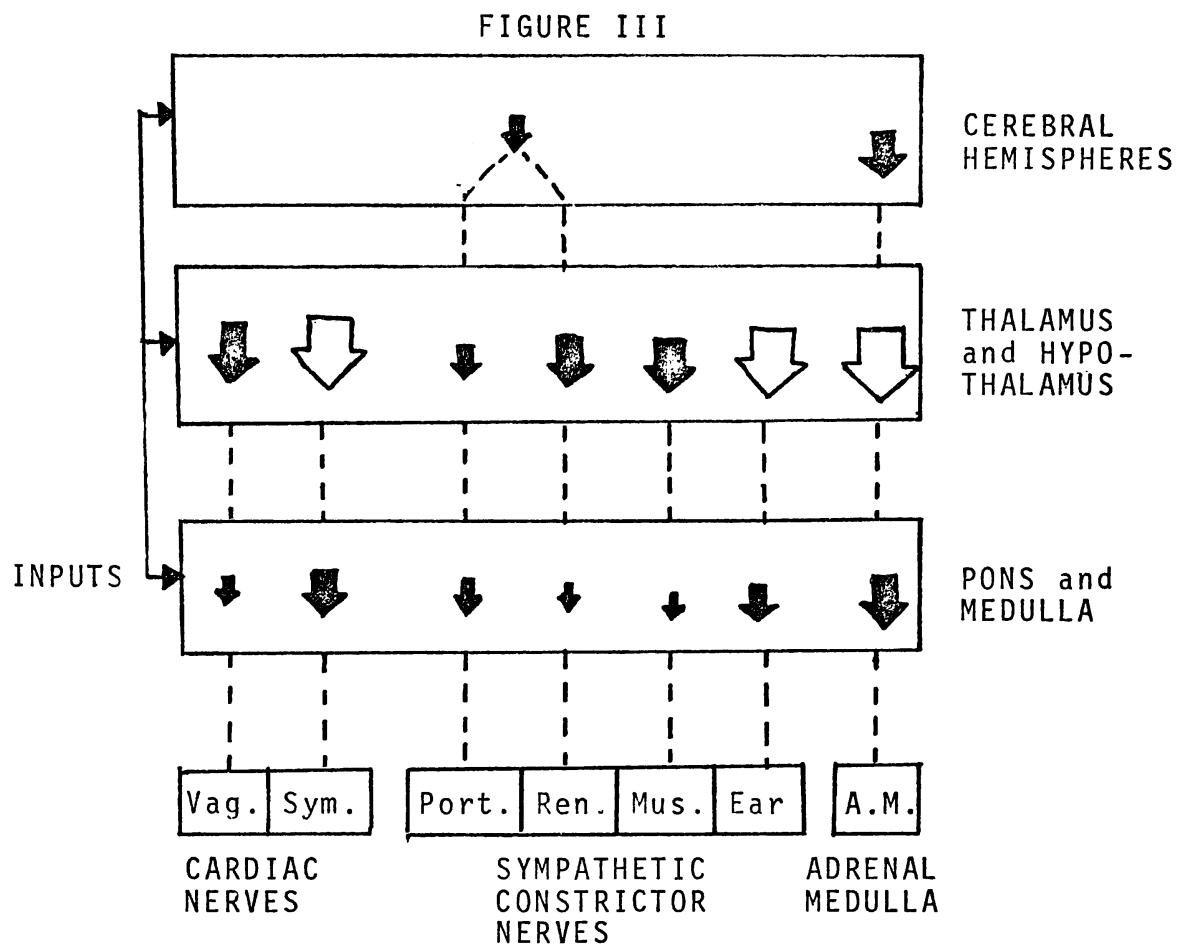
nerves and organs of brain stem and higher pathways in rabbits. This is shown in figure III, where the magnitude of effect is represented by the size of the arrow, excitation by solid arrows and inhibition by open arrows. It is apparent from this graphic portrayal that diencephalic and cerebral mechanisms can have an even greater influence upon cardiovascular and adrenal medullary control than the so-called primary brain stem reflexes. This, along with his own extensive work on (CV) control, prompts Korner, in his 1971 review, to say that "the suprabulbar centers can be regarded as an interneuronal pathway for the central resetting of the blood pressure control system.<sup>1</sup>

The way, then, is paved for the control systems analysis of parameter changes in the various CV units. The basic elements of CV control are then shown in figure IV.<sup>2</sup>

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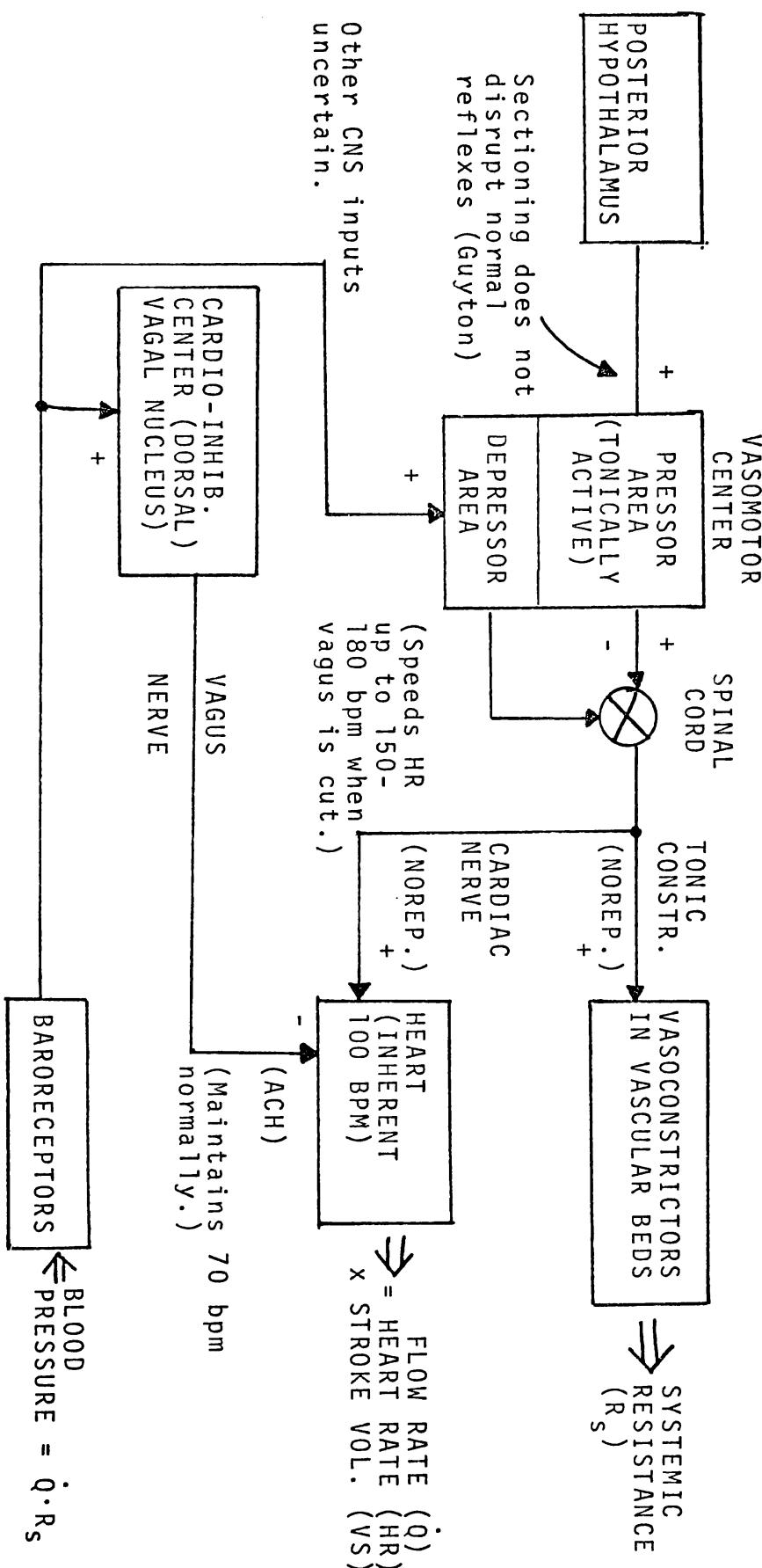
<sup>1</sup>Korner, citing Ulmer's data that gain can change independently of setpoint, finds further than alterations in neuronal excitability in a particular effector pool and changes in its size can account for changes in the setpoint. Shifts in gain, he finds, occur as a result of "facilitative and occlusive convergence onto a certain fraction of motor-neurons common to two or more inputs or on very large changes in excitability of most of the neurons in the pool." In addition, Korner's work also provides good evidence that these mechanisms operate in physiological conditions.

<sup>2</sup>This flow chart, then, constitutes the basic elements of the model. The vasomotor center is constituted by two flow boxes representing the pressor area (which is tonically active) and the depressor one. The outputs of these summate at the level of the spinal cord and effect a tonic constriction in the vascular beds (an effect which is enhanced by norepinephrine secretion). The cardiac nerve from the pressor area can speed the heart up to between 150 and 180 beats per minute when the vagus nerve is cut. Thus, the vasomotor centers have their effect on blood pressure by (1) increasing



From Uther et al (1970).

FIGURE IV

Basic Anatomical Model

the systemic resistance ( $R_s$ ) and the flow rate (Q), which is equal to the product of the heart rate times the stroke volume. The vagal output from the cardioinhibitory center (in the dorsovagal nucleus) affects flow rate by modulating heart rate exclusively (the sympathetic cardiac nerves affect both heart rate and stroke volume).

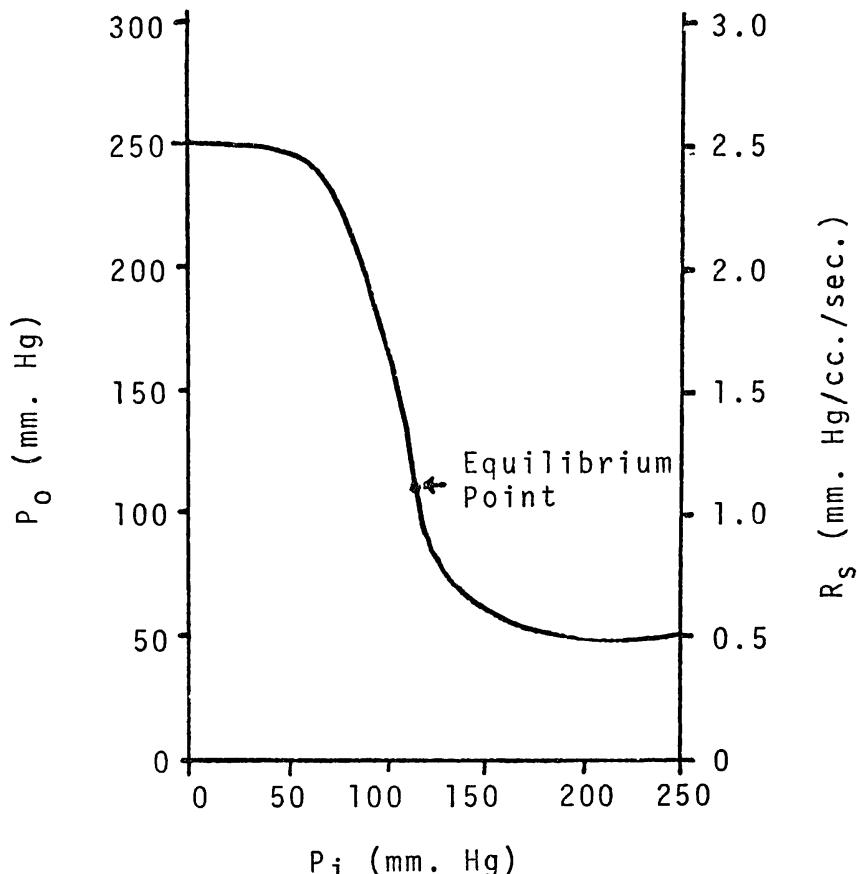
The blood pressure, then, which is a product of the flow rate (Q) times the reciprocal of systemic resistance ( $1/R_s$ ) is sensed by the baroreceptors whose afferents synapse both on the depressor area and upon the cardioinhibitory centers, reflexively maintaining constant pressure.

### Cardiovascular Systems Simulation

Simulation, by the systems approach, of cardiovascular dynamics has been carried out successfully by McAdam (1961)<sup>1</sup> and has focused extensively upon the mechanical as well as neural aspects. A "black box" approach was taken whereby the "error correcting behavior" of a first order regulator system, with open loop gain characteristics experimentally measured, was analyzed. This was accomplished experimentally by opening both baroceptor loops and arbitrarily introducing pressures into the isolated sinuses and recording the resultant changes in systemic pressure. In this way the open loop response was obtained. Steady state values of systemic arterial pressure ( $P_o$ ) are plotted as a function of a constant input pressure into the isolated  $P_o$ . The peripheral resistance  $R_s$  is also plotted vs.  $P_i$ .  $R_s$  is taken to be equal to systemic pressure  $P$  divided by flow  $Q$ .<sup>2</sup> (See top figure on next page.)

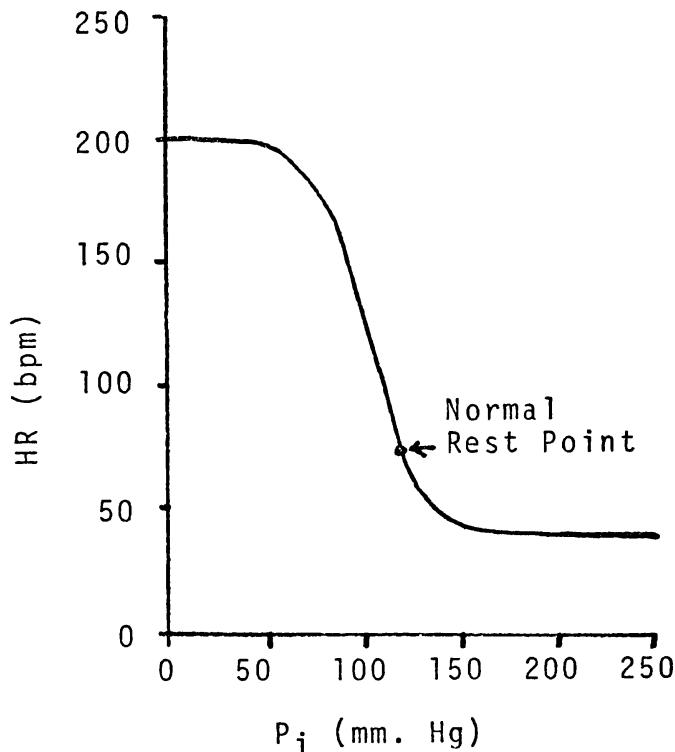
Several factors are immediately apparent from the shape of the curve. The negative slope implies that the system, in the steady state, is a negative feedback one. Secondly, the equilibrium pressure would be expected to occur when  $P_i = P_o$ . This value is at 113 mm Hg which is not far from the intact value of the experimental animals (cats).

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1. See Milhorn (1966).
  2. This assumes the venous pressure much less than arterial so that  $Q = (P_a - P_{ven}) / R_s \approx P/R$ . Also  $Q$  is shown to be relatively independent of heart rate.



Steady-state open-loop relationship between sinus pressure  $P_i$  and systemic arterial pressure  $P_o$ .  
(Redrawn from McAdam.)

Also a tonic inhibition from the baroceptors is indicated since for  $P_i=0$  (or when baroceptor nerves are cut) the system is in a hypertensive state (250 mm Hg). The open loop s.s. gain for cardiac frequency (HR) vs.  $P_i$  is likewise plotted.



Steady-state open-loop relationship between systemic arterial pressure and cardiac frequency. (Redrawn from McAdam.)

In this simulation the neuro humoral factors which control system pressure  $P$  and HR are lumped together and no attempt is made to differentiate between sympathetic or parasympathetic components. But it is just the isolation and identification of these components which is crucial to assessing an organism's history of previous stress and its capacity to tolerate and resolve new stress situations (part I).

In the following simulation the basic system differential equations are taken from Milhorn (p. 237; eqs. 18-20 and 18-21).

$$T_{R_s} \frac{dR_s}{dt} + R_s = R_s (P...) \quad (1)$$

$$T_{HR} \frac{dHR}{dt} + HR = HR(P) - k_f \frac{dP}{dt} \quad (2)$$

where  $R_s$  = peripheral systemic resistance

$P$  = blood pressure

$HR$  = heart rate

$T$  = time constant for  $R_s + HR$

$R_s, HR$

For the steady state solution, equation (2) reduces to:

$$HR \frac{dHR}{dt} = HR(P)$$

and equation (1) remains the same.

Also from Milhorn (18-22):

$$\frac{dP}{dt} = \frac{1}{C} [\dot{Q} \cdot \frac{1}{R_s} (P - P_{venous})]$$

$$\approx \frac{1}{C} [\dot{Q} \cdot \frac{1}{R_s} \cdot P]$$

where  $Q$  is flow and  $C$ , arterial capacitance

$$C_a \approx -1$$

$$\dot{Q} \approx 100 \text{ HR}$$

Therefore:

$$\frac{dP}{dt} = 100 \text{ HR} - \frac{P}{R_s} \quad (3)$$

For the steady state:

$$P = 100 \text{ HR} (R_s)$$

McAdam (Milhorn) considered systems delays to reside mechanically in such factors as muscle compliance, etc., but

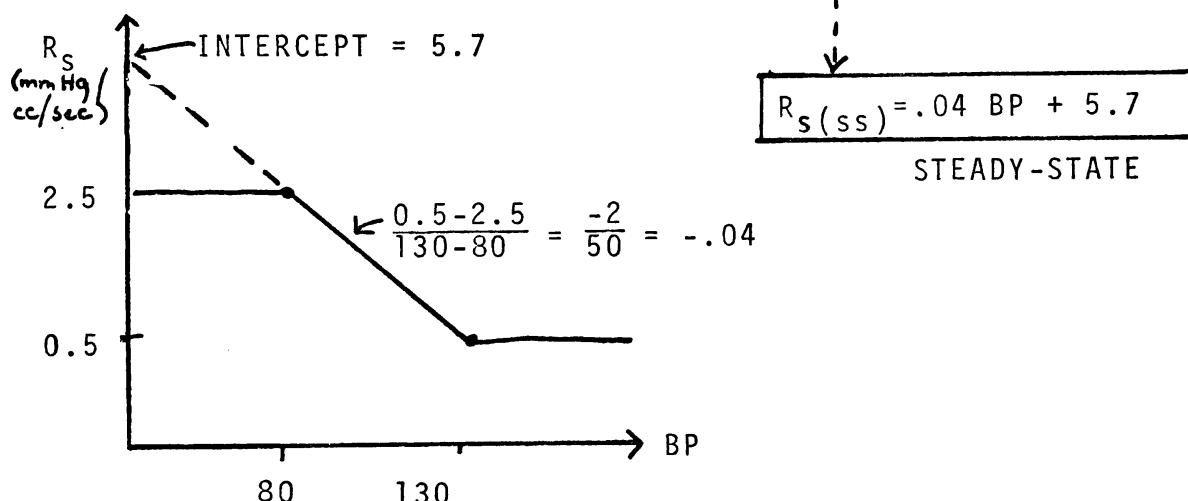
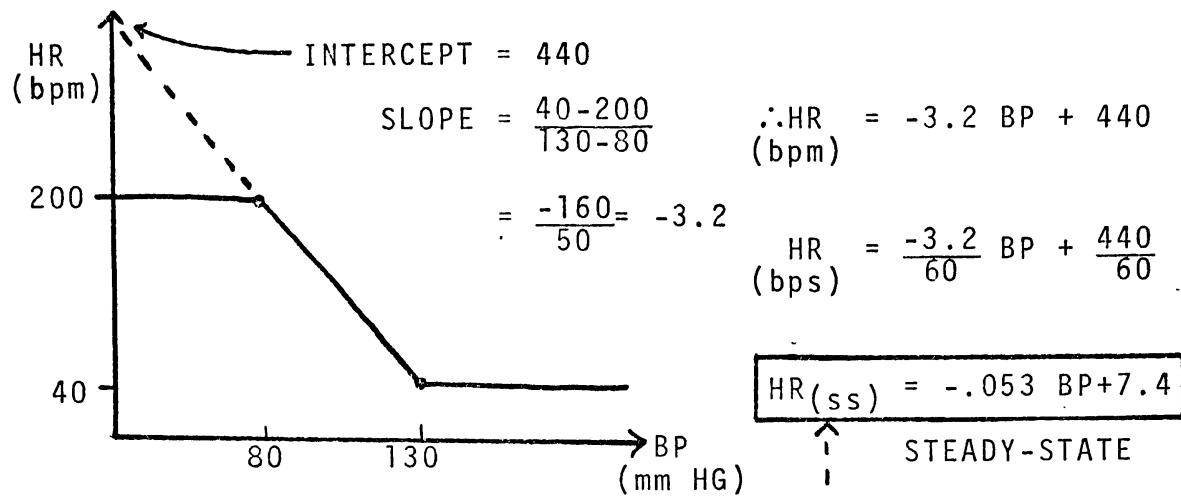
more recent work (Korner, 1971) indicates a lag of 10-20 sec. in the vagus. In this model it will be assumed that the mechanical components follow instantaneously and that the delays reside in neuro-humoral processes. Actually, the overall effect would be the same.

Thus the value of  $T_{RS}$  is assigned the value of 1/3 lag time, i.e., approximately the time taken to level off:

$$T_{RS} = 5 \text{ sec.}$$

$$T_{HR} = 1 \text{ sec.}$$

The key now is to separate the sympathetic and parasympathetic components for the purposes of digital simulation on the PDP-7 King sim program the steady state curves (McAdam) are replaced with a piecewise linear approximation:



From this graph the equation relating HR and  $R_s$  to S.S. pressure is:

$$(HR)_{ss} = -.053 P + 7.6$$

The intrinsic HR is 100 bpm = 1.67 bps.

Thus the change in P due to both sympathetic and vagal control is:

$$(HR)_{ss} = -.053 P - 7.4 - 1.67$$

$$(HR)_{ss} = -.053 P + 5.7$$

Now from the linearized resistance graph:

$$R_s = -.04 P \pm 5.7$$

which is due entirely to the sympathetic pressor/depressor balance.<sup>1</sup> Thus, for a first approximation, the sympathetic depressor gain is equal to -.04 and the vagal gain:

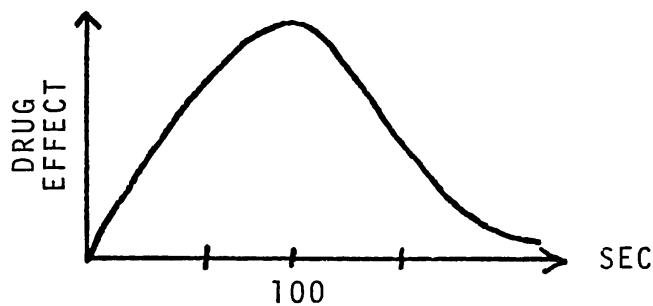
$$G_{vag} = G_{total} - G_{symp}$$

$$G_{vag} = -.053 - (-.04) = -.013^2$$

The constant 5.7 represents tonic activity of the pressor area. Additional extra-medullary sympathetic inputs will be added or subtracted from this.

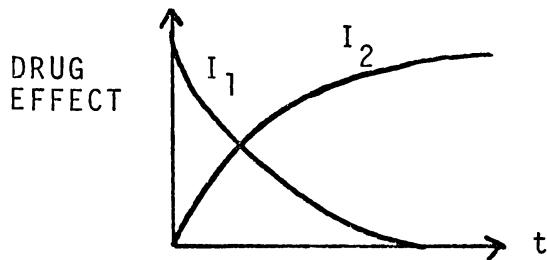
One final consideration and the initial model can be constructed. The drug (i.e. Mecholyl and Noradrenaline) effect (DR) is represented by summation at the  $R_s$  and HR junction points. The system parameters are shown then in figure V.

The initial diffusion effect of the injection (I) is much slower than the system response:



1. Peripheral vasoconstriction is due solely to the sympathetic tone.
2. The depressor gain, after initial programming, was adjusted to -.0375, which gave a basal HR of 69 bpm with the vagus intact and 137 with the vagus cut.

This is the sum of two exponentials:



$$T_1 \frac{dI_1}{dt} = -I_1$$

$$T_2 \frac{dDR}{dt} + DR = I_1$$

where  $I$  is the drug dose injected.

Both  $T_1$  and  $T_2$  are arbitrarily chosen to be = 50 sec, causing the blood pressure to respond properly.

$$\boxed{\frac{dI_1}{dt} = -\frac{I_1}{50} = -.02 I_1}$$

$$\frac{dDR}{dt} = \frac{1}{T_2} [I_1 - DR]$$

$$\boxed{\frac{dDR}{dt} = .02 I_1 - .02 DR}$$

### System Equations

#### 1) Sympathetic

$$\begin{aligned} s.s.: S_{ss} &= \text{Pressor} + \text{ACES} - D \\ &= 5.7 + \text{ACES} - .04 \text{ BP} \end{aligned}$$

The dynamic response is:

$T_s \frac{dS}{dt} + S = S_{ss}$  , where  $T_s = 5$  sec.

$$\frac{dS}{dt} = \frac{1}{T_s} (S_{ss} - S)$$

$$\frac{dS}{dt} = \frac{1}{5} [5.7 + ACES - .04 BP - S]$$

$$\therefore \frac{dS}{dt} = 1.14 + 0.2 ACES - .008 BP - .25$$

## 2) Peripheral Resistance

$$R_s = S + .3 DR$$

In S.S.; no drug, no ACES:

$$R_s = S_{ss} = 5.7 - .04 BP$$

## 3) Vagal

$T_v \frac{dV}{dt} + V = .013 BP$  , where  $T_v = 1$  sec.

$$\therefore \frac{dV}{dt} = \frac{1}{T_v} [.013 BP - V]$$

$$\frac{dV}{dt} = .013 BP - V$$

## 4) Heart Rate

$$HR = s - V + .3 DR + 1.67$$

In S.S., no drug; no ACES input:

$$\begin{aligned}
 \text{HR}_{ss} &= S_{ss} - V_{ss} + 1.67 \\
 &= (5.7 - .04 \text{ BP}) - (.013 \text{ BP}) + 1.67 \\
 \text{HR}_{ss} &= 7.37 - .053 \text{ BP}
 \end{aligned}$$

5) Blood pressure

$$\frac{d\text{BP}}{dt} = 100 \text{ HR} - \frac{\text{BP}}{R_s}$$

The encircled equations represent the total system equation.

Figure V is the systems representation of the physio-anatomic pathways shown in figure IV.

Table I is the basic computer program, while table II is a summary of the simulated data. It is the normalized data which are plotted on figure XII.

FIGURE V

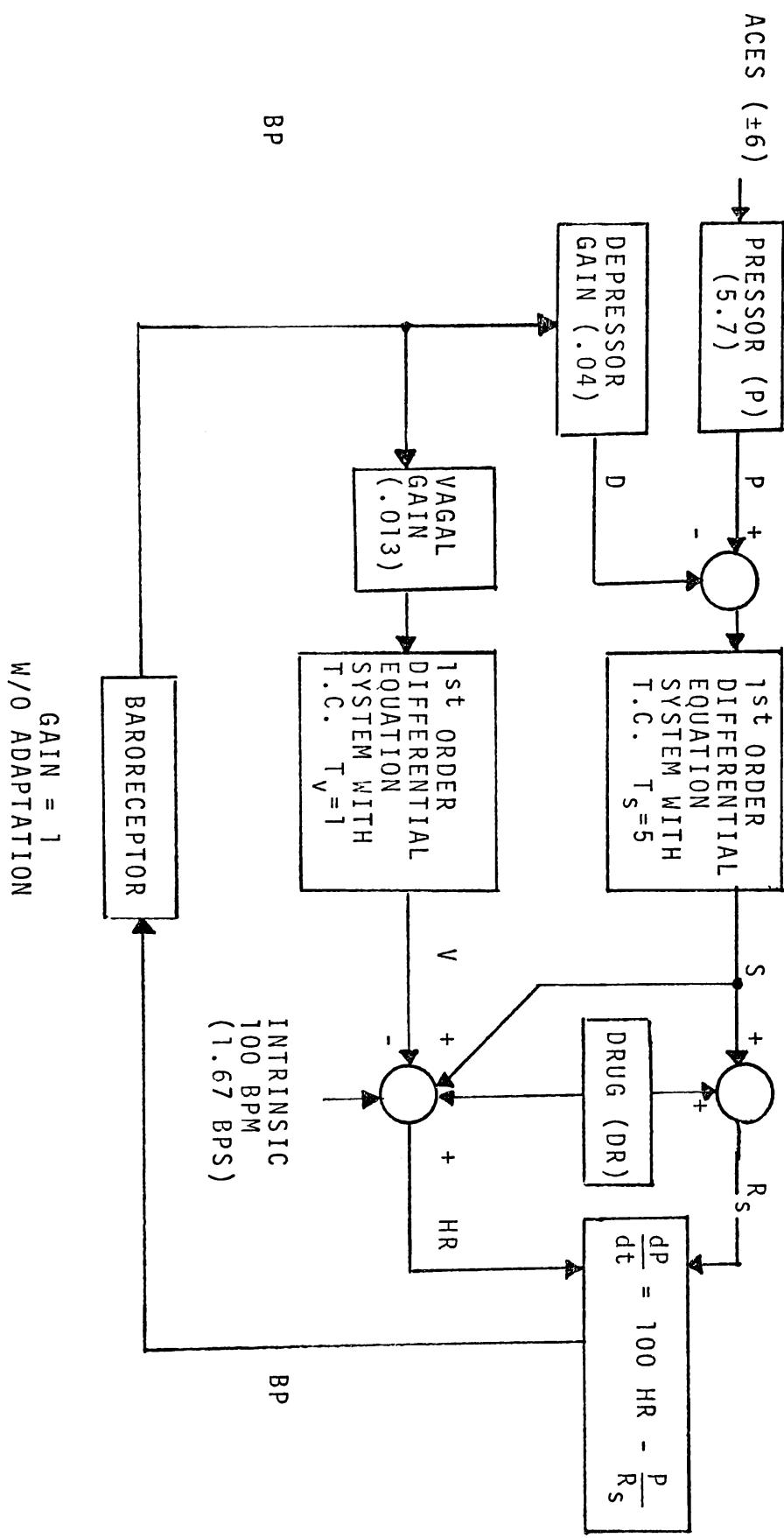


Table I. Basic Program

```

(S)          DX1 = -.2X1 - .0075 W7 + (1.14) + .02X4
(V)          DX2 = -X2 + .013 W7
(BP)         DX3 = 100 W4 - FDIV (W6gW1)
(ACES)       DX4 = (0)
              DX5 = -.02X5 + .02X6
(DRUG)       DX6 = -.02X6
(RS)LIM W1 = FLIM (X15, 2.5, 0.5)
(V)LIM     W2 = FLIM (X2, 5, 0)
(HR)         W3 = (1.67) + W8 - W2 + .3X5
(HR)LIM   W4 = FLIM (W3, 3.33, 0.67)
              W5 = 60W4
(BP)LIM   W6 = FLIM (X3, 250, 50)
              W7 = W6
(S)LIM    W8 = FLIM (X1, 8, 0)
              W15 = W8 + .3X5

```

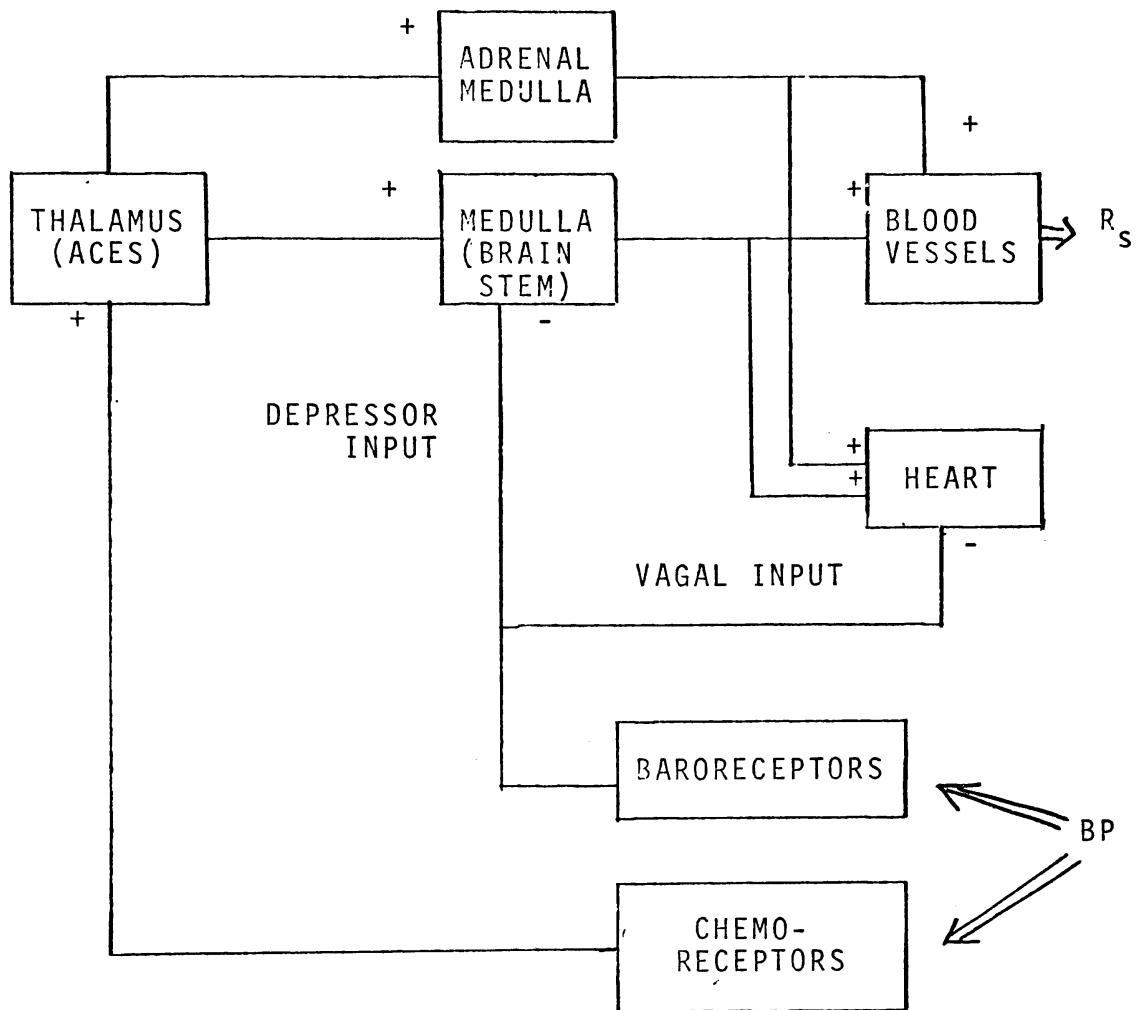
Table II: Summary of Simulated Data

Group	I	II	III	IV	V	VI	VII
Pressor level	-0.6	0	+0.2	+0.2	1.44	1.34	1.6
Depressor gain (dg)	1.4	1.1	1.1	1.1	1.6	1.5	1.22
Vagal gain (vg)	1.0	0.8	1.0	1.0	2.2	1.0	0.8
Parasympathetic spillover	Reversal	-	-	-	✓	✓	✓
Adrenal discharge	-	-	-	-	Tonic at 3.3	Tonic at 3.9	No tonic
Sympathetic spillover	-	-	-	to increasing ACES	-	-	-

Normalized Simulated Data

Group	Symp.	Parasymp.	ΔS	ΔPS	Clinical data % improvement
II, III	0	0	-	-	Control
VII	1.4	0.2	1.4	1.0	100%
VI	5.33	5.0	3.90	4.0	87%
V	6.0	7.0	0.7	2.0	0%
I	6.6	9.0	0.6	0.6	0%

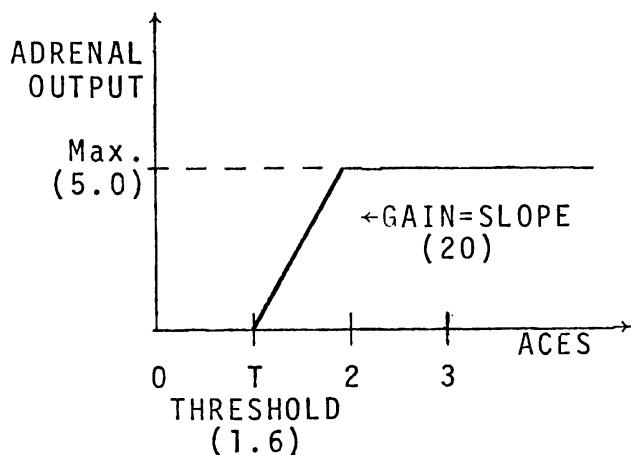
By including the chemoreceptor input to the thalamus, as shown by Korner (in Neural Cardiovascular Control, 1971, figure 16), and the adrenocortical loop the system is extended as follows:



Note, the higher ACES levels activate the adrenals, further stimulating blood vessels and heart. High chemo-receptor output, due to low oxygen levels, increases the ACES, and can thereby stimulate adrenal activity as well.

### Adrenomedullary input-output function

As previously, for H.R., B.P.,  $R_s$ , a steady state gain and a dynamic time constant are required. In addition, an input threshold (i.e., adrenal discharge occurs only above a certain ACES level) as well as a maximum output level of the hormone:



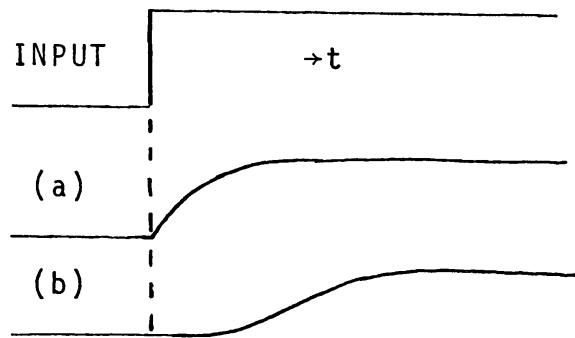
The threshold, gain, and max. levels are all unknown, and are chosen by trial and error. The value (5) for adrenal output is comparable to injecting 5 units of epinephrine I.V. continuously. The equation for this curve is

$$\boxed{ADR_{ss} = 20 \text{ ACES} - 32}$$

with  $ADR_{min} = 0$  and  $ADR_{max} = 5$ .

The equations are based on Gellhorn & Redgate (1958) showing a delay and slow rise as in their figure 2. To simulate this, two successive first order equations are used. A single first order equation gives an exponentially rising

rising curve, (a) below. Two successive first order equations give an inflected curve (b), which is similar to figure 2 cited.



The equations then are:

$$100 \frac{dX}{dt} + X = \text{ADR}_{ss}$$

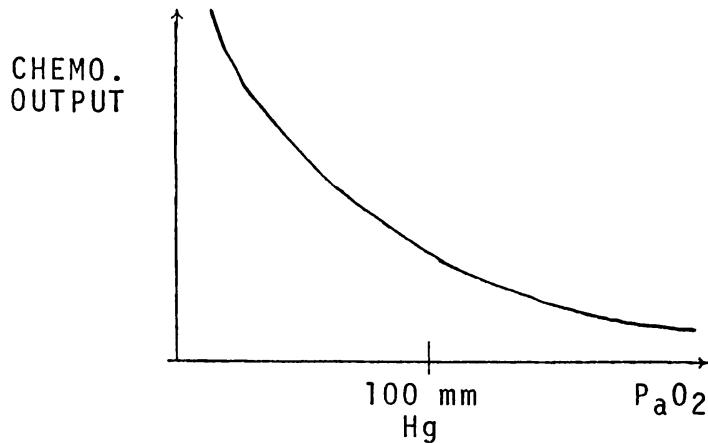
$$30 \frac{d(\text{ADR})}{dt} + \text{ADR} = X$$

$$\text{ADR}_{ss} = 20 \text{ ACES} - 32$$

The inflection is important because it introduces a delay in the onset of action of the adrenal hormone, consistent with the time necessary for release of the hormone and subsequent movement within the blood stream to its sites of action.

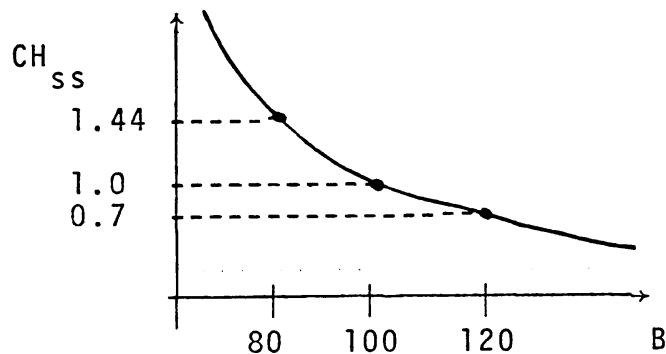
#### Chemoreceptor input-output functions

The basic shape of the steady state curve comes from Korner (1971), figure 5:

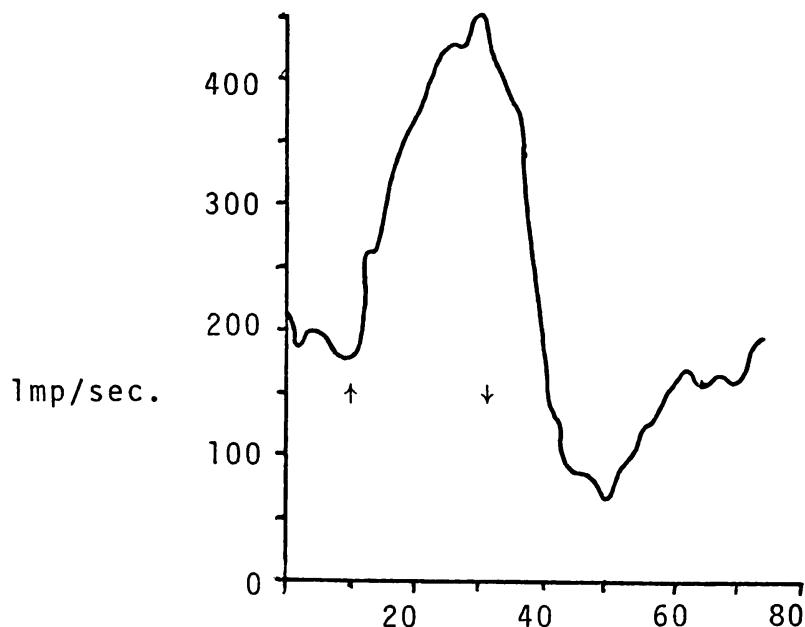


100 mm. Hg is the normal partial pressure of  $O_2$  in the blood. It follows that if blood pressure falls, so will the amount of  $O_2$  getting to the chemoreceptors, and in roughly the same proportion. Using this basic shape, and after some trial and error, the following was derived:

$$CH_{ss} = \left( \frac{100}{BP} \right)^2$$



The time constant of 30-50 sec. is from Eyzaguirre & Lewin (1961).



Carotid-nerve impulses during carotid occlusion. Recording from whole carotid nerve. At 1st (upward) arrow, external carotid artery occluded; at 2nd (downward) arrow, clip removed. Note increase in chemoreceptor discharges and depression after removing clip. (From C. Eyzaguirre and J. Lewin, J. Physiol. 159 (1961)).

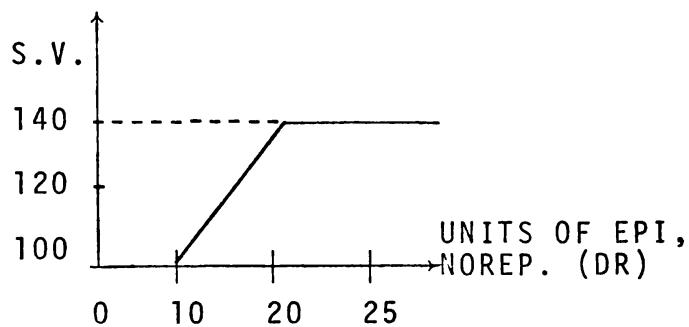
Thus the steady state differential equation for the chemoreceptor:

$$50 \frac{dCH}{dt} + CH = CH_{ss} = \frac{100^2}{BP}$$

The nonlinear shape of this curve is very important because it produces differences in the way the system responds to increases vs. decreases in blood pressure. Note that a decrease in blood pressure results in a much greater change in chemoreceptor output than an increase in blood pressure by the same amount: 44% vs. 30%.

### Stroke volume (SV) adjustment

As an additional correction factor is also introduced because stroke volume is greatly affected by adrenaline and noradrenaline (Goodman & Gilman, 1964, p. 458), the sensitivities of  $R_s$  and HR to norepinephrine, mecholyl, and epinephrine are thus adjusted as follows:



$$SV = 2DR + 100$$

$$\frac{dBP}{dt} = SV \cdot HR - \frac{BP}{R_s}$$

### Section C. Discussion of Simulation

Figure XI, part I (pages 58-65, curves 1-7) shows both the autonomic response to the drugs (dotted lines) and the computer simulation (solid lines) generated by changing the three system parameters: (1) pressor tone (i.e., the tonic input to the medullary pressor area), (2) the depressor gain (DG), and (3) the cardio-inhibitory vagal gain (VG).

It was postulated (and shown on the Catastrophe topology) that the effect of a progressively increasing excitatory level of accumulation is initially a heightened sympathetic tone and then a "spillover" into the parasympathetic. In the model this sympathetic accumulation was simulated by increased pressor vasomotor tone, the spillover effect by increases in both the depressor and vagal gain.

The system curves were generated by varying the value of these three parameters until each of the seven experimental curves was matched. (See figure XI, section I, E.) This, by itself, would not appear to lend "strong" credibility to the uniqueness of the model. even though the results are strikingly close (figure XI). The computer simulation also predicts, explicitly, the heart rate and peripheral resistance response to blood pressure perturbations. To simply measure heart rate, in response to hypo- and hypertensive drugs, would be a useful test of the model. (See figure VI of this section.)

The cardiovascular model was derived independently of, and a priori to, the Funkenstein data and is based entirely upon fundamental well-known physiological data. Only the

effects of changing the three parameters, pressor level, vagal gain and depressor gain, due to supra-medullary influences, are added. There is, in fact, very little range in trade-off between the three parameters.<sup>1</sup> This is shown in figures VIIa, b, c (for baseline levels). Changing the pressor input affects the basal pressure (BBP) (figure VIIa), whereas the vagal gain (figure VIIb) has virtually no effect. Changes in vagal gain, on the other hand, affect the HR, whereas pressor and depressor gain do not (figure

<sup>1</sup>In summary,

- 1) Increasing pressor tone or decreasing Depressor Gain (DG) both increase the setpoint for BP, by increasing peripheral resistance (res), while heart rate (HR) is barely affected.
- 2) Changing the pressor level and DG in the opposite way decreases BP setpoint.
- 3) In contrast, changing vagal gain (VG) hardly affects BP set point, while it greatly affects HR and RES. Increasing VG decreases HR and vice versa.
- 4) Because the vagal and depressor feedback are both negative, increasing either gain will decrease the total BP excursion due to Norepinephrine or Mecholyl, as shown by going from group 2 to 3 (by simply increasing vagal gain).

	<u>BP</u>	<u>HR</u>	<u>RES</u>	(Responsivity) <u>DRUG EFFECT</u>
↑ Pressor	++	0	+	0
↓ Pressor	--	0	-	0
↑ DG	--	0	-	+
↓ DG	++	0	+	-
↑ VG	0	--	+	+
↓ VG	0	++	-	-

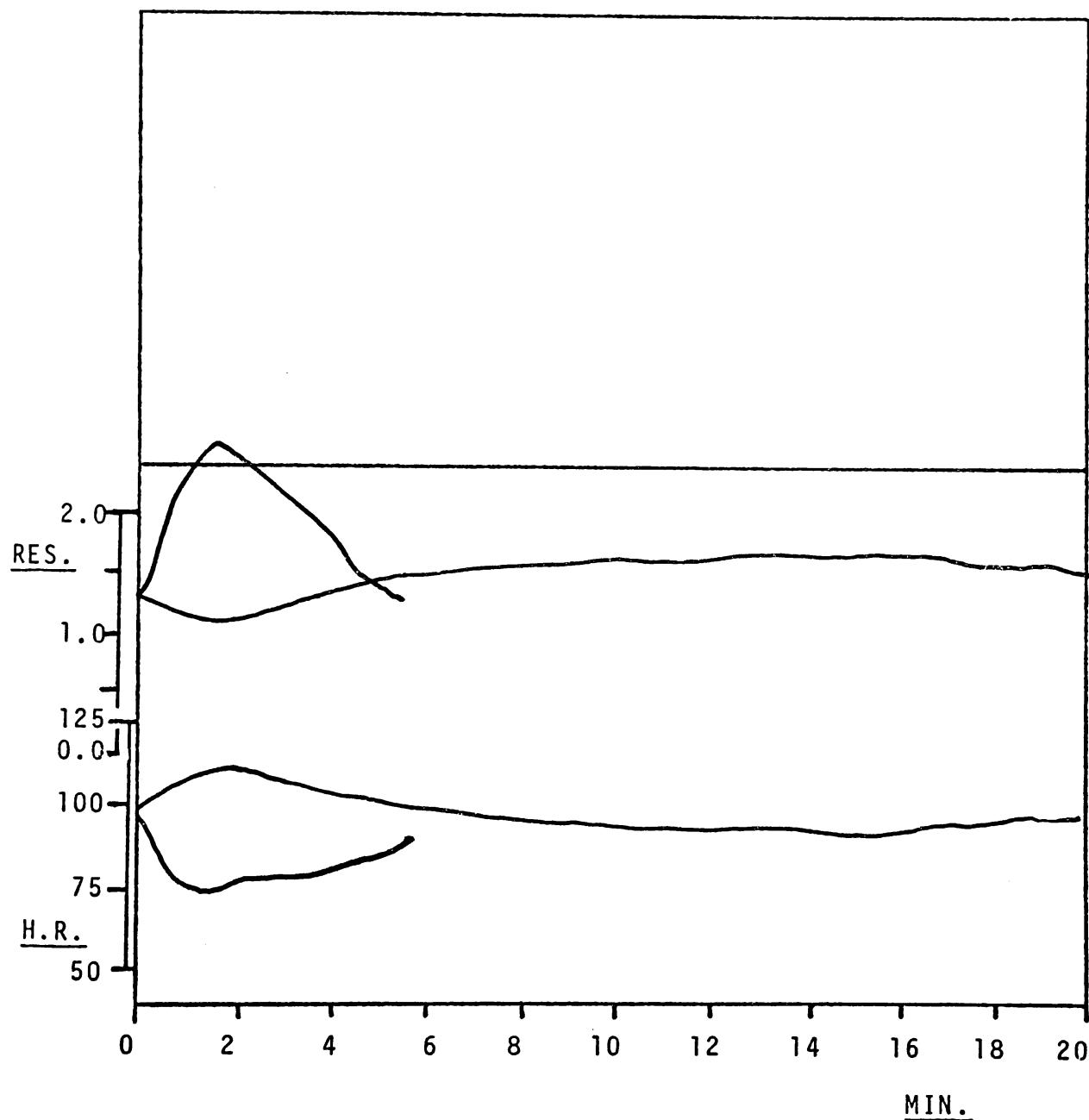
VIIc). Further, small increments in depressor gain result, not only in much larger BBP changes, but the dynamics are also different. This is illustrated in the series of figures VIIIa, b, IXa, b and Xa, b, which show the effect on the dynamics of the response to Norepinephrine (a) and Mecholyl (b) for changes in sympathetic input (VIII), vagal gain (IX) and depressor gain (X). From these curves it can be seen that the relative amplitudes of the blood pressure response curves can, in the case of Noradrenaline, only be separated by changing the vagal gain (figure IXa); and, for Mecholyl, by changing either pressor level (figure VIIb) or depressor gain (figure Xb). But from figure VIIc it is seen that increasing the depressor gain decreases the blood pressure setpoint while increasing it increases the mecholyl response amplitude (figure Xb).

So, while absolute uniqueness cannot be proven, it is strongly inferred that the data cannot at all be arbitrarily simulated.

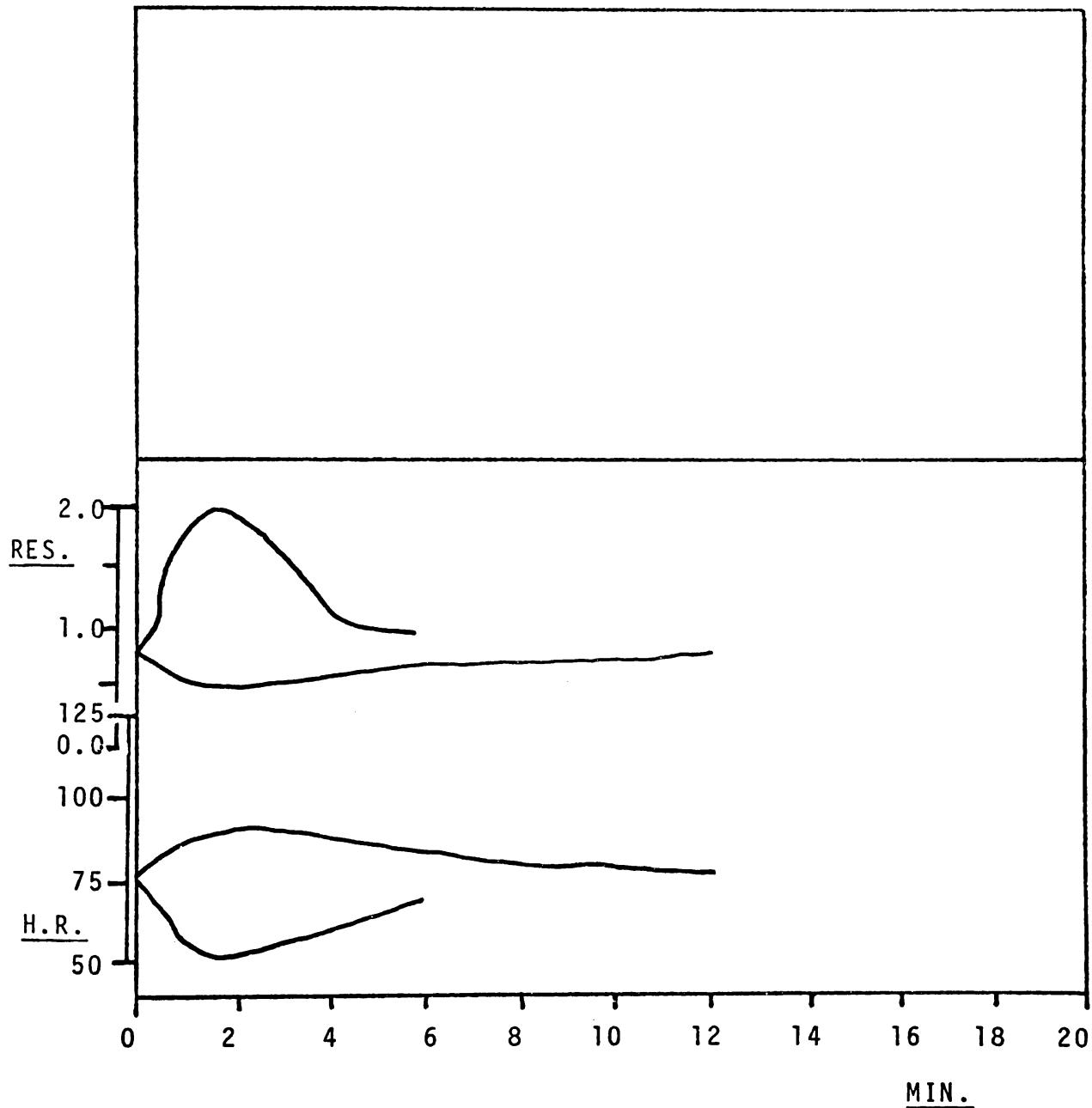
Figure VI, curves 1-7

Predicted response of heart rate (HR) and peripheral resistance (Res) to hyper- and hypotensive perturbations, in simulating the Funkenstein diagnostic categories.

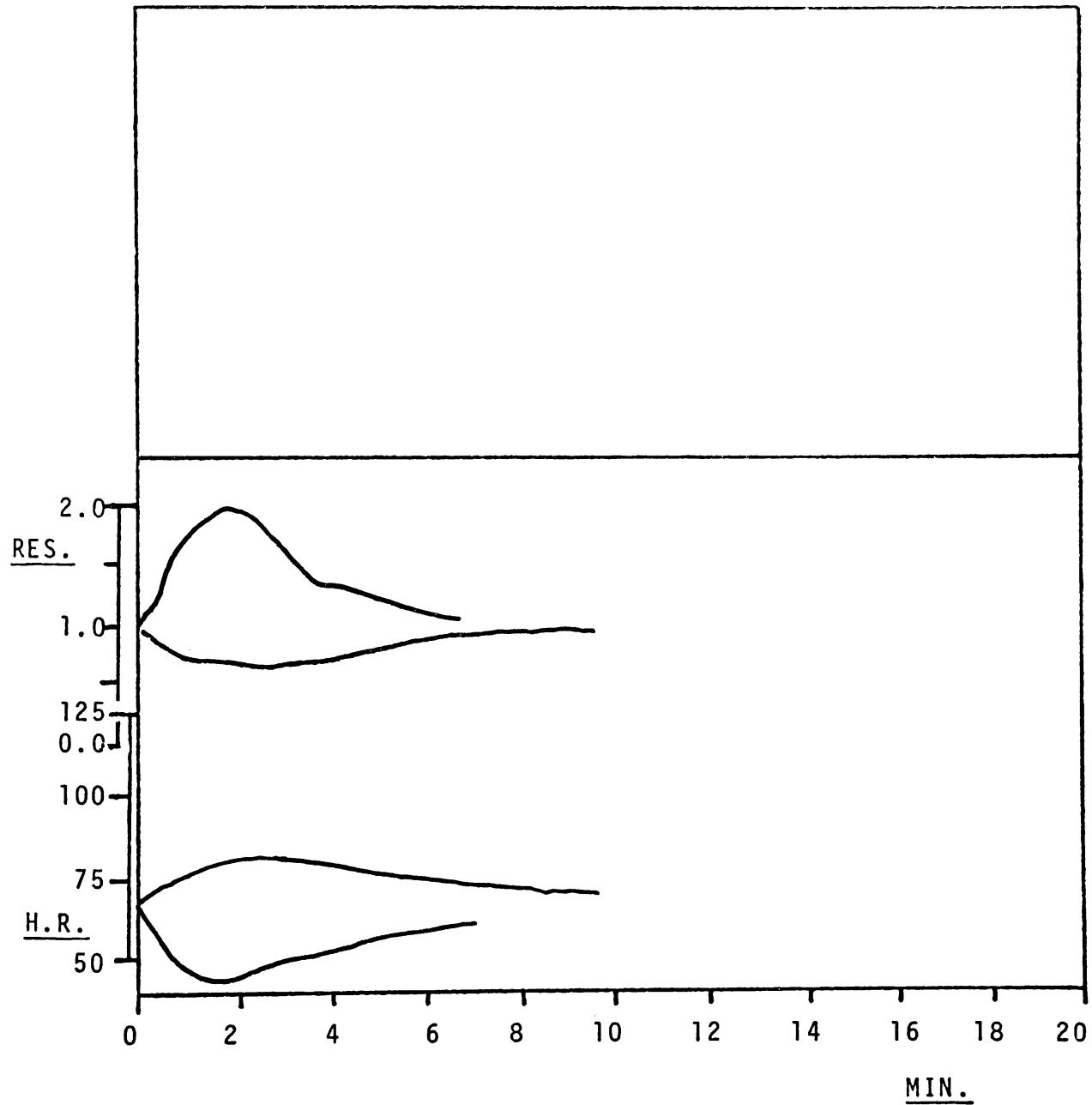
## GROUP 1



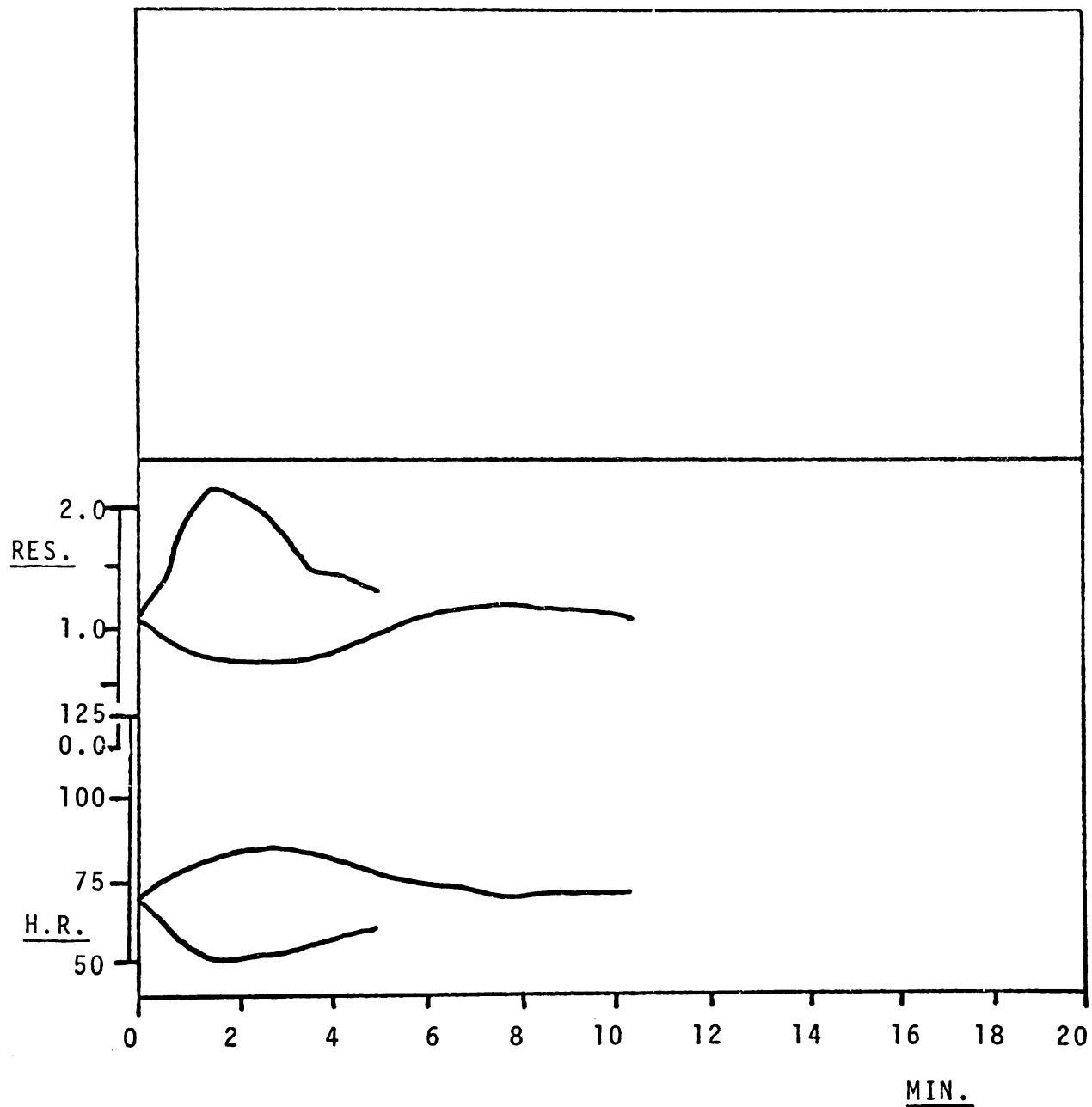
## GROUP 2



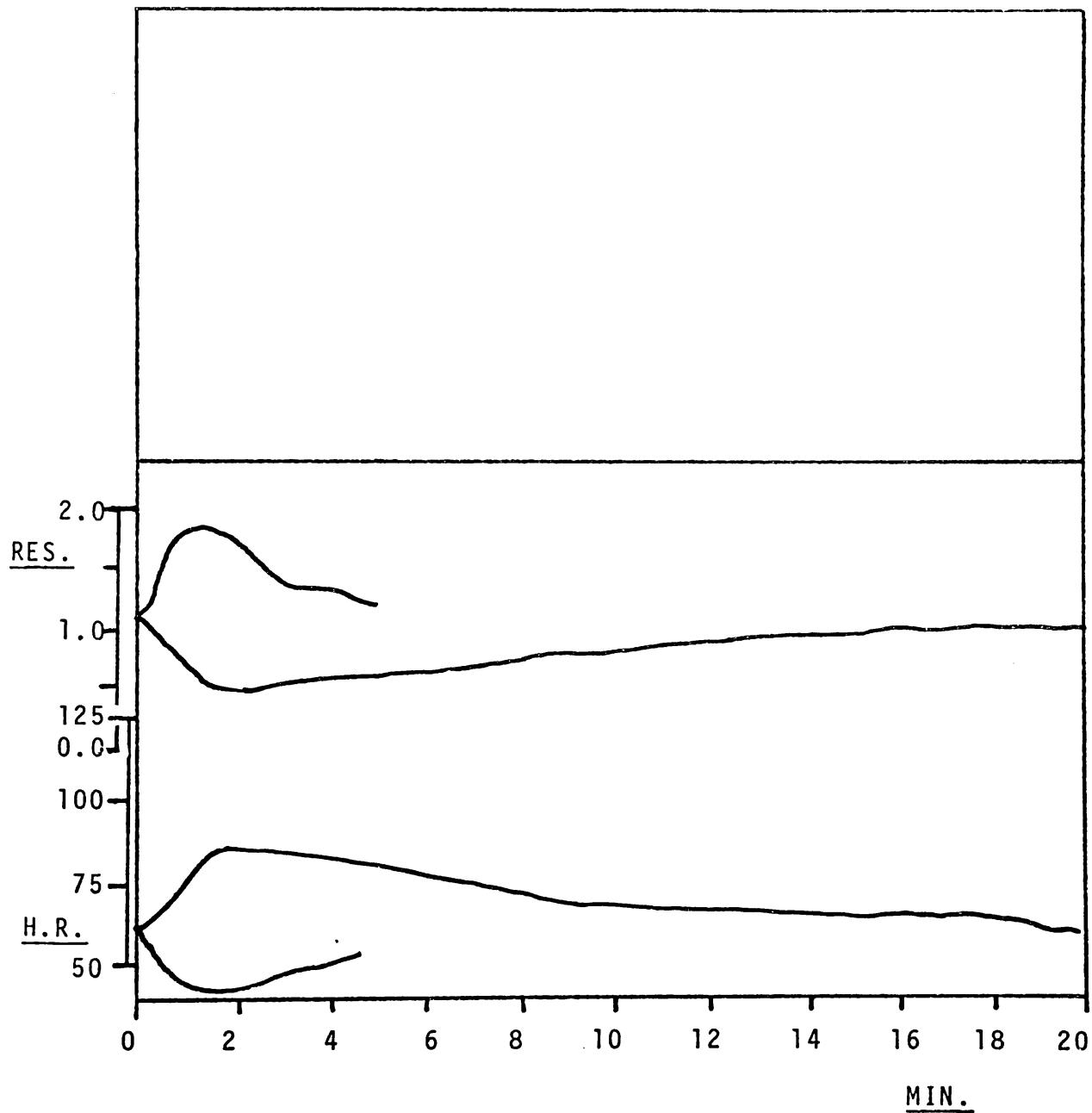
## GROUP 3



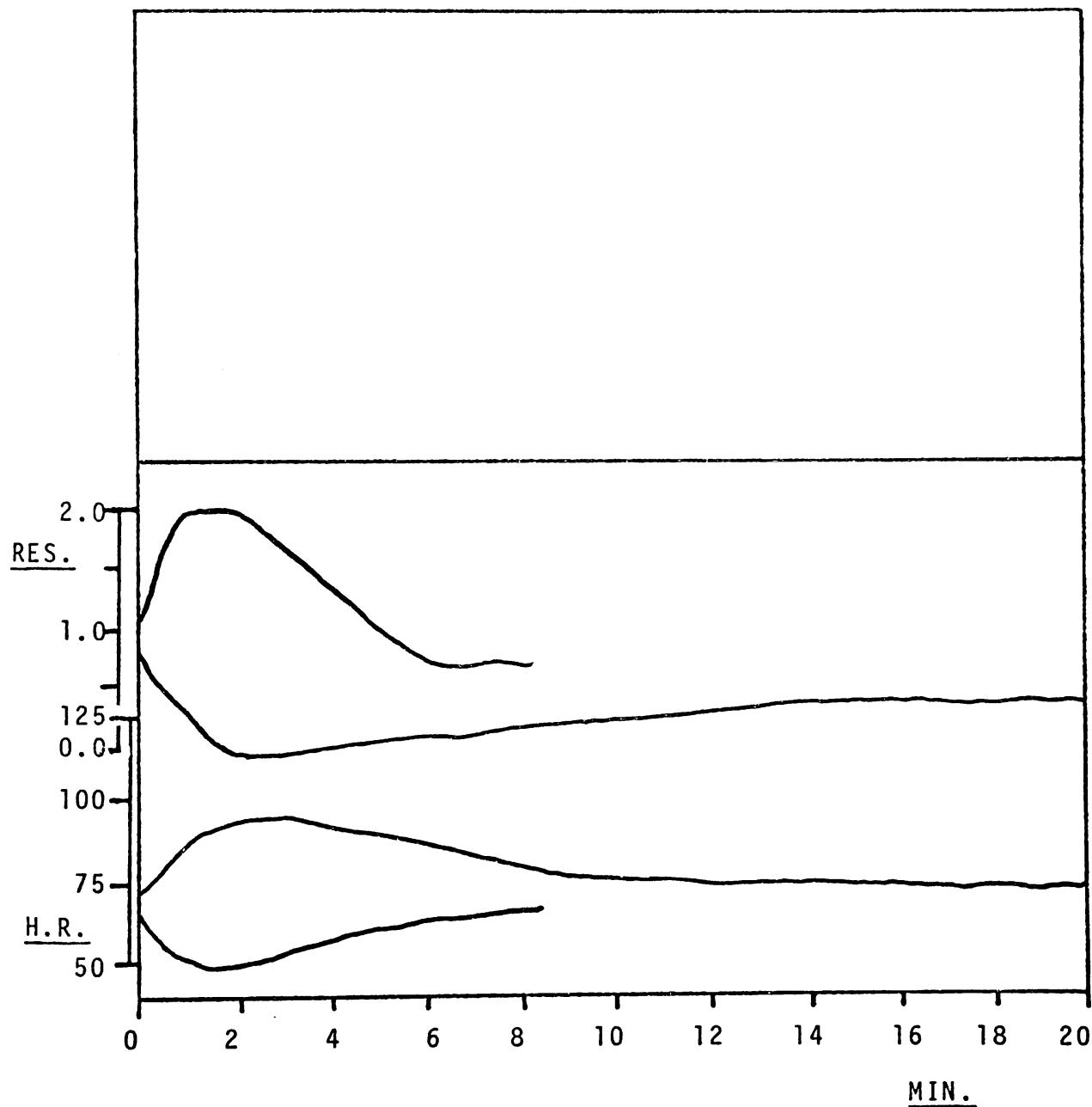
## GROUP 4



## GROUP 5



## GROUP 6



## GROUP 7

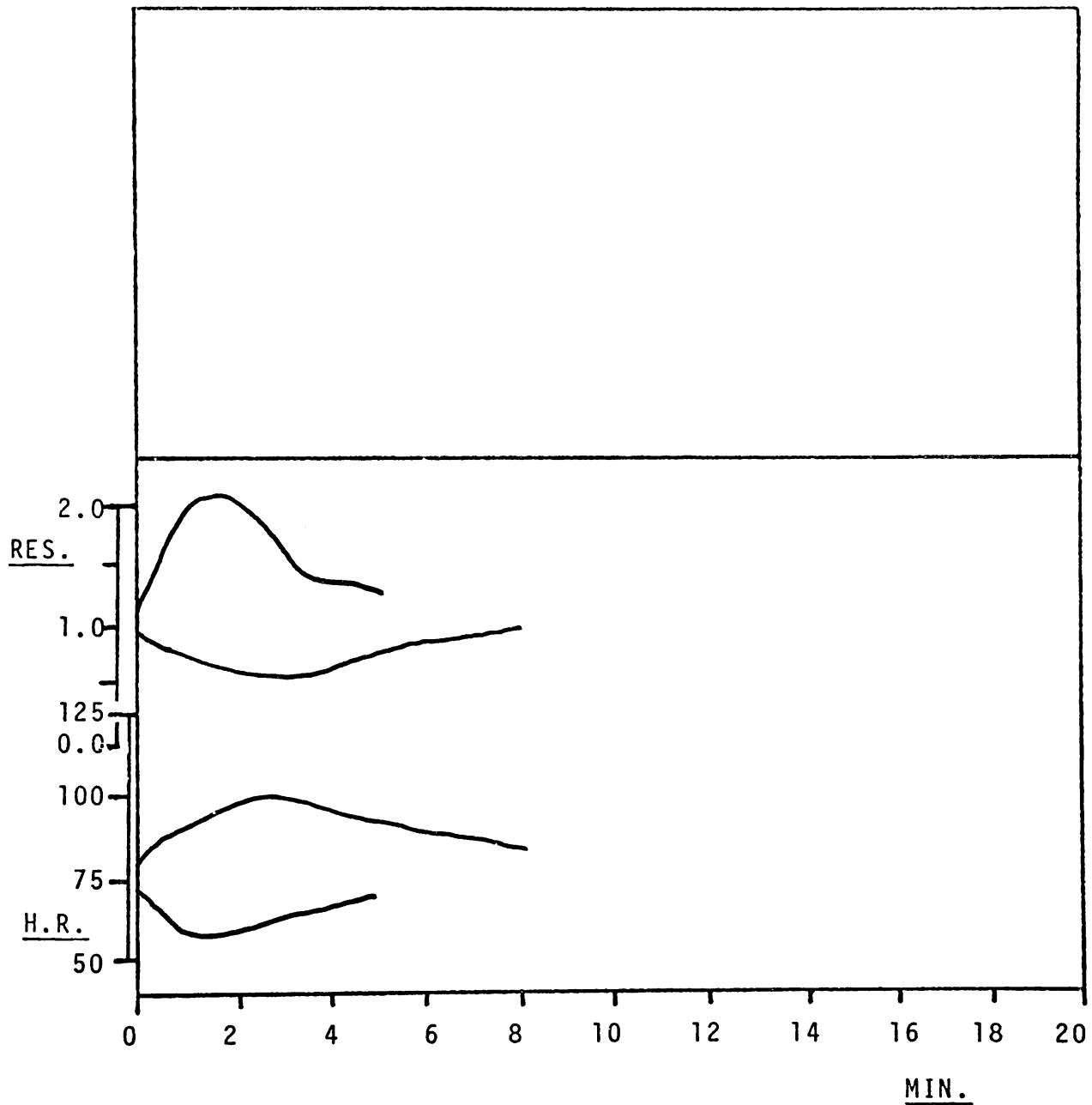
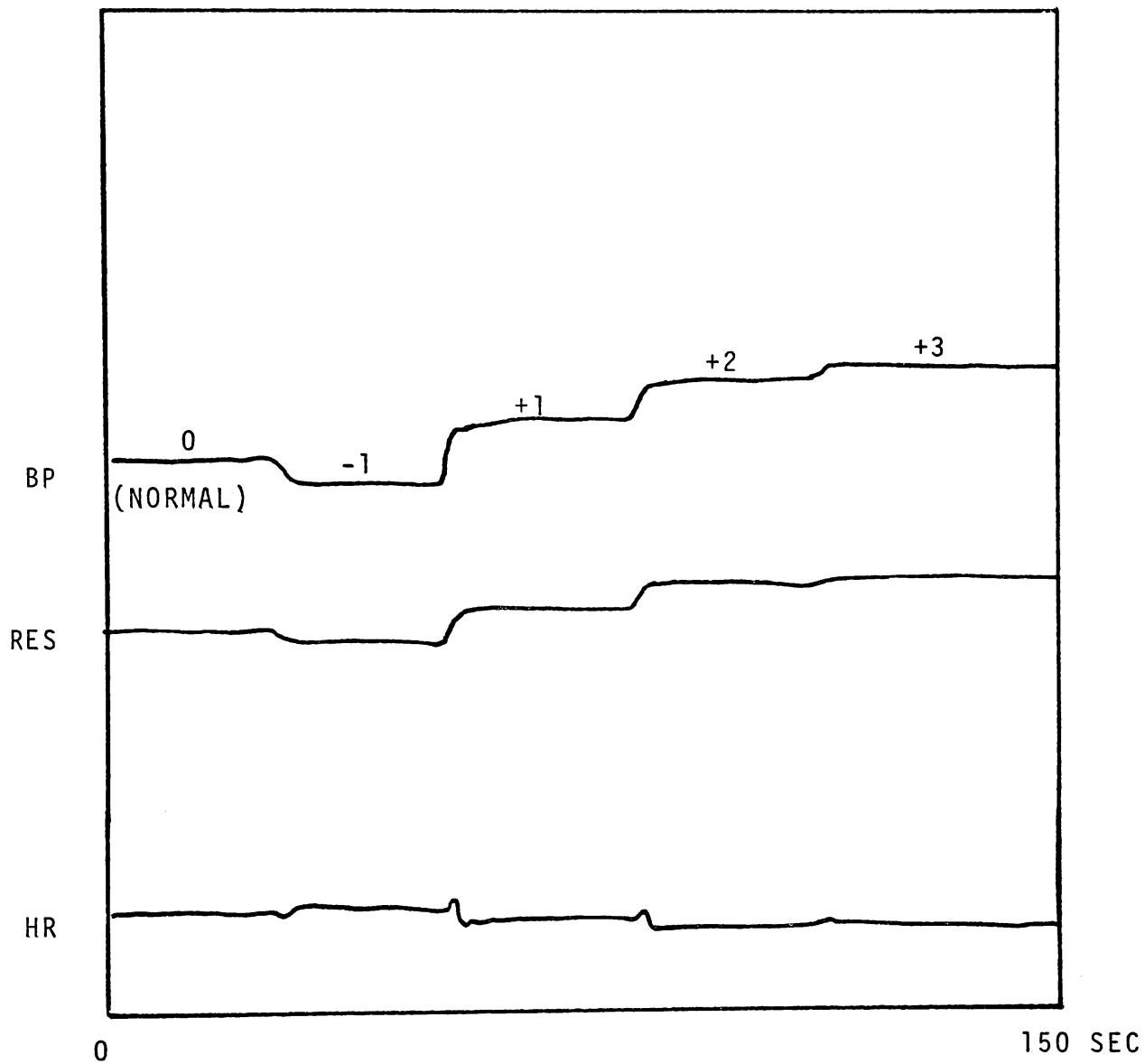


FIGURE VIIa

## EFFECT OF CHANGING PRESSOR INPUT TO VASOMOTOR



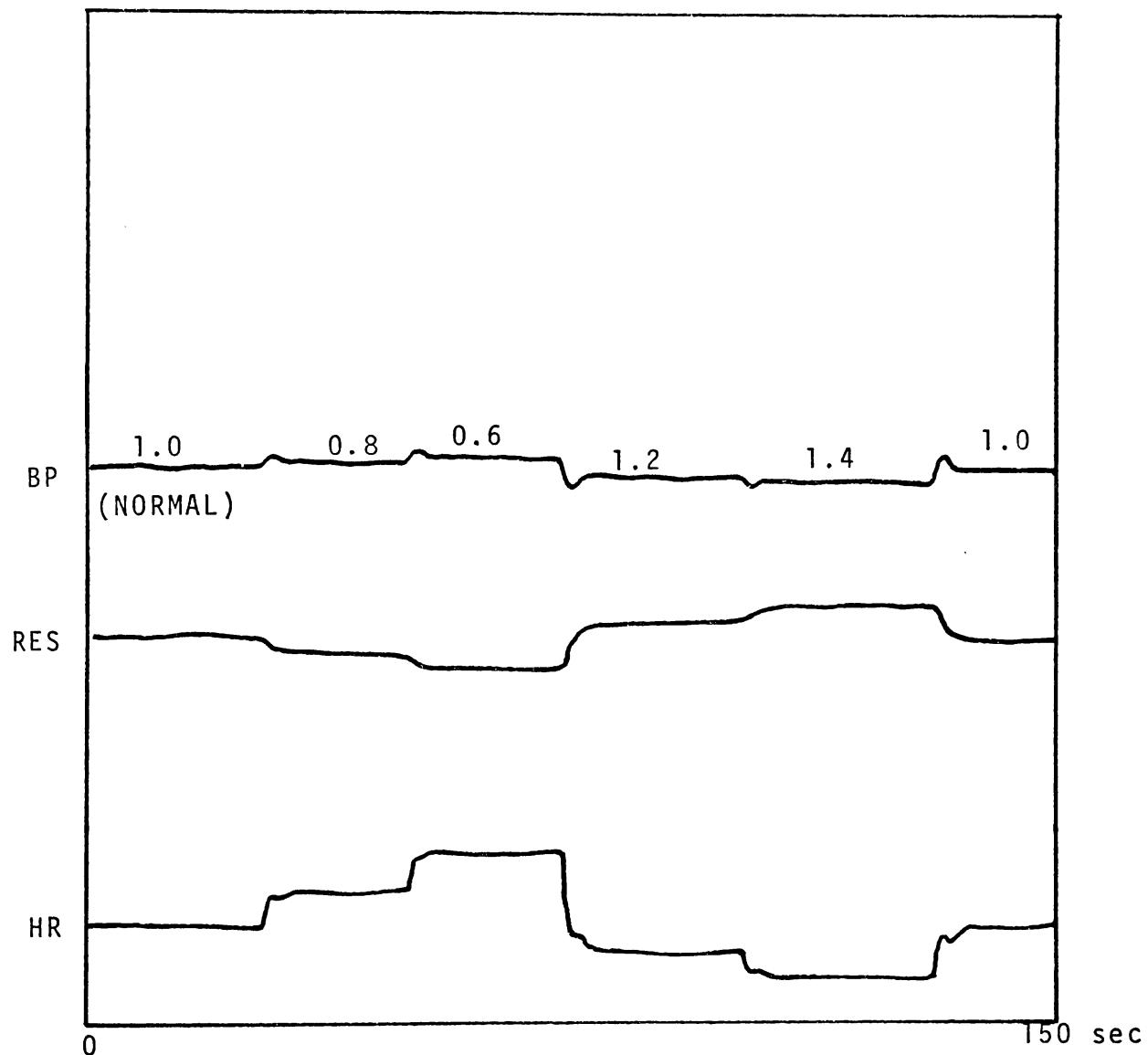
ACES: AS SHOWN ABOVE, CHANGE FROM NORMAL

DEPRESSOR GAIN: NORMAL (1.1)

VAGAL GAIN: NORMAL (1.0)

FIGURE VIIb

## EFFECT OF CHANGING VAGAL GAIN



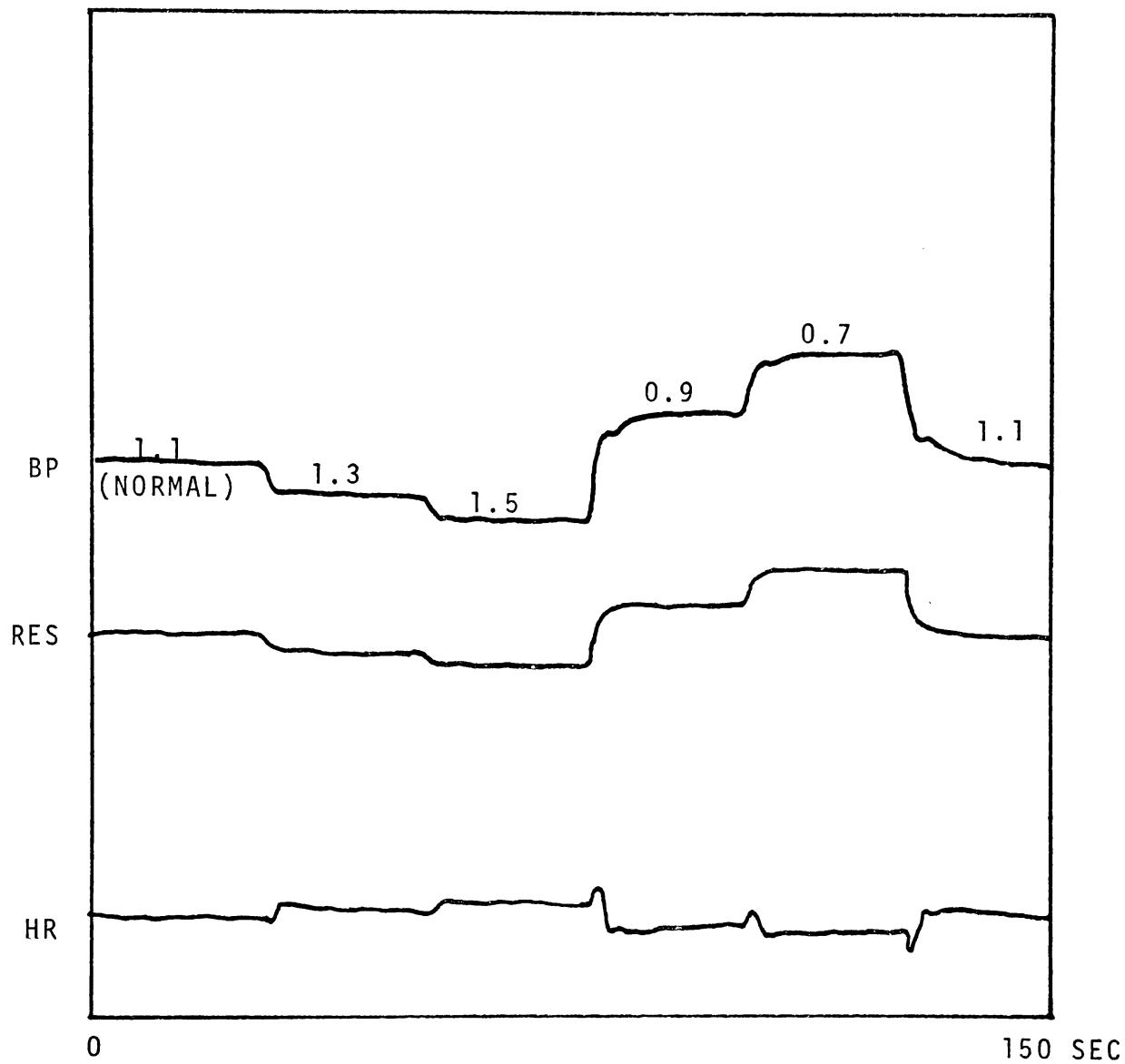
ACES: NORMAL

DEPRESSOR GAIN: NORMAL (1.1)

VAGAL GAIN: SHOWN ABOVE  
(1.0 IS NORMAL, I.E. 0 ACES)

FIGURE VIIc

## EFFECT OF CHANGING DEPRESSOR GAIN



ACES: NORMAL

VAGAL GAIN: NORMAL

DEPRESSOR GAIN: SHOWN ABOVE  
(1.1 IS NORMAL)

FIGURE VIIIa

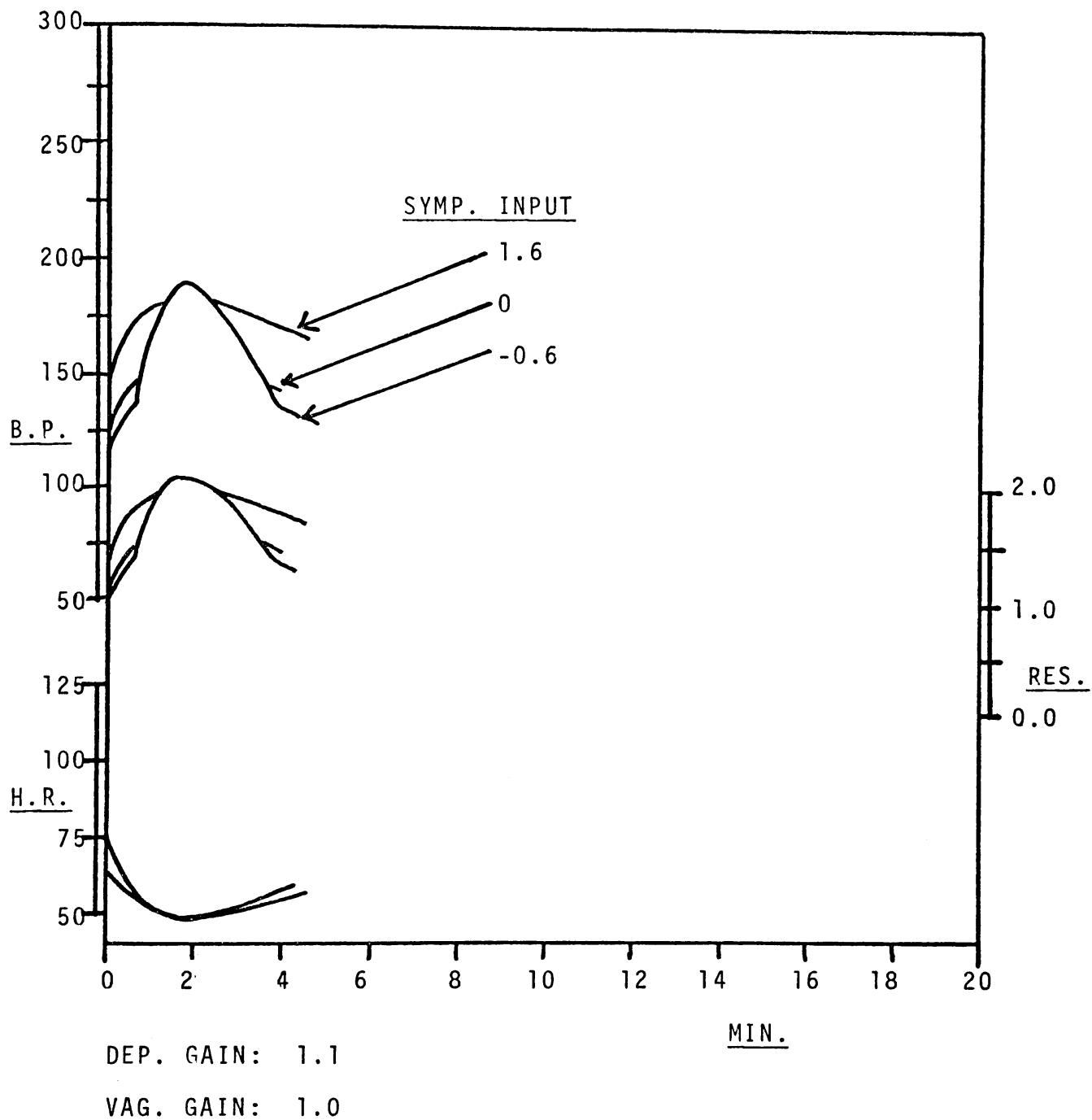
EFFECT OF CHANGING SYMP. INPUT  
(NOREP. RESP.)

FIGURE VIIIb  
EFFECT OF CHANGING SYMP. INPUT  
(MECH. RESP.)

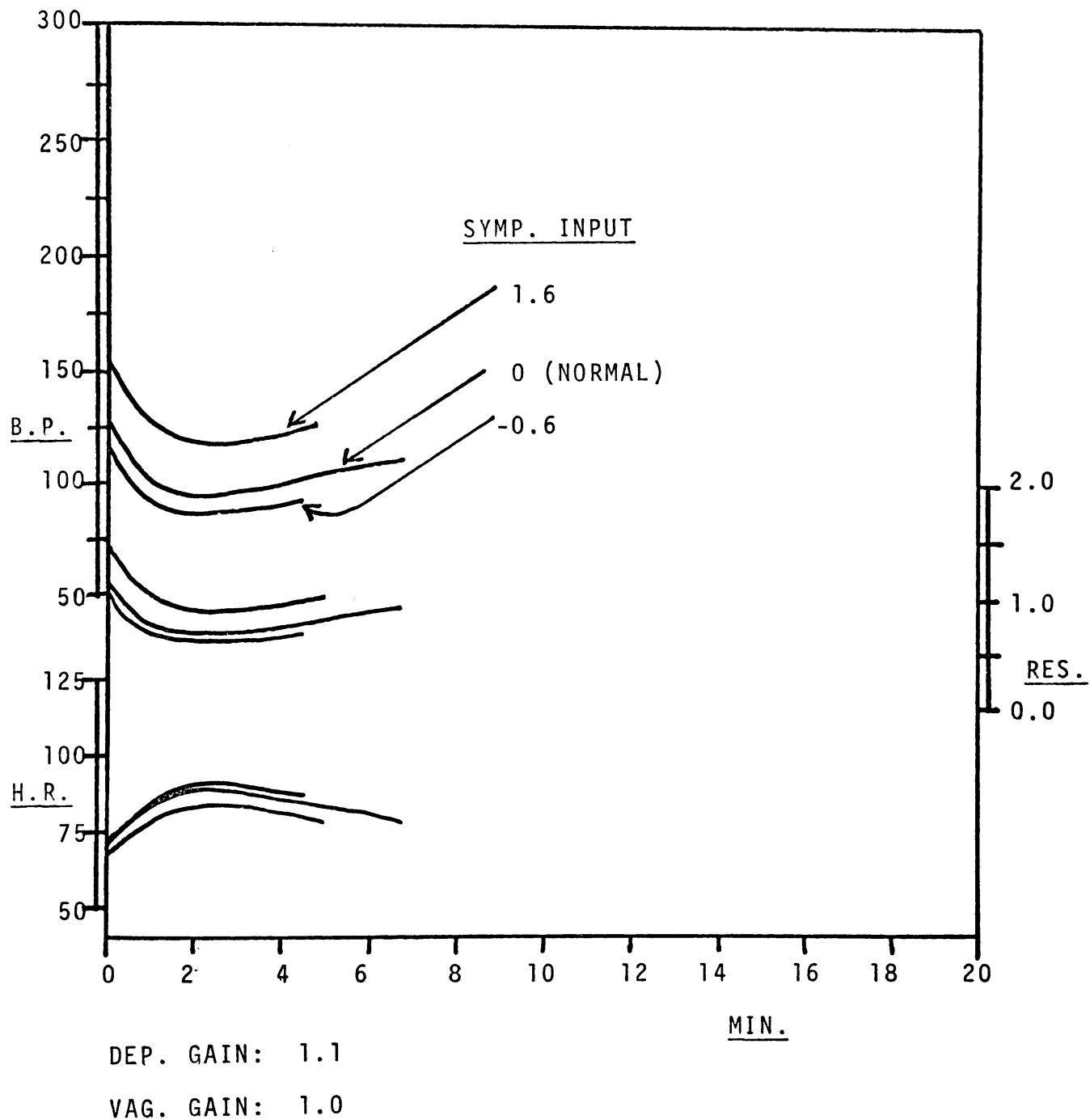


FIGURE IXa

## EFFECT OF CHANGING VAGAL GAIN

(MECH. RESP.)

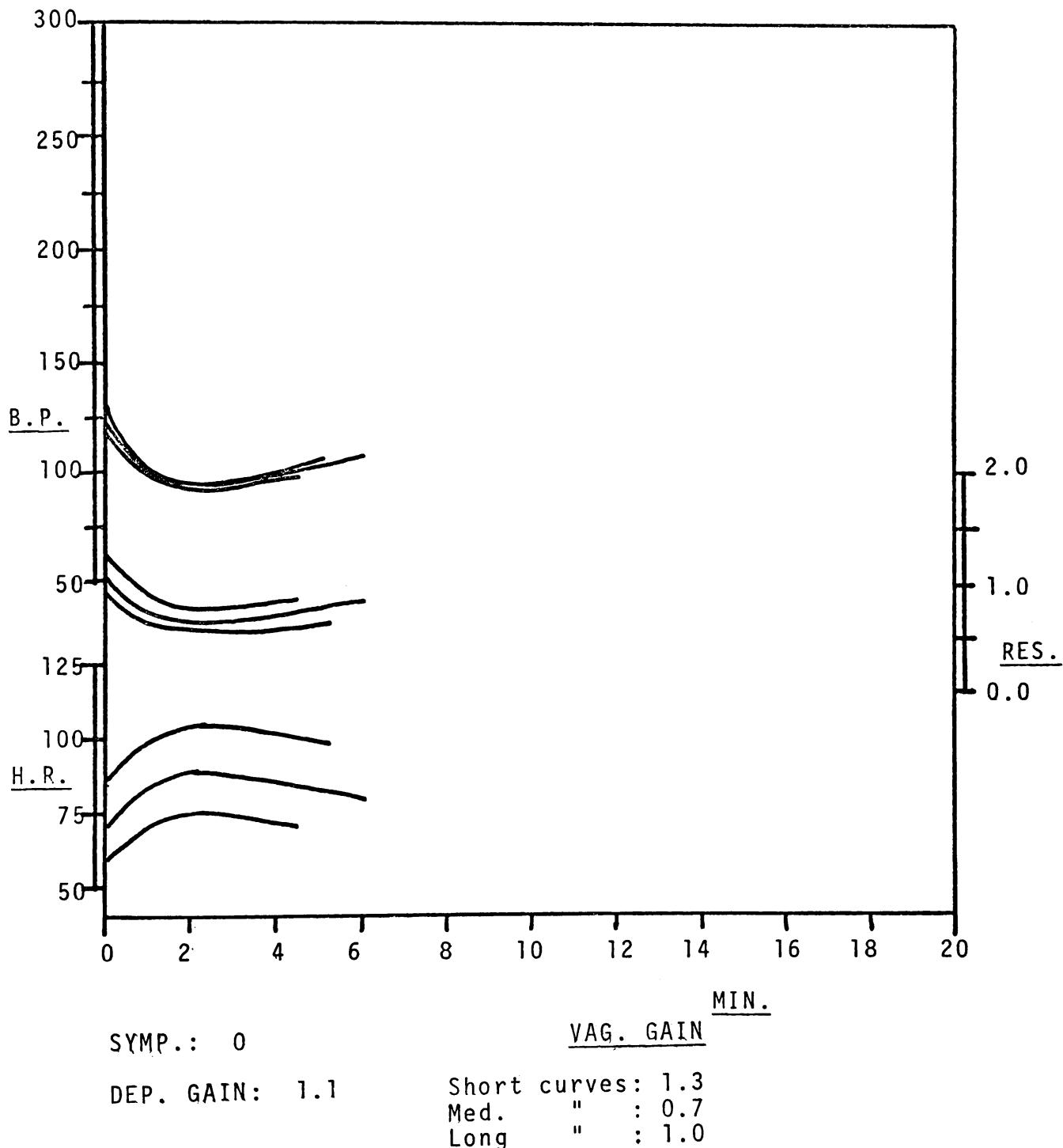
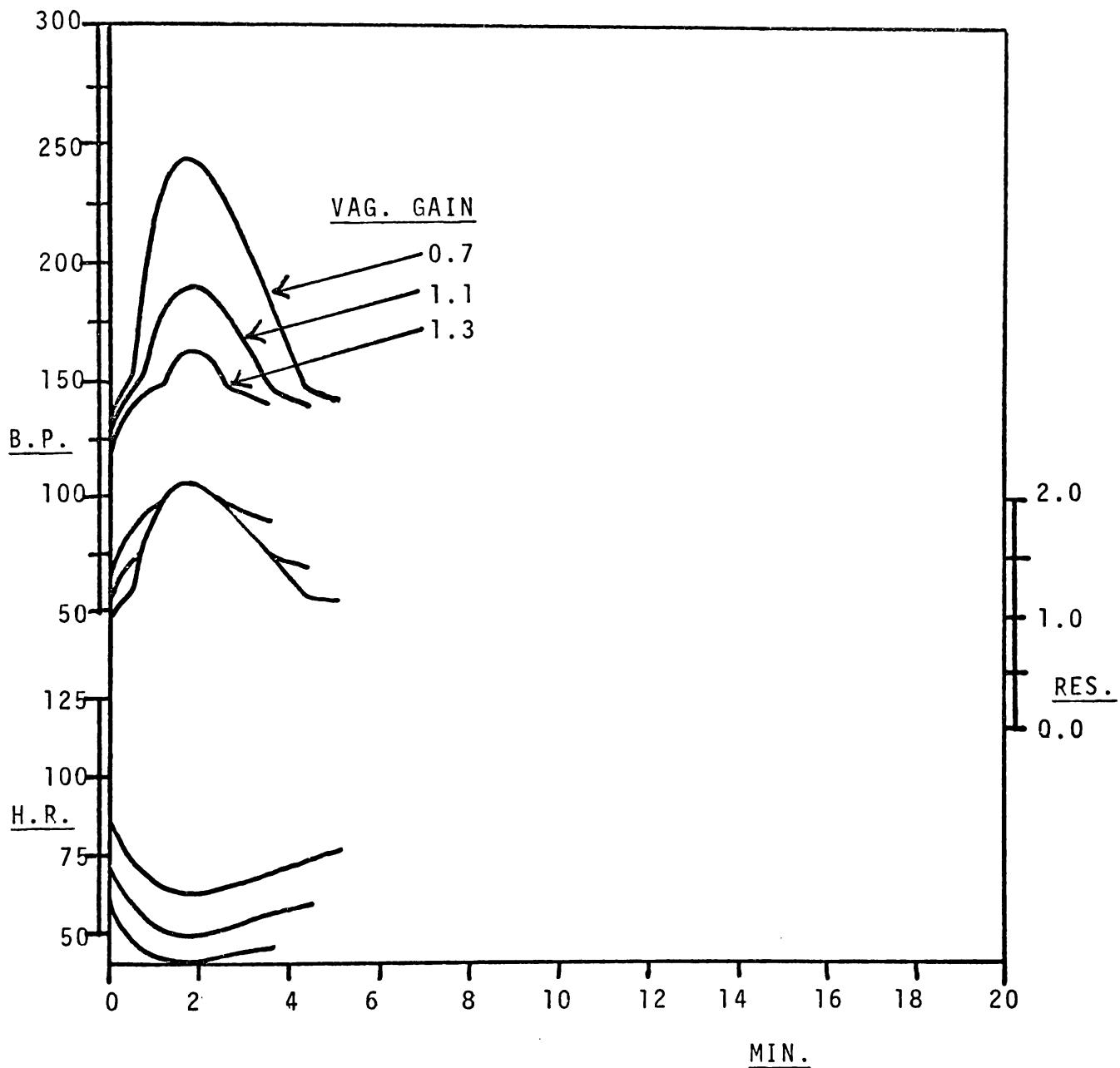


FIGURE IXa

EFFECT OF CHANGING VAGAL GAIN  
(NOREP. RESP.)

SYMP: 0

DEP. GAIN: 1.1

FIGURE IXb

## EFFECT OF CHANGING VAGAL GAIN

(MECH. RESP.)

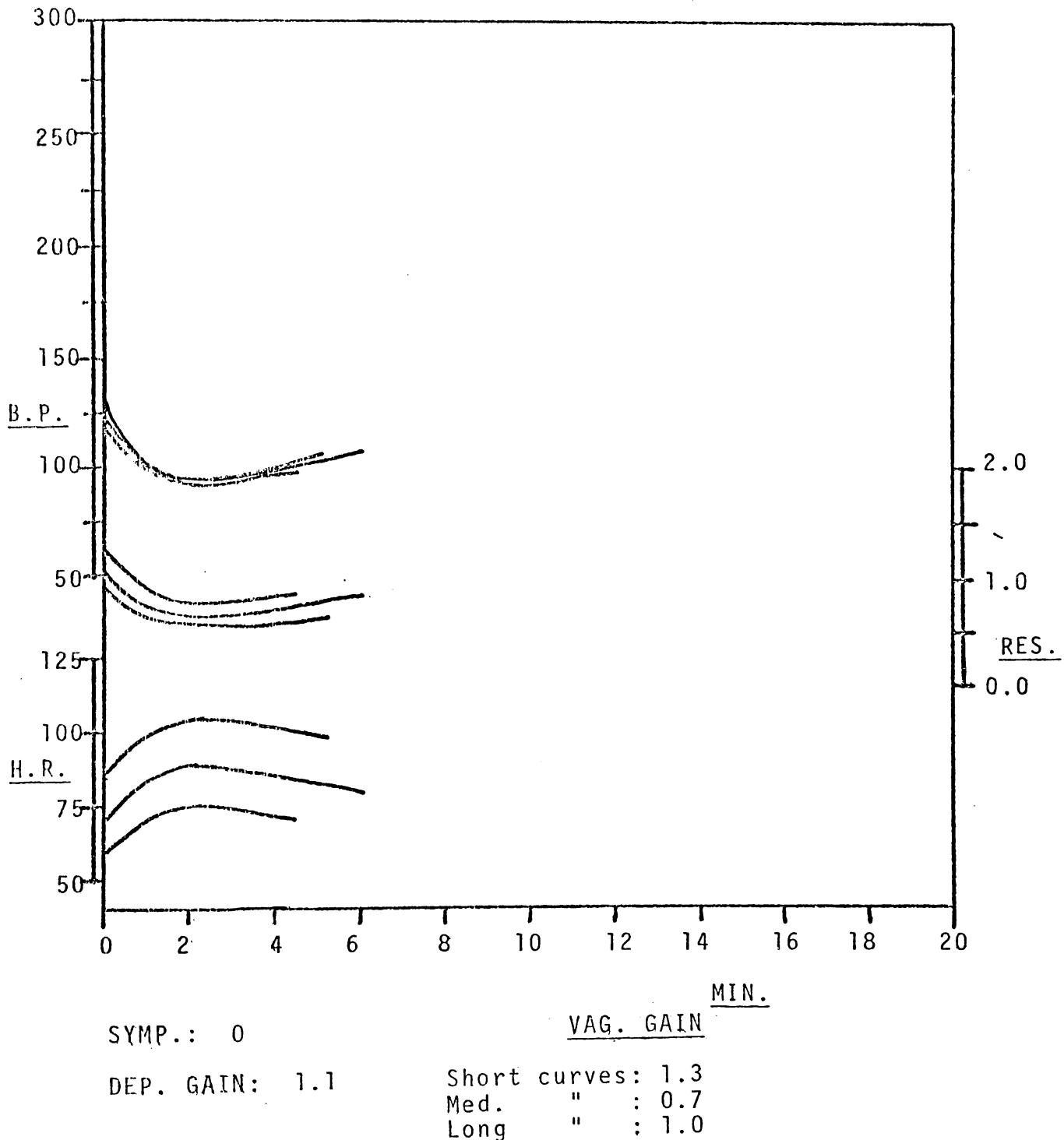
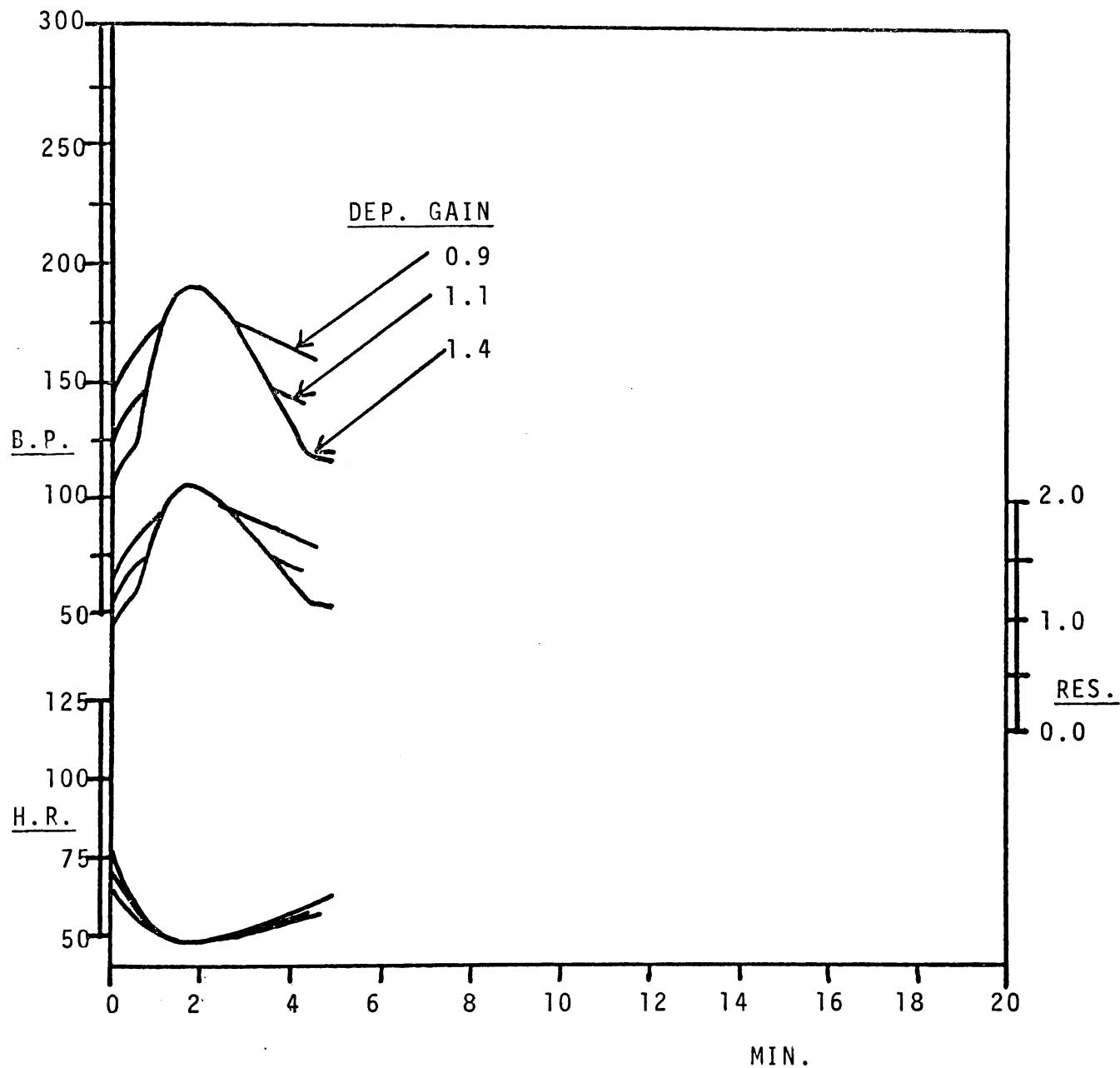


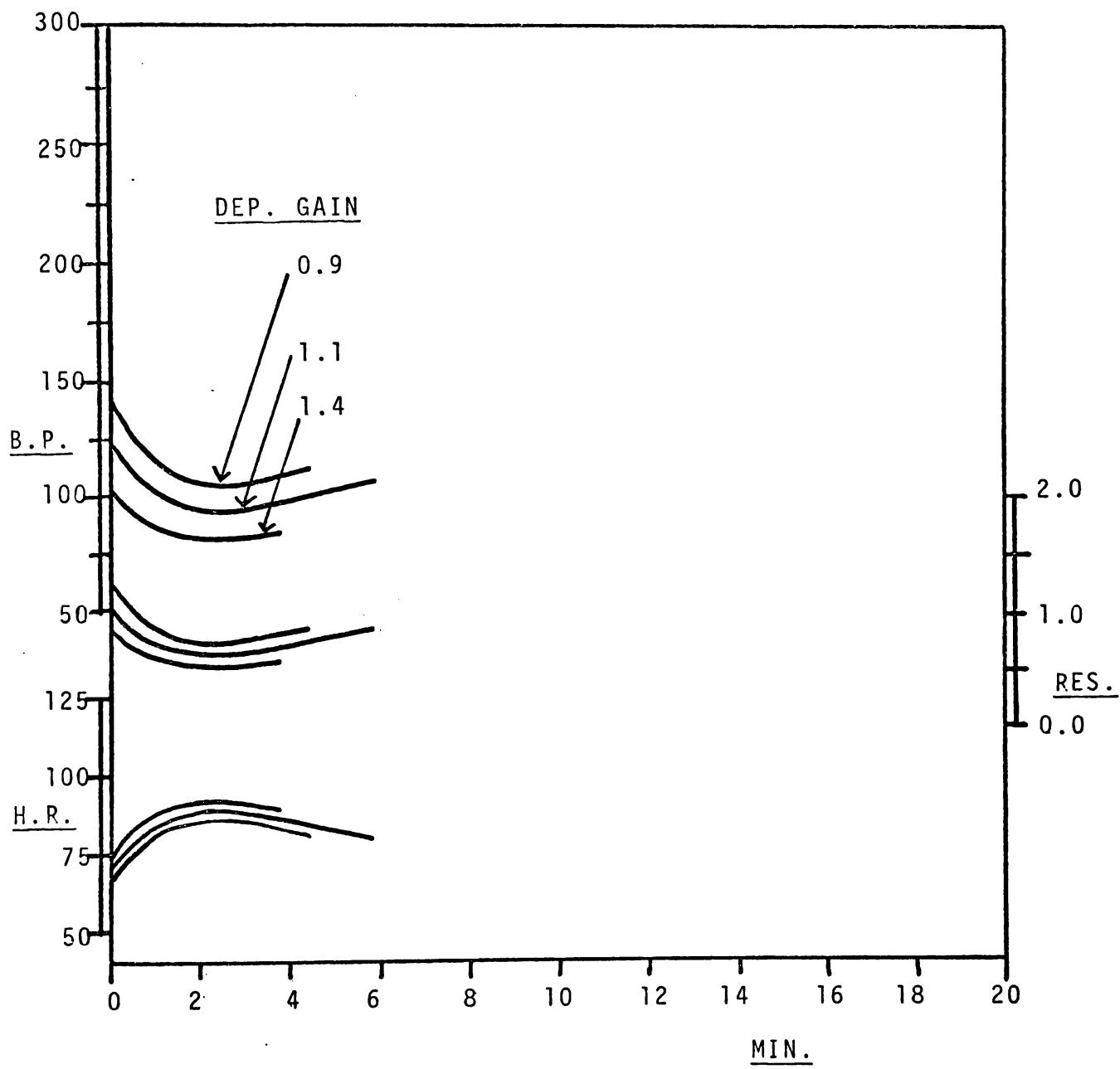
FIGURE Xa.

EFFECT OF CHANGING DEPRESSOR GAIN  
(NOREP. RESP.)

SYMP.: 0

VAGAL GAIN: 1.0

FIGURE Xb

EFFECT OF CHANGING DEPRESSOR GAIN  
(MECH. RESP.)

SYMP: 0

VAGAL GAIN: 1.0

PART VI. HEALTH, DISEASE AND INTEGRATIVE MEDICINEEPILOGUE AND CONCLUSION

It has been the scope of this dissertation to define and discuss the accumulation of stress and its consequences upon organismic function and reserve capacity. When an organism incorporates stress, the result is pervasive, appearing in physical, emotional, mental and behavioral processes. Human beings whose life expression has been reshaped by stress are continually observed by physicians and therapist/teachers.

Yet while all these re-educators, healers, medical persons, etc., know that they are all, in some way, dealing with the effects of stress, there would probably be very little agreement among them as to what stress actually is and how to deal with it for any given individual. The medical solution to symptoms, for example, is all too frequently the management of the various somatic expressions of stress by the use of drugs (e.g., psychoactives--tranquilizers and "mood elevators," blocking agents, smooth muscle stimulants and relaxants, analgesics, antacids, etc.), and sometimes counseling for social and readjustment problems.

George Engle (1960), one of the founders of modern psychosomatic medicine, points out that this implicit assumption, that "disease is a thing in itself," severely limits the search towards understanding of the total

organization of the body." In a definition of the health process along these lines, Romano (1950) proposes:

Health and disease are not static entities, but are phases of life, dependent at any time on the balance maintained by devices, genetically and experientially determined, intent on fulfilling needs and adapting to and mastering stresses as they may arise from within the organism or from without. Health, in a positive sense, consists in the capacity of the organism to maintain a balance in which it may be reasonably free of undue pain, discomfort, disability or limitation of action, including social capacity.

Such a definition, though helpful because it attempts not to dichotomize the process of health and sickness, is too general to be of much concrete use. Such terms as "reasonably free," "failures," "disturbances," "mastering stress" are much closer to value judgments than to definitions. Yet it is important in that it focuses attention away from simple factor theories, such as the cellular concept of disease.

Engle's and Romano's views are echoed by Mason (1970). In his presidential address to the Society of Psychosomatic Medicine, he states:

Psychosomatic medicine really represents a subdivision of a broader field which might be called integrative medicine. While most of medicine pursues a course of viewing disease as a local or regional or unit phenomenon, we pursue a course of viewing disease as a disorder of integration; i.e., a disorder of somehow fallible integrative machinery. Beyond the concept that foreign agents such as bacteria, viruses or toxins can enter the body, disrupt its machinery and produce disease, we still have remarkably little else in the way of fundamental concepts of how disease develops. In particular, medicine has come up with very little so far on the question, 'How can the machinery of the body itself go wrong?' What is the Achilles' heel of so excellent an organism which has emerged from so long a course of evolution? (my italics)

Tracing the history of biology, as Mason does, the road goes from body systems to organs; then to tissues, cells, cytoplasm and most recently to molecules (the place where the physical sciences were only a few decades ago). This approach, isolating and making islands, breaks down the organism into smaller and smaller components in an attempt to understand the basic principles of its operation.

An important exception in modern biology, as Mason points out, was the work of the 19th Century physiologist Claude Bernard. Bernard's vision was to recognize that to understand biological function, it was necessary to discover principles by which the parts of the organism interrelated to produce an integrated whole response. For him it was the coordination necessary to maintain an internal consistency in the face of a changing environment. Mason (1970) points out that against the general analytic trend in biology the "psychosomatic" field (i.e., the broad concept of stress) represents one of the few movements in the direction of the integrative approach since Bernard. He further points to the theoretical and philosophical importance of viewing the "psycho-somatic" field in this perspective: "A basic science of integrative physiology should be a prerequisite for the field of psycho-somatic medicine, rather than an afterthought of its existence." He adds:

No major new discipline has yet emerged to take over the great task of developing this biologic field. So far, research contributions have come mostly from fragmented efforts within endocrinology, neurophysiology, physiology, psychology and psychiatry, more or

less as side efforts. It is certainly a striking paradox in modern biology that we do not yet have a well organized, full-fledged science of integrative physiology devoted to a field of such profound theoretic importance. (Italics in original.)

The efforts of this dissertation are, hopefully, in this direction and can be restated in terms of Mason's question, "What is the Achilles' heel of so excellent an organism which has emerged from so long a course of evolution?" The kernel of this explanation is that this Achillean limitation is inherent within the cyclic pattern of charge and discharge. This rhythm is the basis of a highly tuned and responsive emergency system, with its obvious survival benefits, but which simultaneously predisposes the organism to the loss of reserve capacity, if that cycle is prevented from completion. This maladaptive consequence is seen to occur primarily in situations where the nervous system becomes activated to emergency, but where response can not or does not occur. Obviously, in the context of modern society, this is a very deep and complex issue. The effects of accumulated stress leave their widespread scars, not only in disease but in the deforming of human potential, occurring in their most crippling form as early, perhaps, as birth and even in intra-uterine existence.

A truly holistic approach to these problems can never be complete. It is by its very nature a searching process, involving every form and expression of "life energy" and its negation, no matter how seemingly small and inconsequential. The understanding of the physiologic mechanisms by which

stress accumulates, its prophylaxis, containment and social expression as well as treatment are central components in this search. To quote Tinbergen (1974) once again: "It is stress in its widest sense, the inadequacy of our adjustability, that will become perhaps the most important disruptive influence in our society." And its resolution, one might add, possibly one of its most creative forces.

## Appendix i

### Theories of the Mechanisms of Acupuncture

Unfortunately, there has been, in this country, very little research on the basic physiologic mechanisms of acupuncture and its relevance to "pre-symptomatic imbalances." This is not too surprising, as the concept itself really does not have a niche in Western physiology and medicine. The research that has been carried out here deals mostly with analgesic effects<sup>1</sup> (Levine et al., 1976) and even there, "Although the medical effects of needle puncture ('acupuncture') have been reported extensively by the popular media, there few medically documented reports on the efficacy of needle puncture in a Western clinical setting."

It is the purpose of this section to review the theories proposed to explain the action of acupuncture therapy. Recently there has been objective recording of the specific effects of acupuncture on the activities of various internal organs.<sup>2</sup> For example, changes have been demonstrated in the output of biliary secretion (2), in the action of the

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<sup>1</sup>This particular use of acupuncture is not considered by many authorities to be even related to the five elements of diagnosis and treatment, e.g., J. Worsely (personal communication).

<sup>2</sup>These are reported almost entirely by European investigators. Three excellent review articles do exist in English and are reported in the newly formed American Journal of Acupuncture. These articles by Craciun & Toma (1973); Craciun, Toma, & Turneanu (1973); and Tirgoviste (1973), are summarized and discussed in the following sections.

uterus in labor (4), in endocrine activity (5, 6, 7, 8, 9, 10), in respiratory volume (11, 12) and vascular reactivity (13), to cite only a few.<sup>1</sup>

The question naturally arises as to what are the pathways and the mechanisms involved whereby cutaneous stimuli, applied to a given area, are able to effect these varied internal changes. Various authors, e.g. (14, 15)<sup>2</sup> have suggested that acupuncture has, as its basis, reflexive mechanisms (originally elucidated by Head). He found that in certain diseases the area of the skin belonging to the dermatome to which the affected organ also corresponds exhibits increased sensitivity to touch, and that stimulation of these sensitive areas was often followed by a disappearance of the disease which generated it in the first place. He proposed the existence of a two-way reflex system: viscero-cutaneous pathways constituting a diagnostic parameter and inverse cutaneo-visceral ones to be stimulated for therapeutic purposes.

In this regard the clinical work of Janet Travell (1952) is particularly interesting. She and her colleagues present data drawn from over a thousand patients treated for various pain syndromes by stimulating myofascial "trigger areas" with procaine injections, "dry needling" and ethyl chloride spray.

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<sup>1</sup>These numbered references, more of which are in English, are from Craciun & Toma (1973).

<sup>2</sup>From Tîrgoviste (1973).

She defines the trigger area as a "small hypersensitive region from which impulses bombard the CNS and give rise to referred pain." Conversely, regional pain is set off whenever any trigger area is stimulated by pressure, needling, pronounced hot or cold, or by joint motion which stretches the area. She believes that the trigger areas in the myofascial structures can maintain pain cycles indefinitely, and that the pain cycle is often terminated permanently by these local "block" procedures. Further, she argues that the "efficacy of local block implies that the mechanism which set the pain cycle in motion is not the same as that which keeps it going. The pain cycle continues long after the precipitating cause has vanished."<sup>1</sup>

Two other findings of Travell's are significant to this and later discussions. First is that "a constancy of pattern indicates that impulses concerned in the unfamiliar reference of somatic (like visceral) pain follow fixed anatomical pathways." Second is the fact that the pain cycle may be accompanied by vasoconstriction and other autonomic effects in the zone of the projected pain.<sup>2</sup> These observations acknowledge the existence of "unknown" somatic pathways which have at

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<sup>1</sup>This makes sense in the Catastrophe view, in which similar reflex motility and agonist/antagonist activities would be represented on the behavior and control surface respectively. The original pain stimulus, if prolonged enough, could result in a low motility, co-contraction state (within the cusp). Appropriate stimulation would presumably cause a release through the cusp by initiating an increased momentum into discharge.

<sup>2</sup>These are often areas with no known functional anatomical relation or which may be segmental or involve specific local muscle groups.

least local autonomic effects. More significantly, they support the hypothesis developed in section III, D, that undischarged somatic reflexes can contribute to sympathetic tone in local and adjacent areas, and conversely that diffusely heightened sympathetic activity makes more probable the freezing of reflex discharge.

So while somatic symptoms may be due locally to undischarged reflexes (i.e., reflexes which are chronically contracted), this does not occur in isolation but involves an autonomic component as well, so to interpret acupuncture in these clinically observed phenomena makes some degree of sense.

Thus, some of the results of experimental acupuncture suggest the existence of as yet unknown mappings of functional somatic afferents onto central autonomic centers. The validity of this as an explanation for acupuncture has been questioned by various authors.

In a recent article, Tirgoviste (16) proposes certain interesting reservations in interpreting acupuncture as a (local) "reflexo-therapeutic" method.<sup>1</sup> Direct affirmative

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<sup>1</sup>Firstly, he points out that in treatment, by acupuncture, of a visceral pain there is relief of a greater pain by a stimulation of far less intensity (the reflexo-therapies claimed that it was the powerful cutaneous stimulation which led to inhibition of the medullary section that received the visceral input). What he fails to take into account, for this particular type of situation, however, is that according to "gate theory" an appropriate, though not necessarily "intense" stimulus might serve the same function. Secondly, Tirgoviste points out that the appropriate points which act upon an internal organ are generally found distal to and outside the dermatome of that organ. This point, while

evidence comes from several sets of experimental data: various authors (5-9)<sup>1</sup> have demonstrated an easionphenic reaction after stimulation of selected acupuncture points, strongly implicating activation of the hypothalamic-adreno-cortical axis. In recent investigations Craciun *et al.*, (17, 18)<sup>2</sup> have shown that acupuncture treatment induces reactions from the diencephalic centers, manifesting growth of the phagocytic activity and an increase in the normalization of the fibrinolytic blood activity (i.e., the direction of change is dependent on the initial level and therefore has an equilibrating effect). The authors also show an increase in leukocytes and an activation of the fibrinolytic and kinin-forming systems, lending additional support to diencephalic site of stimulation. Further, Daniaud (15) cites the work of Hideji Fuji, who has shown that various of the biologic and hematologic changes which appear after

still plausible, does not deal with the possibility of multi-segmental reflexes. His third objection is that two points situated close to one another in an area innervated by the same somatic nerve may have different or opposite action on an organ. There is a similar problem with this argument: one branch of the somatic nerve could be involved in a homo-segmental reflex, while the other could be involved in a hetero-segmental one. His other two arguments--that one cannot explain why, when a needle is introduced into the center of an active point, a maximum response is elicited, while a few mm away no response is evoked, as well as the specificity of points along the same meridian--are also somewhat weakened by the unknown possibility of a micro-organization of segmental and inter-segmental reflexes. Nevertheless, his points do impose a definite critique upon a simple reflexogenic model.

<sup>1</sup>In Craciun & Toma (1973).

<sup>2</sup>From Craciun, Toma, & Turneanu (1973).

treatment no longer occur if the skin area of the points is denerivated autonomically by resection of the paravertebral ganglion. These data would implicate very strongly action of the autonomic nervous system in mediating the effects of acupuncture treatment, even if reflexogenic mechanisms also play an important role.

Some further data<sup>1</sup> indirectly suggestive of autonomic mediation is that the electrical resistance is significantly lower at the acupuncture points, implying an increased autonomic tonus (19-25). In corroboration with this, Kellner (26) notes that the acupuncture points are areas where the nerve endings are more numerous, and Bergsmann and Wooley-Hart (27) see this related to its specific electrical properties and increased blood flow. The "reasons" for these "vegetative concentration zones" can be discussed in embryological terms: it is the epidermal layer of the skin which has its common origin with the nervous system, while the dermal layer (part of the double plexiform vascular layer) is of mesodermal origin. It is well known that a point-by-point projection of the entire skin area exists in the brain and that there is also an accurate projection of the internal organs. Since this includes, also, the derm (a true internal organ as by its mesodermal origin) it is likely that, by their common projection at higher nervous centers, there is a precise relation between certain dermal points on the skin

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<sup>1</sup>From Traian & Toma (1973).

and the activity of the internal organs. And that these dermal points, when stimulated, will, via their rich autonomic receptor system, initiate a series of autonomic "reflexes." Further, these "super reflexes" are mediated, via diencephalic mechanisms, and result in a shifting of the autonomic balance.

The physiologic data, previously mentioned, on acupuncture therapy, as well as its "meta-theoretical" base, suggest that the method somehow works towards a normalization of autonomic function. A particularly interesting observation, in this regard, is that the same cutaneous acupuncture stimulation will either increase or decrease fibrinolytic blood activity, depending on whether its initial value is above or below baseline.<sup>1</sup> This suggests that autonomic stimuli do not summate linearly but exhibit properties more consistent with the double surface properties characteristic of the Catastrophe point of view.

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<sup>1</sup>This is particularly interesting in light of the work by Sato, reported in section IV,A.

## Appendix ii

### Hyperventilation--Vegetative Therapy

In attempting to assess the physiologic effects of the "hyper-respiratory" patterns and techniques employed in the Reichian vegetative work, one comes up against a number of problems. It would appear at first that the physiology of hyperventilation would readily provide these mechanisms. But this seems not to be the case. Even the measurements and explanations of hyperventilation effects are frequently unexplained and contradictory (see Lowry, 1967),<sup>1</sup> and often opposite to those evoked in the Reichian work.

Nevertheless, it is useful to look at some of these observations and theories (and associated "syndromes") towards framing an understanding of some of the phenomena which occur in vegetotherapy.

The effects of overbreathing or hyperventilation on the physiology and cellular chemistry of an organism are expressed at virtually every level.

Respiration controls the internal milieu by regulating both oxygen and carbon dioxide levels as well as the acid-base relationships. It is well known that the caliber of the cerebral blood vessels is influenced (Wolf & Lennox (1930); Schmidt (1936) and Cobb et al. (1931)): carbon dioxide tension dilates cerebral arteries and lowering it

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<sup>1</sup>"The"modern book on this subject, bringing together the history and modern development in this field.

results in vasoconstriction. The opposite effect occurs in the arm and leg in direct response to carbon dioxide tension shifts (Lennox & Gibbs, 1932). Hyperventilation exerts profound and wide ranging effects on nervous function, some directly attributable to the lowered arterial carbon dioxide tension.<sup>1</sup>

Lewis (1957, 1959) observed CNS effects of hyperventilation as a pronounced slowing and synchronization of electroencephalograph (eeg). Meyer and Gotch (1960) found that hyperventilation led to a lowered alveolar carbon dioxide concentration, resulting in a lowered blood carbon dioxide tension. The direct (local) effect of this on the blood vessels was a constriction of the arterioles<sup>2</sup> which was sufficient to cause anoxia. They found also that diencephalic structures became anoxic sooner than cortical ones.

This condition of central anoxia, along with increased blood supply to the limbs, suggests the pattern of an emergency situation<sup>3</sup> being prepared for by increased blood supply to the members which need to be mobilized for fight and flight.

It is, however, well established that the effect of "clinical hyperventilation" is a slowing of the eeg in a

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<sup>1</sup>Due to a decrease in alveolar CO<sub>2</sub> concentration.

<sup>2</sup>The direct effect of low CO<sub>2</sub> tension on the peripheral vessels is vasodilation--the opposite effect.

<sup>3</sup>Anoxia is perhaps the most extreme threat, in terms of survival hierarchy, that an organism can be subjected to.

pattern similar to that of sleep. Thus we have a paradoxical situation where an extreme emergency situation is coupled with a state of central deactivation.<sup>1</sup>

So, in summary, the results of clinical hyperventilation appear to result in a highly maladaptive state. It is most interesting in this regard that in the hyper-respiratory patterns evoked in the Reichian vegetative work an initial response often is extreme tiredness and the client, if not pushed, may even fall asleep. If, however, specific patterns of breathing are pushed considerably past this point, then extreme restlessness occurs and resistance to any more breathing becomes great. If at this point the therapist/teacher is skillful in altering the pattern or, in some way, providing the support for this difficult period, a sudden transition occurs where this buildup of charge becomes expressed spontaneously, either in the form of autonomic-somatic discharge, or affective expression.<sup>2</sup> Sometimes there occurs with this, a connection (memory, lifestyle situation, etc.). While emotional expression may occur frequently in early stages of the work, as it progresses, the client is encouraged to "contain" the buildup of the hyper-respiratory charge until the expression (discharge) occurs spontaneously

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<sup>1</sup>The effect of anoxia produced by tracheal clamping (Gellhorn, 1964) results in extreme heightened ergotropic symptoms including cortical dysynchronization (alert wakefulness condition.

<sup>2</sup>This may happen spontaneously, or as a consequence of muscular manipulation; the connection of a passing thought, etc., memory, etc.

and preferably results in an often extremely pleasurable rebound into a trophotropically dominated state.

Lewis (1957, 1959), one of the most active researchers in hyperventilation, administers a hyperventilation test in diagnosing patients. During the test he will sometimes push on the lower chest with his palms to encourage greater thoracic excursion. He reports that in nearly all of his patients who developed hyperventilation symptoms<sup>1</sup> there was "a marked emotional catharsis with weeping and revelation of important historical material." It is also very interesting that in his early explorations he often was unable to reproduce the symptoms for which his patients originally sought help unless he put them "in a state of mind similar to that in which the original attack occurred."

The comparison of this to Reich's work (of several decades prior) is instructive and interesting. First of all, the "pushing on the chest" spoken of by Lewis is but one of a multitude of manipulative techniques used in the Reichian and other body oriented work. Secondly, the eliciting of affective material is certainly corroborative to a degree. The further development which really characterizes Reich's work is the "re-patterning" of the autonomic function. This allows for the progressive containment of charge, so that the discharge begins to occur spontaneously. As this happens, the emotional fixations and memories become less

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<sup>1</sup>E.g., anxiety, heart symptoms, sweating, tremor, palpitations.

coupled to the charge and the process begins to be accompanied by a sense of well-being.<sup>1</sup>

Thus we can see that, in terms of the Catastrophe model, hyper-respiration is used to cause an initial autonomic shift, and then to precipitate impulsive expression which might trace out a path like the one (i-ii) shown in figure IX, page 49. Further, the building towards the spontaneous discharge evoked by the progressive building and containing of charge might continue the pathway into phase iii, towards a return to baseline homeostasis and fuller resolution.<sup>2</sup>

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<sup>1</sup> Reich, in a concise perception, viewed the symptoms (both psychic and somatic) of the neurosis, as well as negative feelings and attitudes, as a consequence of the person being deprived, so to speak, of this capacity for self-regulatory discharge. In his analysis it was the muscular blocks which were the "active and causative agent" in maintaining the neurosis and psycho-somatic symptoms. In other words, he found that to the extent that the cycle of charge→discharge could be experienced comfortably so that stress could be effectively regulated, the entire attitude and vitality of the individual would begin to shift more positively along with the dissolution of the physical symptoms.

<sup>2</sup> I.e., if this phase of the pathway (iii) were not established the organism, to regulate its activation, might continue to charge and discharge (explosively) between the high and low motility surfaces (i→ii→i→ii...). This could create on the topology surface a discharge pattern, which while being intense would not re-establish the functional pattern of organismic self regulation.

## Appendix iii

Background Anatomy and Physiology of the Hypothalamus and Pituitary

Hormones are secreted into the systemic circulation from the three divisions of the pituitary: adrenocorticotrophic hormone (ACTH), thyroid stimulating hormone (TSH), follicle-stimulating hormone (FSH), luteotrophic hormone (LH), growth hormone (GH), and prolactin (PL) from the anterior pituitary; melanocyte-stimulating hormone (MSH) from the middle pituitary; and anti-diuretic hormone (ADH or vasopressin) and oxytocin from the posterior pituitary.

Secretions from the anterior and middle pituitary are controlled by (1) releasing or inhibiting factors, which are carried to the anterior pituitary from the hypothalamus in the hypothalamic-pituitary portal blood vessels, and (2) to a certain extent, by feedback from substances carried in the systemic circulation, e.g., see Tepperman (1970).

According to Halasz (1972), the releasing and inhibiting factors are produced in the medial basal hypothalamus, the so-called hypophysiotrophic area (HTA)<sup>1</sup> (see figure I).

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1. This area includes the arcuate nuclei, the ventral part of the anterior or periventricular nuclei, the medial part of the retrochiasmatic region and the median eminence, for those who are familiar with the terrain.

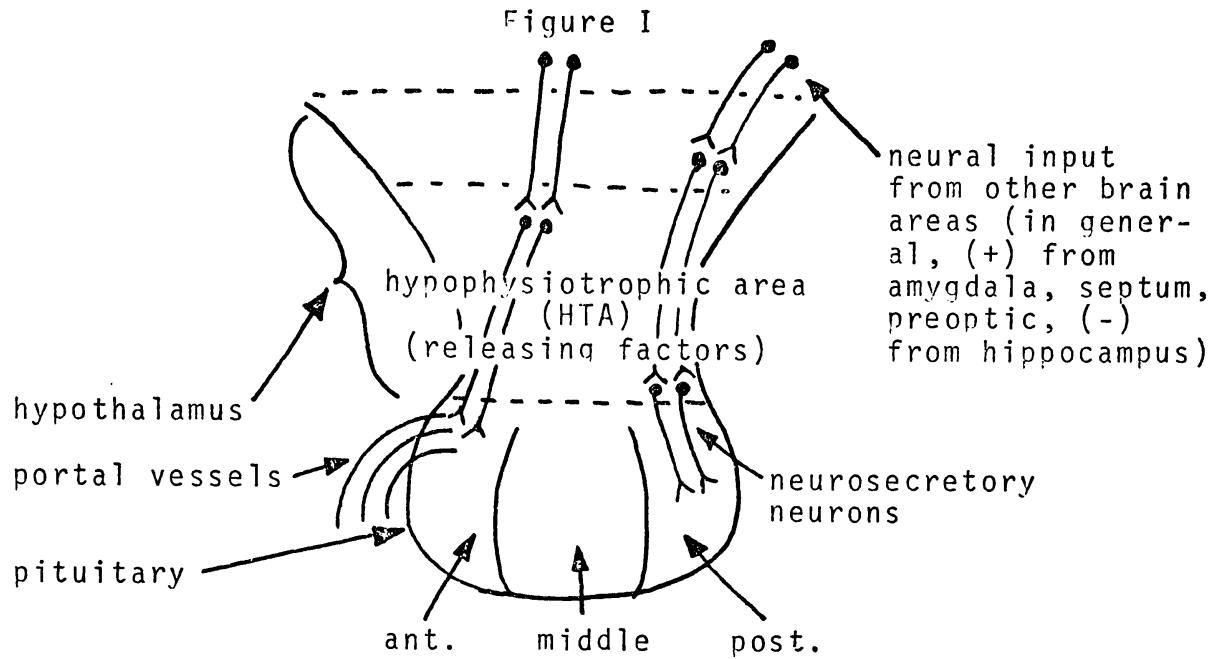
When the portal system is intact, but the HTA is neurally isolated, the basal secretions of most trophic hormones are maintained,<sup>1</sup> hence the name. Secretions from the posterior pituitary are controlled by neurosecretory neurons which have their cell bodies in the hypothalamus and their endings in the pituitary. Upon stimulation one population of cells releases ADH and the other releases vasopressin. Both the HTA neurons and the neurosecretory neurons are in turn controlled by (1) synaptic input from other parts of the hypothalamus and from other parts of the brain, and (2) by circulating substances which usually are part of a feedback loop, i.e., have been secreted by an endocrine target organ in response to a pituitary hormone.

Extrahypothalamic neural input to the HTA is the means by which environmental stimuli exert their influence on the anterior pituitary. This input is generally (a) excitatory from the amygdala, septum, preoptic area and certain ill-defined mesencephalic regions, and (b) inhibitory from the hippocampus and probably some other mesencephalic structures. The hypothalamic and extrahypothalamic input to the HTA is not well-defined, but is most certainly integrative.

In addition to regulation of pituitary hormones via the HTA, the hypothalamus controls the autonomic nervous system—the anterior hypothalamus associated with parasympathetic responses, the posterior with sympathetic. The responses

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1. ACTH, however, increases, thyroxine decreases, but the rest remain the same at a basal level.



hypo-thalamic control	pituitary hormone	secreted from	target organ & primary effects	feedback substance
CRF	ACTH	anterior pituitary	adrenal cortex (glucocorticoids in particular increases blood glucose, in general, catabolic, increases excitability of neurons)	glucocorticoids
TRF	TSH	"	thyroid gland increases metabolism of all cells	thyroxine
FRF	FSH	"	ovarian follicle; seminiferous tubules	estrogens, progesterone; testosterone
LRF	LH	"	follicle; interstitial cells	estrogens, progesterone, testosterone

hypo-thalamic control	pituitary hormone	secreted from	target organ & primary effects	feedback substance
GRF, GIF (somato-statin)	GH	anterior pituitary	bones in sub-adult; otherwise anabolic, particularly by increasing amino acid uptake into cells	?
PRF, PIF (?)	PL	"	breasts, milk glands	?
MRF	MSH	middle	melanocytes	?
neuro-secretory neurons	ADH	posterior	distal tubule & collecting duct of kidney --increases H <sub>2</sub> O absorption	osmolarity in hypothalamus
"	oxytocin	"	smooth muscle, particularly nipple, uterus --causes contraction	

hypothalamus integrates neural and hormonal inputs and coordinates, among others, the endocrine, autonomic, and behavioral (somatic) aspects of thirst, temperature regulation, hunger, sex or pleasure, rage (aggression) or fear (defense).

As a generalization about the functional control of the hypothalamus and its output systems, a statement by Halász is worthy of consideration. Referring to the extra feeder neural control of the HTA he states:<sup>1</sup>

1. The statement could just as easily apply to control of the other output systems of the hypothalamus: autonomic and behavioral.

Concerning localization of the control functions of the various [pituitary] trophic hormones, there are probably no special cell groups, i.e., 'centers', which control distinct functions, but rather functional patterns might exist. [This] control level [of the HTA] can be envisaged as a kind of computer which, according to a number of built-in programs, elaborates the solution for each actual situation on the basis of a large body of information partly stored, partly flowing in continuously through neural and hormonal channels. The 'results' are then distributed over a number of 'print-out' channels.

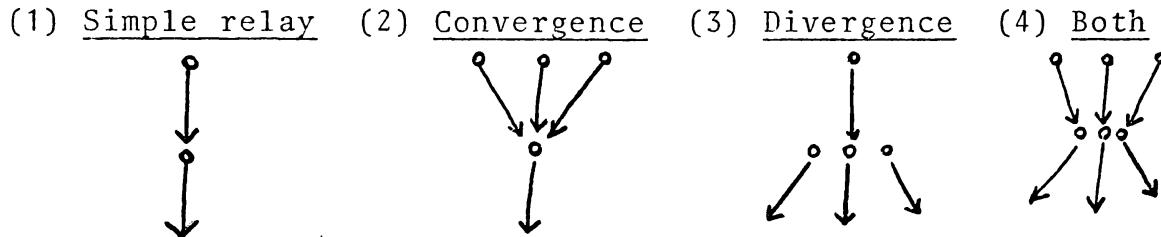
In this paragraph Halász summarizes the most current notions about localization of function in the hypothalamus. While many workers have claimed specific localizations, so many have claimed entirely different areas for the same function that the whole notion of specific centers may well have to be re-examined. Perhaps one should be looking for functional patterns instead. The concept of cells controlling a particular function being scattered anatomically throughout the hypothalamus makes it easier to imagine functional diversity as well. That is, if TRF-secreting cells are spread throughout the HTA, as they seem to be, it is more likely that the TRF function will be exposed to and influenced by neural input from many sources than if TRF were secreted only by a discrete group of cells in one area of the hypothalamus.

#### Functional overlap between control systems in the hypothalamus

Four possible cases of functional patterns exist with respect to input-output relations of the hypothalamus:

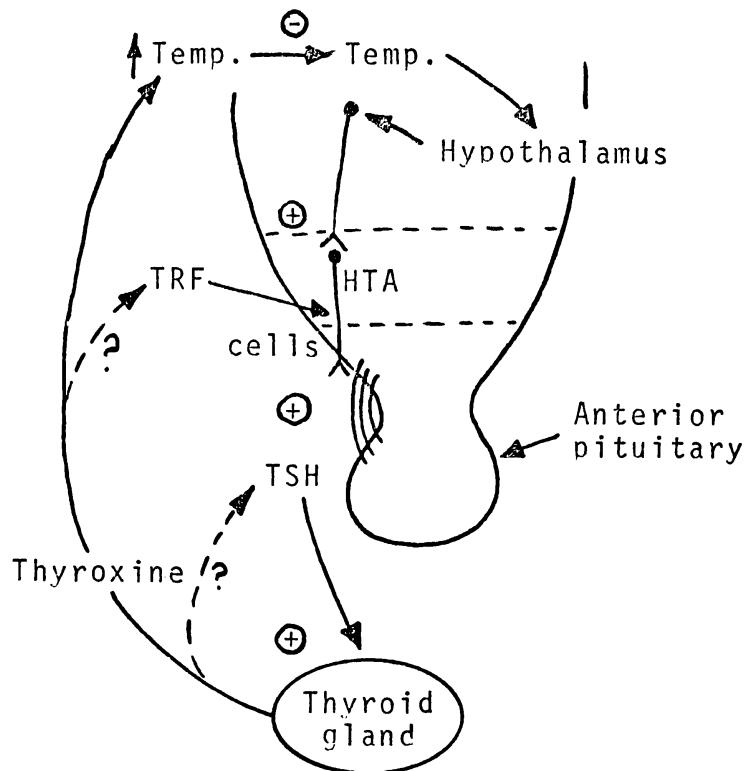
1. One type of input affecting a single output.
2. Many (several types of input affecting a single output.)
3. One type of input affecting several outputs.
4. Many types of input affecting several types of output.

Diagrammatically:



One input-one output

Usually discussions of neuroendocrine relations focus on one type of input affecting a single output. This has been more for simplicity's sake than intrinsic reason that the system is really thought to be organized on that principle. It has been convenient to think of TSH, for instance, as operating by a simple feedback loop. Cooling the hypothalamus excites certain cells which turn on the TRF-secreting neurons. TRF causes release of pituitary TSH, which stimulates thyroxine secretion from the thyroid. Thyroxine causes increased basal metabolic rate and the evolution of heat in the tissues, including the hypothalamus. Thus the temperature in the hypothalamus (and in the animal) is restored. The stimulus to CRF is removed and the thyroxine system returns to normal. (With some pituitary hormones, feedback control by the end-organ is probably also exerted at the pituitary and releasing factor levels.)



It is, however, not really known how specific a response the system is capable of making. The single feedback loop idea has been a convenient but probably misleading fiction. It was good for discussion of homeostasis but, as demonstrated in the body of the paper, does not at all account for the effects of hypothalamic and extra-hypothalamic inputs on endocrine levels.

## Appendix iv

### Autonomic-Endocrine Relations

That a single type of input to the hypothalamus can affect multiple outputs and that several inputs influence the same output can be shown by several examples of specific behavioral functions in addition to the generalized E and T functions of Hess. For example, either dehydration or a salt load stimulate osmoreceptors in the hypothalamus, and the neurosecretory neurons put out more anti-diuretic hormone (ADH) and more H<sub>2</sub>O is returned by the

kidneys. At the same time, and also perhaps via some of the same hypothalamic neurons, behavioral drinking occurs in the presence of H<sub>2</sub>O. That drinking is controlled by the hypothalamus is known from the fact that no compensatory drinking to make up a H<sub>2</sub>O loss occurs if certain areas of the hypothalamus are ablated. Both of these elements of H<sub>2</sub>O control, ADH and drinking, are induced by the same stimulus to the osmoreceptors in the hypothalamus.

The second example of a single input to the hypothalamus affecting multiple outputs is that cold, or specifically, lowered hypothalamic temperature, has endocrine, autonomic and somatic consequences. With local cooling of the hypothalamus, thyroxine output is increased markedly, therefore TRF and TSH necessarily have been affected. Peripheral vasoconstriction occurs which is mediated via hypothalamic autonomic centers. Increased muscle tone and shivering are also responses to the hypothalamic stimulus, probably mediated via the gamma efferents. In addition to these integrated and appropriate responses based on specific information, a stimulus such as cold also produces a meshwork of generalized responses, such as increased ACTH secretion and decreased prolactin, which do not necessarily serve any function in thermoregulation. Therefore, whether one is referring to specific responses or more generalized ones, these kinds of observations lead to the conclusion that one type of stimulus can induce several kinds of responses mediated through the hypothalamus.

Multiple inputs affecting one kind of output

Selye was impressed by what he saw as the "non-specificity" of the stress response; that a variety of stressors could all cause an increase in glucocorticoid secretion. Stimuli as disparate as pain and hypoxia, to name two, are capable of causing glucocorticoid release. A common element to all stimuli which evoke this response is, of course, their ability to cause CRF and thus ACTH release. The prior chain of events is just now being investigated. In an attempt to understand this process, John Mason (1968) has separated physical and psychological components of stressors to some extent. Tentatively, he concludes that some stimuli such as muscular exercise are only capable of inducing glucocorticoid secretion to the extent that they also produce "emotionality."<sup>1</sup>

All of these "non-specific" stimuli, which primarily have in common their "specific" ability to cause "emotional arousal," must stimulate the final common path of the hypothalamic CRF-secreting neurons. It is therefore reasonable to put the two facts together and conclude that "emotional arousal" at the hypothalamus is a proper stimulus for the CRF neurons. To the extent that arousal at the hypothalamus, or HES, is a potent stimulus for the CRF-secreting neurons, HES would be an indicator or correlate in a general way with the

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1. So far, hemorrhage is the only stimulus studied which may be primarily physical, i.e., which may produce glucocorticoid secretion even when no emotional arousal is manifest.

activity of the CRF-secreting neuron.<sup>1</sup>

In conclusion, a variety of different agents evoke the same mode of output from the hypothalamus, which is probably mediated through generalized arousal of the hypothalamus.

#### Single stimulus affecting multiple outputs

Conversely to the case just considered, to understand the pattern of output of the hypothalamus, Mason (1968) studied all the pertinent endocrine responses to one kind of stimulus situation known to be stressful.

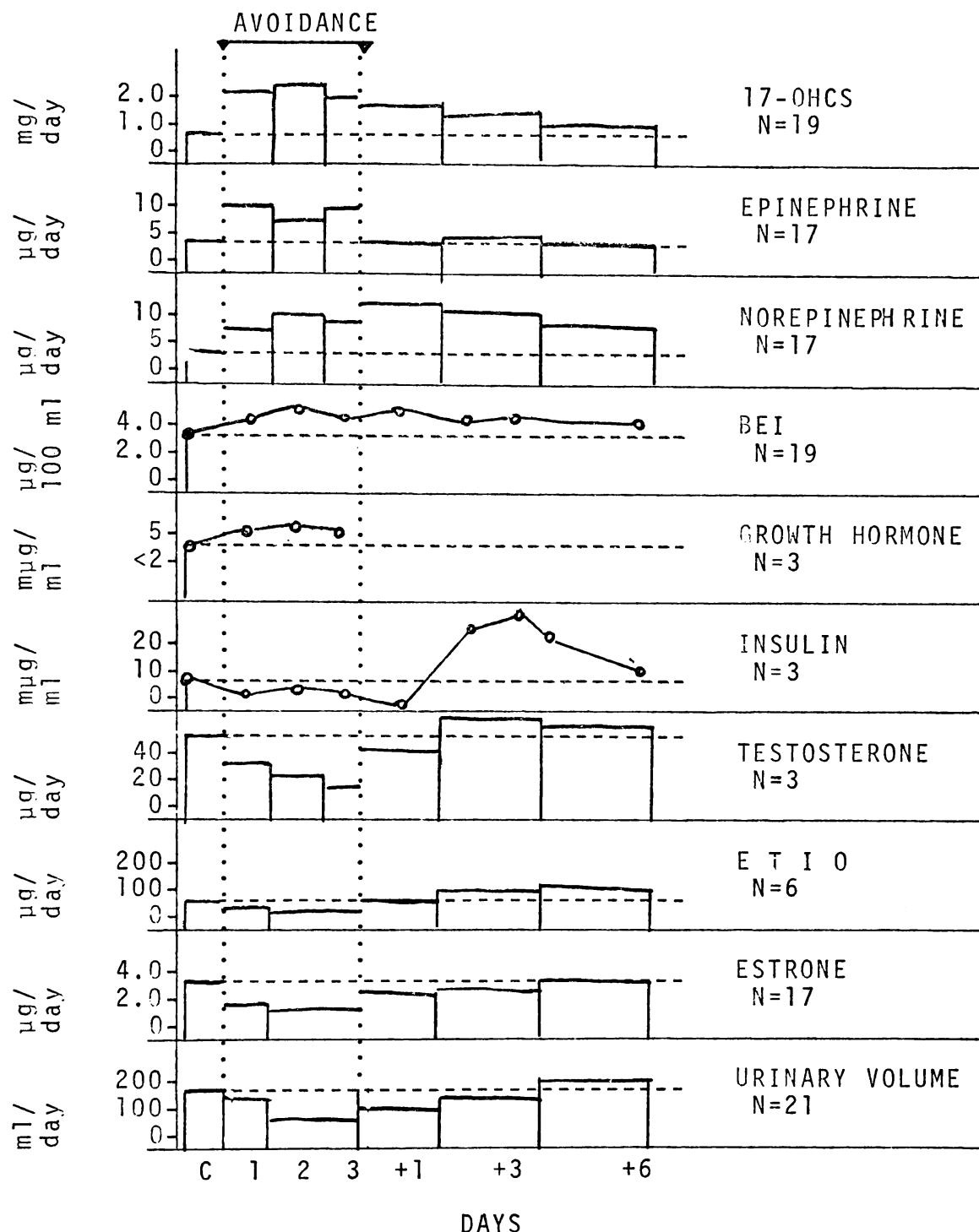
Plasma and/or urinary hormone levels in monkeys were measured during and after shock avoidance training maintained for 72 hours. The specific pattern (see figure II) was interesting from a functional standpoint in that "catabolic" hormones tended to be secreted during the trial while "anabolic" hormones were suppressed, with a reversal after the trial. But the interesting point for this discussion is that all these hormones were affected, again presumably via the hypothalamus, some via the autonomic and some via the pituitary.

#### Multiple inputs affecting multiple outputs

So what initially appeared to be an ACTH response alone to a variety of stimuli proved to be multiple responses to

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1. The mechanisms of influence at the synaptic or micro-environmental level are dealt with starting on page



After Mason (1968)

multiple stimuli. Presumably, the intense activation of one stimulus channel (cold or thirst), or many kinds of channels ("non-specific" stress) in a less intense way lead to similar kinds of activation, the most important parameter being the hypothalamic excitatory state (HES). (Which also makes intuitive sense, because someone aroused by one stimulus becomes more irritable to others.) Even though an organism is often capable of making an integrated and appropriate response, the diffuseness of the physiological response in the above-mentioned cases is remarkable.

#### Stimuli affecting impulse activity in the hypothalamus

By studying the various stimuli which cause evoked responses in various areas of the hypothalamus, it can be concluded that certain stimuli which affect the ANS also affect the endocrine system, or more generally, affect other outputs. The difficulty in describing this overlap of functions has been in the fact that workers have tended to study only endocrine, or only ANS effects, or only electrical responses, or only behavior. Evoked potential studies, nonetheless (or more properly, massed activity) and single unit studies give support to the same conclusion: that many incoming signals to the hypothalamus not only affect a discrete output but probably also influence a variety of autonomic, behavioral and endocrine functions. Table I illustrates the kinds of results obtained.

Two examples from table I will show the line of

Table I: Evoked-potential Studies in the Hypothalamus (Cats)

<u>References</u>	<u>Stimuli</u>	<u>Recording Sites</u>
Feldman, Van der Heide & Porter (1959)	Sciatic nerve shocks	Lateral and posterior areas Medial and anterior areas
Feldman & Porter (1960)	Sciatic nerve shocks	Several areas
Massopust & Daigle (1961)	Light flashes	All areas
Abrahams, Hilton & Malcolm (1962)	Cutaneous shocks Clicks Light flashes	All areas
Feldman (1964)	Light flashes	Anterior and preoptic areas Posterior area
Rudomin, Malliani, Borlone & Zanchetti (1965)	Stimulation of sciatic, superior radial and infra-orbital nerves	All areas

From "Electrophysiological Studies on Hypothalamus," B.A. Cross & I.A. Silver, Brit. Med. Bull. 22:197 (1966).

reasoning. Massopust and Daigle (1961) and Abrahams et al (1962) found responses to light flashes in all areas of the hypothalamus. Feldman's work with light flashes in cats (1964) shows that this stimulus caused evoked potentials in anterior and preoptic areas and in the posterior area, with different latencies. As mentioned previously, stimulation of anterior HTH causes typical parasympathetic responses; stimulation of posterior causes sympathetic ones. The other HTH areas are associated with releasing factors, neurosecretion or behavioral affects. Therefore, stimuli such as light flashes which can affect all these areas can presumably affect these various outputs. The second example involves sciatic nerve shocks (Feldman et al 1959; Feldman & Porter, 1960; and Rudomin et al 1965) on evoked potentials. Again this stimulus is seen to affect all HTH areas, and therefore presumably all outputs to a greater or lesser degree. Since some caution should be used in interpreting these results due to the relative imprecision of the evoked potential, single unit recordings are more valid in this respect. In certain instances single unit studies also lend support for the above conclusion. In particular, Cross and Silver (1963) noted responses in all hypothalamic areas when a variety of stimuli were applied: touch, pain, cold, auditory, hypoxia, hypercapnia. A particular stimulus, such as sciatic nerve stimulation, gives responses in the following areas when studied by different workers: all areas (Wendt & Adey, 1960), supraoptic (Brooks et al, 1962), anterior and posterior

(Stuart et al, 1964), and posterior (Stuart et al, 1964b).

If a particular stimulus such as simple light flashes can have these varied responses, generalized arousal must be even more effective.

In order to understand hypothalamic control function, we must conclude that the simplified idea of the single isolated feedback loop usually considered should be replaced by the view of multiple inputs leading, at any one time, to a pattern of outputs from the hypothalamus.

#### Neuronal and endocrine influence on the hypothalamic set-point

The influences on the hypothalamus which have been considered so far have been transitory. A stimulus is applied, a response is noted. The longest experiment has been three days for the avoidance training. But what happens with a prolonged stimulus, applied for an indefinite amount of time? Could it lead to a new steady state, a new "set-point?"

The concept of set-point appears in a systems analysis approach to some hypothalamic functions by Schadé (1970). In a feedback loop, recall, a set-point is the level at which the system registers change in input by a change in output. In a thermostat, for example, if the temperature drops below the set-point, the heater goes on until that temperature is again reached. In the hypothalamus, a rise in the level of circulating glucocorticoids above a certain set-point turns

off the CRF-secreting neurons,<sup>1</sup> and to a certain extent, a lowering below the set-point turns on the CRF-secreting neurons. The set-point of the thermostat is exogenously changed by someone changing the setting. All the influences on the changing of the set-point in the hypothalamus are not known, but two general categories of exogenous influence impinge on what Schadé calls the "hypothalamic integrating neuron" (the hypothetical cell which makes sense of incoming signals to the hypothalamus). The two categories of exogenous influence are: (1) synaptic (inhibitory and excitatory) and (2) microenvironmental factors. Within these two categories of influence, a distinction should be made between (1) factors inside the feedback loop and presumably responsive to the set-point, and (2) factors capable of changing the set-point. In general, factors within the feedback loop, such as specific microenvironmental "fact stimuli" for specific cells (e.g., temperature for thermostat cells; glucose for "glucostat" cells; and hormones, such as glucocorticoids, for "steroidostat" cells) are responsive to the set-point, but not capable of changing it. This is usually true when the stimulus is applied for a short period of time. However, some of these stimuli have their own metabolic effects on cells. If applied for a long period of time, they would be

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1. This statement is an oversimplification. In the hypothalamus, the set-point is not really an all-or-none point. All the incoming signals on a cell determine the nearness to threshold for a single neuron and all the cells that are firing determine the output of the hypothalamus.

capable of indirectly changing set-points by affecting the firing of all cells. Cortisol is a good example. It is capable of decreasing the electroshock convulsion threshold by increasing the excitability of all cells. In this way increased cortisol could participate in all set-points, including its own feedback loop (and in a direction of potential instability).

#### Environmental influences: glucocorticoids

Those cells which are involved in specific feedbacks are sensitive to the specific hormone or appropriate environmental change. The steroid-sensitive hypothalamic neuron is used as a prototype for this discussion.

Ruf and Steiner (1972b) and Steiner and co-workers (1968, 1969) iontophoretically applied glucocorticoid and ACTH directly to neuronal membranes and found steroid-sensitive neurons scattered widely in the hypothalamus, but none elsewhere. The number of steroid "minus-sensors," in Schadé's terms--those units which respond to corticoids by a decrease in firing rate--far exceed the number of steroid "plus-sensors." Most cells decrease firing rate (multiunit background activity) while some cells increase (single unit detects this).<sup>1</sup>

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1. Using single-unit recordings, Feldman & Dafney (1966) found that intravenous cortisol increased the firing rate of anterior hypothalamic cells as well as altering their responsiveness to incoming signals. Others (Ruf & Steiner, 1967; Sawyer et al., 1968) found that an analog of cortisol depressed multiunit activity in hypothalamic cells. An

The responses of steroid-sensitive neurons in the hypothalamus have several other characteristics important in the dynamics of control. (1) They may or may not be specific for glucocorticoids. A single neuron may be sensitive to different hormones and thus be part of several feedback loops. (2) These responses are part of the feedback loop. They are responsive to the set-point; they do not directly change the set-point. (3) However, the metabolic action of hormones must also be taken into account as capable of changing set-points, particularly in the case of glucocorticoids, which decrease the electroshock-induced seizure threshold in rats (Timiras, 1974) and are known to increase the electrical excitability of all neurons, indirect metabolic effects on all set-points.

Activating the glucocorticoid system by long-term stress is dangerous in this respect: An external stimulus is applied which transiently changes the set-point of steroid-sensors via synaptic inputs. More CRF, ACTH, and glucocorticoids are released and glucocorticoids negatively feed back onto the CRF cells to shut off their increased secretion. However, because of a maintained synaptic input, a compromise, higher-than-normal level of cortisol output is maintained. This increased cortisol increases the excitability of neurons metabolically, and if the stimulus is

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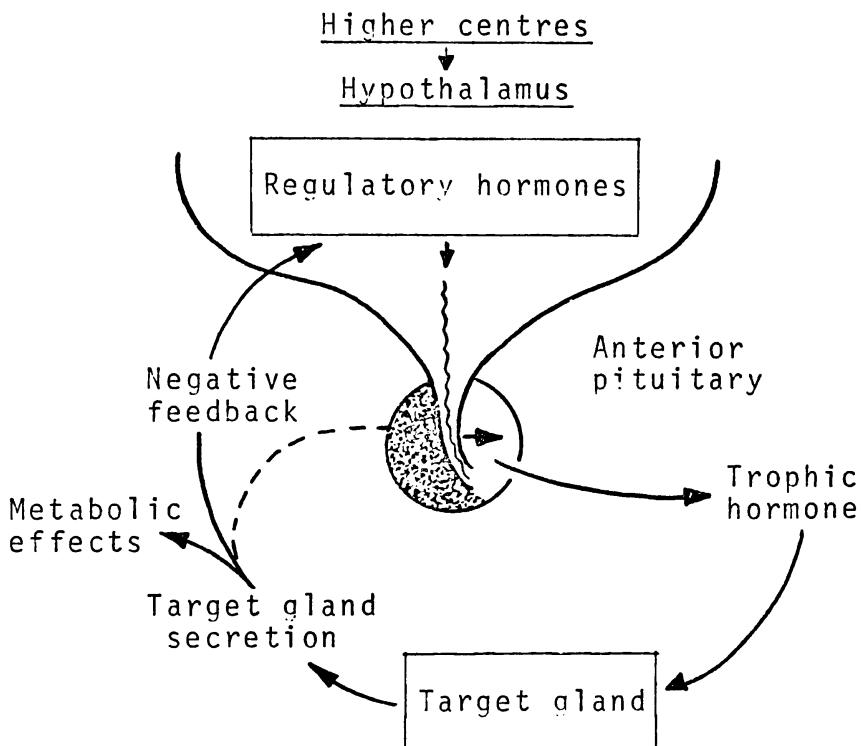
explanation of these two kinds of results with glucocorticoids is possible. Sawyer's group looked at multiunit background activity, while Feldman and Dafney studied single units.

maintained, a new steady state will be reached. The new steady state has a higher level of excitability for neurons and increased cortisol secretion. The metabolism in all cells will then be altered. Inasmuch as the set-point is determined by the steady-state level of (1) impulse activity impinging on the neuron and (2) the microenvironment, including hormone levels, cell metabolism, etc., and since both have been changed by the increased excitability from the increased cortisol, the set-point has been changed accordingly. If then the initial stimulus is removed, since the set-point has been changed, the resultant drop in cortisol will be read as too low a level of cortisol. CRF neurons will release more to compensate for the apparent deficit. Thus the baseline of cortisol, as well as increased sensitivity to environmental change could be expected.

#### Synaptic influence--override of feedback

The control of thyroxine secretion illustrates the principle that the activation of synaptic pathways and thus the level of excitation in the hypothalamus may be more important for determining the final output of even a specific system than individual, specific endocrine feedback systems. The relative significance of endocrine feedback directly on the hypothalamus as compared to other CNS inputs important distinction here. This is aptly summarized in a review article by G.M. Besser (1974):

The mechanism whereby the hypothalamus controls the anterior pituitary seems to be more subtle than merely constituting a simple sequence of chain reactions. The hypothalamic hormones are synthesized within the cell bodies of the nuclei of the hypothalamus and neurosecreted down their axons to be stored in their terminal dendrites in the region of the median eminence. The release of the stored hormone into the blood is under neurological control from higher centres involved in establishing time-dependant rhythms, responses to psychological factors such as stress, feedback control, and in reflex responses mediated by the peripheral nerves. In this way the system is entirely analogous to that related to the posterior pituitary.



After Besser (1974)

The total content of hypothalamic hormone in the median eminence seems to be very small (a few nanograms,  $10^{-9}$ g) and only minute amounts are secreted into the portal capillary blood at any one time. These substances then act on the pituitary cells to cause synthesis and release of trophic hormones in amounts which are probably a thousand or a million times greater than those of the incident hormone. In turn the pituitary hormones act on their target glands to cause them once again to produce between a thousand and a million times as much hormone. There thus seems

to be a "cascading amplifier" system greatly multiplying the original hypothalamic "signal." (My italics.) In a sense there is an additional amplification of the signal for there are behavioural changes induced by the target organ hormones both in the subject and in his environment which can be regarded as end results of the hypothalamic hormone secretion, but these are not easily measurable.

The hormonal amplifier model may be taken further for there are at least three levels at which the amplified signals may be "sensed" and the degree of amplification modulated. Chemical feedback occurs at the pituitary cell since target organ hormone levels interfere with the actions of the hypothalamic hormones and this is one way in which the classical negative feedback mechanisms work. In addition, circulating hormonal levels alter the secretion of the hypothalamic hormones themselves. Cerebral and psychogenic factors operating through an interaction between normal sensations and conscious and subconscious mechanisms within the reticular formation and through a final common path at the median eminence of the hypothalamus clearly can alter regulatory hormone secretion, and these mechanisms may be disturbed in disease.

In summary, then, whereas most of the simple regulatory models for feedback systems in the hypothalamus-pituitary-ANS axis describe the way a return to "normal" pre-stimulus state is effected, the purpose of this discussion is to outline a mechanism whereby maintained changes in the level of a hormone occur, via a change in set-point (either by direct neural changes or by certain changes in the internal environment). As a specific example, in thyroid control, hypothalamic stimulation can maintain increased thyroid activity even when the blood levels of PBI<sup>131</sup> (protein-bound iodine, a measure of thyroxine in blood) are elevated (Harris, 1960). This is a clearly demonstrated case where the CNS influence overrides the feedback control of an endocrine function. Thus if the general level of activity impinging on the hypothalamus is

increased or decreased, the circulating levels of thyroxine will be changed accordingly. It is not known how general a phenomenon it is, but other hormones under hypothalamic control may be similarly subject to the HES.

#### Synaptic influence: neurotransmitters

Besides being subjected to feedback hormones, steroid-sensitive neurons described by Schadé were exposed to neurotransmitters in order to mimic the activity of excitatory and inhibitory terminals on the sensors.<sup>1</sup> As could be expected from the difference in action upon the neuronal membranes of hormones and neurotransmitters, the hormones acted more slowly but lasted longer. Here a dual sensitivity is shown, both to circulating substances and to neurotransmitters presumably acting via presynaptic endings. Schadé presents similar characteristics and conclusions for a hypothalamic "thermostat." (Hellon, 1967; Eisenman, 1965; Feldberg, 1970; Schute & Lewis, 1967; Dyball & Koizumi, 1969) and a "glucostat" (Anand, 1967; Domura *et al*, 1969).

Schadé's overall conclusion concerning the "hypothalamic integrating neuron" is that it shows dual sensitivities: to excitatory and inhibitory neurotransmitters, and to environmental factors, such as temperature, glucose and hormones. Either environmental (metabolic, e.g., glucocorticoids

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1. In general, ACH increased the firing rate, while noradrenalin and dopamine decreased the firing rate, dopamine being the more potent inhibitor.

on excitability of nervous tissue) or synaptic mechanisms may be responsible for adjustment of the hypothalamic set-point. To make an argument for how such an adjustment occurs, take the case of corticoid-sensitive neurons. If excitatory input to these cells in the form of generalized arousal is somewhat greater than usual, they are brought closer to threshold. Then even the normal inhibitory effect of cortisol on the "minus-sensors" would be less likely to decrease the firing rate. At the same time, the effect on the "plus-sensors" would be enhanced. By moving the two populations of corticoid-sensors to a more activated state, the system is thus moved toward a positive cortisol-sensitive feedback loop. The minus sensors have been effectively neutralized. This would then be a probable instance in addition to thyroid control where central nervous effects can override a negative endocrine feedback loop.

The effect of converting a negative feedback loop into a positive one in such an important metabolic and immunologic regulatory system as the glucocorticoid would be profound. It is not even necessary for the negative feedback to be pushed all the way into a positive one. Just moving the hypothalamic set-point in the direction of greater CRF release (or less suppression of CRF) for a given stimulus reduces the adaptational range of the animal. Presumably it would also lead to exhaustion of the adrenals more quickly.<sup>1</sup>

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1. It is not inconceivable that this relates to the third stage of Selye's general adaptation syndrome.

Hypothalamic excitation, change in set-point and adaptational capacity

The simplistic notion that endocrine outputs of the hypothalamus are controlled by a single negative feedback ignores the basic question of how the steady-state levels of hormone secretion become established in the first place. It has been shown that (1) multiple inputs to the hypothalamus can influence electrical excitation in many of its areas, (2) multiple inputs can influence multiple types of output (hormonal, autonomic, behavioral) and (3) incoming electrical signals can and do control the steady-state level of hormonal secretion; therefore: (1) the level of hypothalamic excitation affects the various setpoints, hormonal and otherwise, and (2) any stimulus or stimuli which cause a change in central excitation over a period of time will probably result in changes in many, if not all, of the setpoints under hypothalamic control, including hormonal, autonomic and behavioral functions.

Adjustment of the setpoints will obligate the organism to reside, then, in different operational ranges, not all of which will be optimal or allow for greatest flexibility. In particular, it has been shown how stimulation of the CRF neurons for a prolonged period of time can have an unanticipated and self-perpetuating positive feedback effect on the CRF setpoint.<sup>1</sup>

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<sup>1</sup>Presumably all other neural setpoints are also affected due to cortisol's ability to increase the excitability of neurons generally.

## Appendix v

Consequences of Restricted Behavioral Response (Mobilization) to Stress

Two experimental examples, illustrating the possible consequences of stress activation where no behavioral mobilizing response occurs are now discussed. The first example is an experiment where an attempt was made to assess the relative importance of psychological versus physical determinants of the stress reaction. Urinary 17-hydroxycorticosteroid (17-OHCS) was used as a measure of stress when monkeys were required to exercise on a treadmill or to lift heavy weights in order to get their daily food (Miller & Mason, 1965). The monkeys displayed obvious signs of displeasure and emotional reaction at having to perform, and their urinary 17-OHCS response was marked; but it was highest on days when they refused to do the labor rather than on days when a substantial amount of work was performed. When, instead, they performed a climbing task for food, little emotional reaction and little, if any, urinary 17-OHCS change were observed, although a considerable amount of work was performed. Likewise, human subjects exercising in a relatively pleasant, non-competitive situation exhibit little, if any change, in plasma or urinary 17-OHCS at relatively substantial workloads (Jones *et al.*, 1970). Two conclusions can be drawn from these observations: (1) that exercise per se is not a particularly stress-inducing activity, and (2) that

lack of activity in the face of environmental pressure seems to be very stressful, and certainly more stressful than behavioral activity.

The second example is of experiments involving controllable versus uncontrollable shock situations using dogs (Seligman, 1972). The controllable shock situation is the typical escape-avoidance training in a shuttle box. At first the animal escapes from painful shock by jumping to a second compartment. It gradually learns to avoid the shock altogether. In the uncontrollable shock situation, the shock goes on or off independent of anything the animal does. At first, in this situation, the animal behaves as the dog in the controllable shock situation: it runs frantically about, defecating, urinating, and howling, but soon stops and sits or lies, quietly whining. In addition to impaired voluntary responding after being taken from the shock situation, uncontrollable shock produces more stress than controllable shock even when the amounts of shock received are the same (as measured by behavioral suppression, by defecation and conditioned fear, and by subjective report in humans). In rats, more weight loss, anorexia, and whole brain depletion of norepinephrine is found in animals experiencing uncontrollable as opposed to controllable shock. Again, it can be inferred from these experiments that lack of behavioral activity produces more stress than behavioral response when the noxious stimuli are contained in the environment.

## Appendix vi

Basic Anatomical-Physiological Considerations of Cardio-Vascular Control

The primary facts of cardiovascular control are well known and are sufficiently summarized in most advanced level physiology texts.<sup>1</sup> There are many factors which control blood pressure and heart rate. For example, in the case of BP, the peripheral resistance is influenced not only by sympathetic nerves and circulating plasma norepinephrine, but locally by such agents as  $\text{CO}_2$ ,  $\text{O}_2$ ,  $\text{H}^+$ ,  $\text{K}^+$ , and various metabolites and histamines as well.

Systemic control, of course, is affected by the dual enervation of the autonomic efferent system. Adrenergic (sympathetic) fibers end on all vessels in all parts of the body. Except for the heart and probably the brain, sympathetic fibers are vasoconstrictive in function. In addition to their adrenergic vasoconstrictor enervation, vessels of the skeletal muscles are enervated by vasodilator fibers which, although they are associated with sympathetic nerves, are cholinergic. This system, which is activated by centers in the hypothalamus, is called the sympathetic vaso-dilator system. These fibers are not tonically active, in contrast to the vasoconstrictor ones of most other vascular beds.<sup>2</sup>

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<sup>1</sup>E.g., Ganong, Medical Physiology (1971), chapter 31.

<sup>2</sup>Sympathectomy results in the dilation of blood vessels. The vasodilation is therefore produced by decreasing the rate of tonic discharge in the vasoconstrictor nerves.

In contrast to the enervation of the blood vessels, the heart is affected by impulses from both the sympathetic and parasympathetic. Impulses from the sympathetic adrenergic nerves increase the cardiac rate and the force of cardiac contractions. Impulses from the vagal (cholinergic) cardiac fibers decrease heart rate. And, although there is some tonic discharge from the sympathetic nerves, most tonic activity is from vagal discharge (vagal tone). Thus, when the vagi are cut in experimental animals, the heart rate increases. Similarly, after administering parasympathetic blocking agents such as atropine, the cardiac rate, in humans, increases to between 150 and 180 beats per minute.

The tonic vagal discharge is initiated at the dorsal motor nucleus of the cardio-inhibitory center of the medulla. (There appears to be no separate "cardio-acceleratory center.") Afferents from the baro-receptors of the heart and large arteries go directly and synapse in the cardio-inhibitory center. The reflex slowing of heart rate initiated by increased systemic arterial pressure is due to stimulation of this center.

The control of sympathetic vasoconstrictor discharge is controlled only to a minor degree directly by spinal reflex activity, and, for the most part, by the vasomotor center in the medulla oblongata. This center "is a diffusely extending one in the reticular formation starting just below the obex to the region of the vestibular nuclei and extending all the way to the floor of the fourth ventricle ventrally almost to

the pyramids." (Ganong, 1971) Stimulation of the rostral and lateral portions of this center causes a rise in blood pressure and tachycardia, whereas stimulation of a smaller region around the obex produces a fall in blood pressure and bradycardia (heart rate slowing). Originally, on the basis of these observations, it was postulated that separate vasoconstrictor and vasodilator centers existed with distinct efferent output; it now seems clear, however, that the influences are exerted solely through variations in the rate of tonic discharge in the vasoconstrictor nerves. The terms pressor area and depressor area, therefore, within a single vasomotor center, are generally accepted. It is known that excitatory fibers from the pressor area and inhibitory ones from the depressor area descend in different portions of the spinal cord and presumably converge on the pre-ganglionic vasoconstrictor neurons, which are the final viscero-motor pathways to blood vessels.

Thus, when vasoconstrictor tone is increased by an increase in the activity of the pressor (or by a decrease in the activity of the depressor area), there is an increased arteriolar constriction, a rise in blood pressure, (and, in addition, venoconstriction and a decrease in the store of blood in the venous reservoirs). On the other hand, a decrease in the discharge of the vasoconstrictor fibers causes vasodilation, a fall in blood pressure (and also an increase in the storage blood in the venous capacitance vessels). There is usually a concomitant decrease in

heart rate, but this is due to a separate direct stimulation of the vagal cardioinhibitory center. There is, again, no tonic discharge from the cardiac sympathetic nerves at rest.

The afferents that converge on the vasomotor center include, not only the very important fibers from the arterial baroreceptors and from the carotid and aortic chemoreceptors, but fibers from other parts of the nervous system as well, particularly from the limbic cortex relayed through the hypothalamus. Classically, these fibers are said to be responsible for the blood pressure rise and tachycardia produced by emotions and excitement. Pain also presumably causes an increase in blood pressure via these pathways and from the reticular formation.

The baroreceptors, which are anatomically stretch receptors, are located in the walls of the heart and blood vessels. The most important and best known, the carotid sinus and aortic arch, feed impulses directly back to medullary centers, where they inhibit the tonic discharge of the vasoconstrictor nerves and excite the cardioinhibitory center. This produces vasodilation, a drop in blood pressure, bradycardia, and a decrease in the cardiac output.

At normal blood pressure, fibers from the carotid sinus and aortic arch (so-called the buffer nerves) discharge at a slow rate. When pressure in the sinus and arch rise the discharge rate increases, and when it falls the rate declines. The response produced by increased discharge is a compensatory fall in blood pressure due to inhibition of

tonic discharge in the vasoconstrictor nerves. In experimental preparations, the carotid sinus of a dog, for example, is isolated and perfused. There is no discharge in the afferent fibers from the isolated sinus and no drop in the animal's arterial pressure or heart rate when the perfusion pressure is below 70 millimeters of mercury. At higher perfusion pressures (70 to 150 millimeters of mercury), there is an essentially linear relationship between the perfusion pressure and the fall in blood pressure and also the heart rate. As the perfusion pressure increases to 150 millimeters of mercury, there is no further fall in blood pressure. The carotid receptors respond both to sustained pressure and to pulse pressure, so that a decline in carotid pulse pressure without any change in mean pressure also decreases the rate of baroreceptor discharge.

Thus, the arterial baroreceptors with their afferent and efferent pathways constitute a reflex feedback mechanism that operates to stabilize the blood pressure and the heart rate. A drop in systemic arterial pressure decreases the inhibitory discharge in the buffer nerves, resulting in a compensatory rise in blood pressure and cardiac output. A rise in blood pressure produces dilation of the arterioles and decreases cardiac output until the blood pressure returns to its previous normal level.

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