PART IV

The Process of Chronic Disease Development

A. What is Health?

The concept of health is in evolution. Even today, in for example Guyton and Hall's well-regarded Principles of Medical Physiology, 2000, the underlying physiological principle of wellbeing is the "autonomaticity" of homeostatic regulation - echoing the predictability of a chemical reaction:

> "The very fact that we are alive is almost beyond our own control, for hunger makes us seek food and fear makes us seek refuge…Thus the human being is actually an automaton.(p.5) each cell benefits from homeostasis, and in turn each cell contributes its share toward the maintenance of homeostasis. This reciprocal interplay provides continuous autonomaticity of the body until one or more functional systems loose their ability to contribute their share of function." (p. 7)

Some readers may feel that such a summary perspective sounds "too predetermined" to work for our stress paradigm where a more proactive interface to the Environment may be needed. The same homeostatic self-regulatory platform that has allowed our ancestors to endure for ages in difficult environments, has in more recent millenia allowed us to shape our own environments. Ironically, it now allows some of us to shape environments in ways which are difficult for others of us to endure, in a manner not previously encountered in our natural experience. The salience of social demands in our contemporary world requires a model of active agency - for Homo sapiens sapiens at least - and thus an extended physiological model to match.

Recent emphasis is stress theory has focused on the organism's active engagement with its social environment and its costs. Allostasis (Sterling and Eyer, 1988) refers the organism's attempt to maintain its life sustaining stable flows though adaptation to environmental challenges, whether predictable daily routines or acute defenses. The physiological costs and health risks of this accommodation to external demands is labeled "allostatic load" (McEwan, 1998). Adapting the concept somewhat for this paper: allostasis refers to coordination of internal subsystems to respond to an external challenge (Figure _). Homeostasis refers to internally focused actions to maintain a baseline of capacity to support effective future allostatic actions.

A. Healthy Adult Capability Equilibria, Figure 2-A

Our definition of health in this paper is consistent with the overall Second Law approach in terms of its generality, adapted for living organism interaction with a demanding social environment (Figure 2-G). This model allow description of active control, and allows assessment of the costs of adaptation. Health is the organism's maintenance of the maximum operating capacity with respect to meeting environmental challenges - in the long term. The healthy individual seeks to maintain the most effective equilibrium-based processes for sub-system organization (its "capabilities"). This goal of "capability maintenance" means that the organism resists forced transformation of its internal organizing routines in a manner which causes reduction in capacity - toward a less effective set of equilibrium processes - and in fact naturally moves periodically toward increases in capability. Such resistance to degenerative shifts of internal equilibria is consistent with the near-to-equilibrium situations discussed in the above thermodynamics review. The healthy adult response capacity is summarized in Figure 2-A below where, as discussed above, Work to be done by the organism requires the "controller" to coordinate the organism's sub-systems into unitary action in a maximally effective manner to meet a specific environmental challenge.

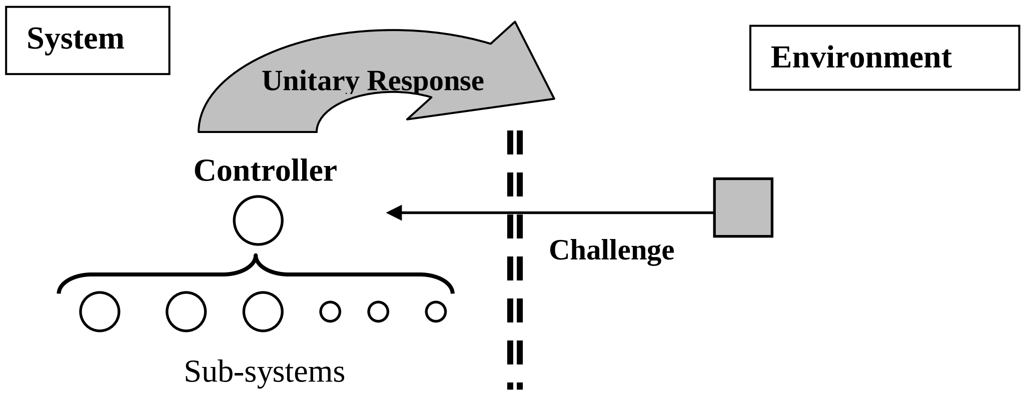
The process of movement toward less effective equilibria under conditions of loss of organism's control capacity is defined as chronic disease development (section __). Building on our Extended Thermodynamic Model's multi-level order and energy concepts, we can now further deduce several specific Implications of the Control Capacity perspective - for the organism's growth, as well as its disease, extending the list of Presumptions and Principles of the previous section.

(#8) Implication IIa

A level which cannot coordinate its sub-elements, or whose sub-elements cannot maintain their functions, may not be able to maintain an equilibrium based on past levels of environmental flows. Instability may occur, followed by development of alternative integrations of sub-elements at a diminished level of environmental flows (as in a chronic disease of the system).

(#9) Implication IIb

From time-to-time it occurs that multiple lower level elements coordinate their functions and differentiate their actions to create a new unitary capability at a higher level. They organize themselves in a new, collaborative manner so as to be able to gain increased energy/inputs from their environment, in such a way as to be able to sustain themselves with these new inputs (creation of a new, high-level function).



B. Early Childhood and Growth of Adaptive Capabilities, Figure 2-B

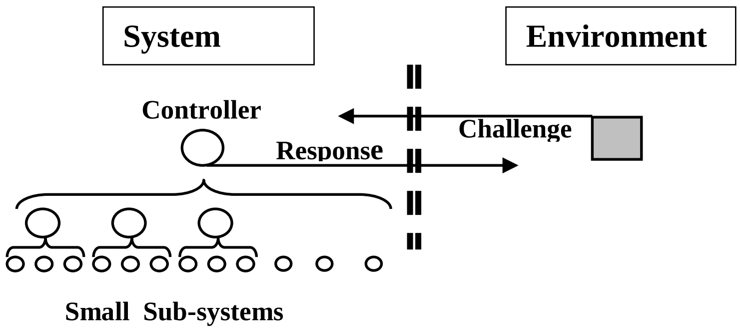


Figure 2-B actually logically precedes 2-A: it represents in the simplest schematic form, how sub-systems might have been organized into high-level "learning" in childhood or at other times during the process of growth and development

As we will see in Figure -B, the larger sub-system circles actually represent integrated function of even smaller sub-system - but these are operating in a form that requires minimal information for coordination (a patterned response) and thus the smaller sub-systems are no longer shown individually in Figure 2-a.

Utilizing the conceptual schemes of thermodynamics, we would calculate the number of states that each small subsystem could occupy - thus calculating the phase space and partition function discussed above - and thus the maximum entropy or control capacity. If each of the nine small sub-systems had 4 possible states, the total number of possible response to be reviewed by the controller would be very large (4 to the 9^{th} power = 16 million alternatives), a huge information processing task. However, consolidated into large, fixed "routines" of three small sub-systems each, perhaps each with two final states to choose between, the total is only 8 alternatives - a dramatic reduction which can bring feasibility to the decision process.

The process of development is based on collection of non-integrated sub-skills into a macro-level combination, for which the cost of organizing information have been dramatically reduced. There is a new "dance step" which now becomes routine - it becomes a learned or patterned response. Rather than each time making a weighty decision about what the state of the organism is supposed to be before coordinating a response to low levels of blood glucose (wherein molecule A must be linked to molecule B, and they both transported to location C), this response can be done through chemical mechanism that occur automatically, and in sequence: a patterned response. The set of sub-activities which before required much micro level information (costly in terms of entropy), now is initiated at a higher level in a manner which requires very low information content. Of course, the routine cannot any longer adapt to details of the situation, but that may be practically unnecessary. At this point the organism is clearly operating in a mode which can best be explained by the Next Higher Level of organizational explanation.

Freed from this micro-control burden, the controller can then focus its control capacity on higher level challenges: new explorations of the environment. Children progressively master very simple skills, make them routine, get on to more complex challenges which take them deeper into the environment. Thus, higher level organisms go much further in their active engagement with the environment. They become self-sustaining for long periods of time without parental help. At the beginning of their lives, however, the primary challenge is to coordinate breathing muscle moments with blood oxygen concentrations - a task requiring the first days of the infant's life - which soon becomes almost completely patterned and routine, and the platform for the next level of growth.

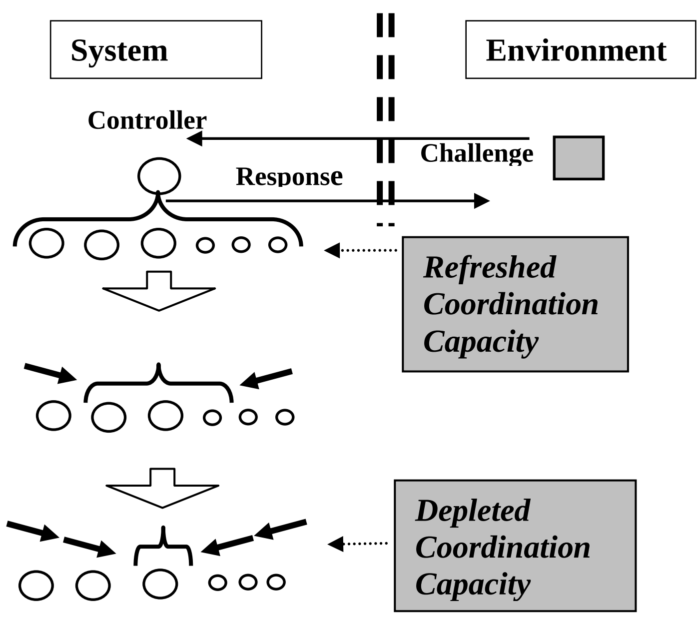
Growth is thus the systematic process of integrating micro-skills into lower information cost macro-programs to extend organizing capacity. (processes of growth and "regeneration" are also discussed at length in Karasek, et al, 1982, and creative skill development in an work organization context - "jazz behaviors" - in Karasek, 2004).

This may be a fairly routine behavior, but not " fully automatic," because the large scale routines need to easily adjust to very specific features of the challenge.

C. Threatened Equilibria: The Early Path of Disease Development - Figure 2-C and Figure 2-D

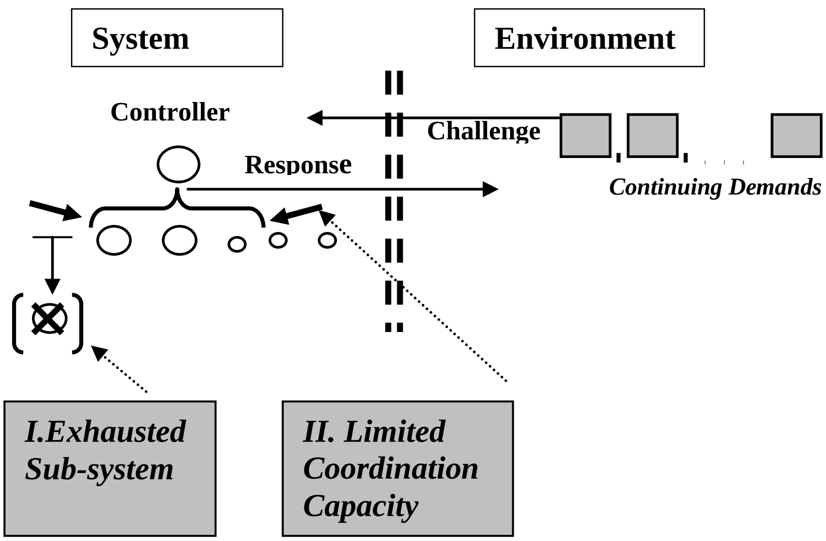
The stability that the organism normally enjoys may be disrupted by an overload of environmental demands - either larger demands, or more incessant in duration. Selye's classic stress physiology describes the resultant process of disease development, for example disturbed corticosteriod production as a result of long term stressor exposure (1956), and more recently, McEwan (1998) organizes human physiological evidence of the disease risks of these "allostatic loads." The model in diagram 2-D shows the depletion of one of the organism's physiological sub-systems in response to an environmental overload (I).

However, a second form of problem (II) has been focal is this paper: depletion of the control capacity of the central controller, depicted in Figure 2-C. In this case the controller has insufficient Control Capacity, fewer degrees-of-freedom, to maintain the highly coordinated response necessary to effectively respond to the challenge. This is more likely to be the case of a long-term external constraint on function - many more control states are removed from possibility, and for a longer period.



We recall from section __ above that the restricted control capacity in Figure 2C could be the result of the effects of low external control exerted in multiple locations: (1.) environmental interference with the organism's use of its optimal actions; (2.) Inhibition of anabolism both in terms of restricted investments in Platform Structure creation or inhibition of the NegEntropy transformation process. Additionally, it could be the result of social regulatory process above the organism level: (3.) such as the Division of Labor principles for organizations, or limitations on individual skill acquisition. Furthermore, there could even be (4.) restricted nutrient intake (although this later is actually a basal, First Law limitation).

Thus, both continual high levels of Demands without relaxation, or overwhelmed or restricted Control capacities can contribute to the equilibrium shifts of the disease process, in Figure 2-D. This is a physiological explanation of the high demand, low control "job strain" hypothesis. The Demand/Control model was based on sociological findings about the contingency of work demand effects dependent on work control on both salutogenic and pathogenic outcomes, the contingency of control effects dependent on demands - combined with the physiological evidence from Dement's sleep deprivation research relating to depleted control capacity (see Webnote#1), (Karasek, 1974, 1976, 1979, Karasek, et al, 1982, Karasek and Theorell, 1990, and Theorell and Karasek, 1996). Thus, the Stress-Diseqilibrium theory could be said to attempt to provide a more articulated explanation of the Demand-Control model hypotheses.



D. Transformation: Re-adaptation to A New Equilibrium - Lower Functional Level (Chronic Disease)

1. Step I: Stable Equilibrium and Homeostasis

The homeostatic equilibrium has a stability based on complex, inter-connected feedback linkages. Weaving of feedback linkages between sub-system components is what Prigogene refers to as "communication" (discussed in Briggs and Peat, 1989, p. 143), and through such communication the system holds itself intact. Biological systems remain stable is this way by damping most small pertubations through negative feedback. Such processes are mathematically "linear" and thus predictable - as long as they are relatively close to equilibrium (Prigogene, 1978, p. 778). This is important, it means much of the disease process explanation below, just at the edge of healthy response, is "linear"and therefore does not require the more complex explanations based on far-from-equilibrium non-linear thermodynamics - until Step III below.

2. Step II: Temporary Sub-System Compensation

After an initial successful response to a stressor, the stressor exposure may unfortunately continue, initiating the preliminary stages of a disease process: "exhaustion." The important next step in Selye's description of the stages of disease development is that to handle the load which is overwhelming its primary response system, the organism shifts to an alternative sub-system ("compensation," Selye, ••). Compensation is sought by reliance on other sub-system with available capacity (but possibly involving a distortion of their normal function), and may implicitly involve re-coordination of sub-systems to handle the load. This shifting is also noted by McEwan (1998), and discussed further below and in Figure 2-G.

The alternative of insufficient control capacity will yield the same result: high costs of response with a diminished complement of sub-systems, with small sub-systems responding in a non typical manner. Three types of processes that could occur - reducing the degrees-of-freedom - would be (a.) loss of balance in negative and (b.) positive feedback loop regulation, and (c.) consequent "resetting" or down-regulation phenomena (see evidence below_).

There is self-reported confirmation by human subjects of emotional correlates of such physiological processes: reported "exhaustion" is indeed predictive of future chronic disease development (Appels and Otten, 1992; Prescott, et al, 2003). We interpret "exhaustion" as the depletion of regulatory capacity (in section _•).

3. Step III: Equilibrium Shift

After a long time attempting to mange the load with an overwhelmed sub-systems, the transient costs of this poor performance mount up. The secondary systems are slower by definition, are harder to coordinate (since their precision for the new task has not been designed for), and less energy efficient. A spontaneous reorganization, reflecting the ambient resource limitation, and representing a lower overall cost of organization in the context the disrupted situation (a lower NegEntropic costs in the long term), will be sought. This organization will permanently change the equilibrium (see evidence below).

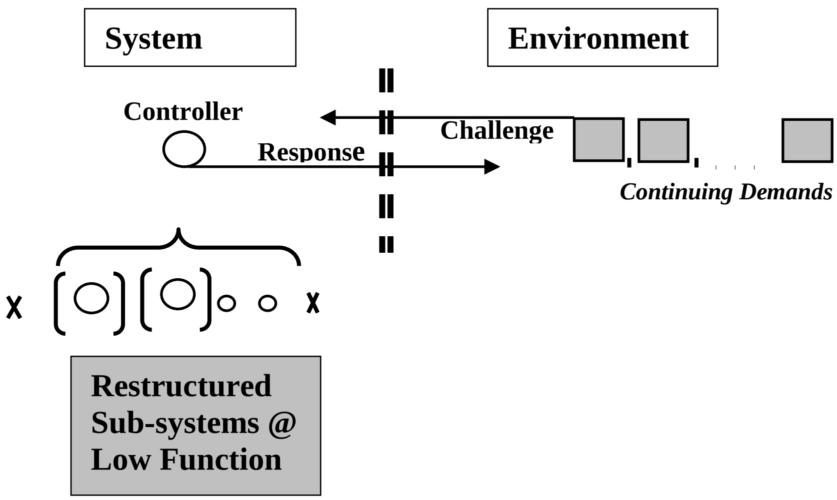
In the process the system may move"far-from-equilibrium, "loosing its balance," and system's response will becomes non-linear. An entirely new set of mathematical properties begins to govern the system from this point on (the dynamics of self-organizing systems) and it cannot be definitely predicted which new equilibrium will eventually develop. Prigogene's thermodynamic theories of new forms of organization in "energy-dissipating systems" (Nobel Lecture, 1978), and "chaos theory" apply at this point.

4. Step IV: Restabilized Operation with Diminished Capacity: Chronic Disease, Figure 2-E

Since the circumstance is a reaction to having insufficient ordered energy (by contrast to the excess ordered energy observed in the growth example above, 2-B) the system will tend to find an equilibrium of diminished capabilities (Figure 2-E) to adapt to its depleted potential. The remaining available systems will be, for example, slower in response or less efficient in transfoermation of energy into order.. Thus significant change of state of the organism occurs, possibly in conjunction with a disengagement from environmental demands.

Eventually the remaining sub-systems will now mutually adapt to this "impoverished" response and lock in on it as depicted in Figure 2-E, creating new sets of feedback loops with each other to stabilize the configuration. A new set of stable and linear "homeostatic" regulatory processes will now consistently reestablish the new sub-optimal system equilibrium: stabilizing the chronic disease state for the long term.

Such a very general explanation of the chronic disease process could fit any number of physiological systems - or several similtaneously. Indeed, this explanation would be expected to lead to multiple, related chronic disease - a situation termed "co-morbidity." The evidence for co-morbidity is strong is the case of a variety of stress-related chronic diseases such as Metabolic Syndrome X, involving diabetes, obesity, hypertension, and coronary heart disease (Brunner, et al 2002).



5. Equilibrum Shifting and Delayed Response Time, Figure 2-F

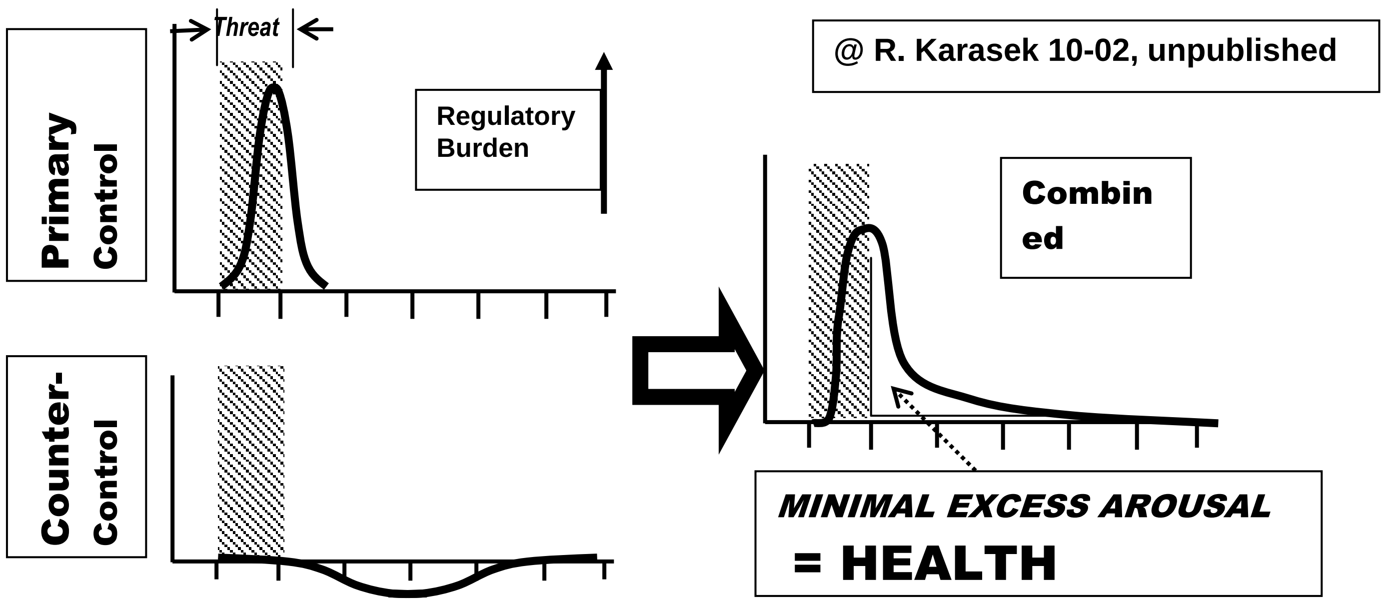
Figure 2-F tells the story of Figure 2-A to Figure 2-E from the perspective of stress-induced delays in physiological response over time. The upper section of the Figure - Healthy Response -shows an organism exposed to a normal stressor. This organism, for descriptive simplicity, is discussed as having one "primary physiological sub-system" that is dominant in the organism's response to the environment - the fastest, and more efficient response system. Furthermore, a physiological system's response is almost always counterbalanced by another counteracting sub-system - to maintain tight regulatory control. The response of the opposing systems will help counteract the first and return the organism relatively quickly to baseline - as can be seen to the upper right in the Figure. The quick return to base-line insures that the organism will be prepared to handle the next external stressor. This is the most efficient response pattern, where system arousal only occurs when it is needed.

In the bottom half of the Figure - Disease Risk - the organism is exposed to a continuing succession of stress. After this repeated exposure of the primary sub-system without sufficient time to return to baseline - or if the controller's degree-of freedom are restricted - the response of the organism becomes exhausted. The organism can no longer "get-its-job-done" in the environment, but the organism will, of course, not "expire" at this point. Instead, a secondary system will be activated to replace the depleted first-line system, a system which, almost by definition, responds more slowly. The rich multiplicity of systems available for cardiac output regulation and their time scales are shown by Guyton and Hall (2000, p. 207). The second system's counteracting system in turn, will yield a much slower overall return to baseline, and will likely be much less efficient in getting external Work accomplished, than the primary response system.

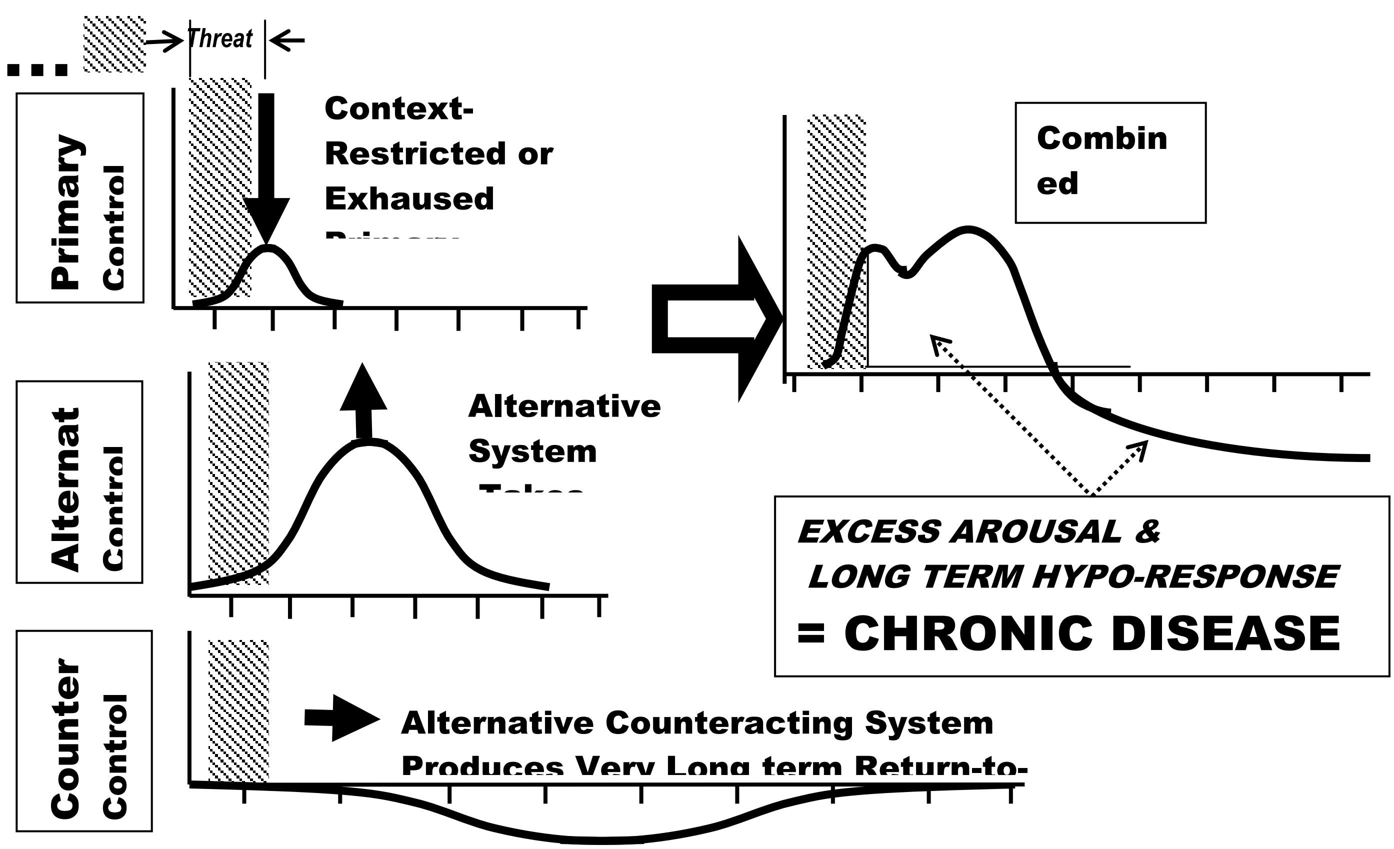
The organism will be in a costly, unneeded state of arousal for a long period of time. If the organism persists in facing the same level of external demands (for example: continues to go to work even when sick), it will soon exhaust the secondary system. This will require activation of a tertiary system to handle the load, and its counteracting sub-system will be slower still. The very slow response and chronic inability to re-attain a baseline state from which to effectively meet further demands becomes a quasi-permanent long-term reduction in adaptive capacity. Not only is this is uneconomic, but the prolonged duration out of an efficient equilibrium will facilitate a final shift of the organism to a permanently less effective equilibrium (Figure 2-E above). This is our definition of chronic disease.

STRESS DISEQUILIBRIUM HYPOTHESIS
of Chronic Disease Development

I. *Healthy* System Response



II. *Context-Restricted or Exhausted* System Response



Evidence for the Disease Process Hypothesis

Evidence I. Possible Evidence of Low Control-Induced Regulation Shifts

Much research now exists which specifically measures social situation and physiological response. However, typically, the details of "external control" are not directly measured in much of this material, but in some cases they can be clearly inferred.

Hans Selye describes a stress-related disruption of a negative feedback mechanism through with corticoids automatically depress the secretion of the very ACTH which normally stimulates the adrenal glands to produce corticoids. This feedback linkage during basal conditions is central in maintaining steady corticoid circulation in the blood. During stress, however, this mechanism is largely bypassed - a necessary result to maintain life during a stressful event, as with the baroreceptor response changes. However, the resulting elevation of corticoids can, if sustained over long periods due to chronic stress, have the major disease inducing consequences that Selye documented in decades of research - further noted below (Selye, 1956, p. 199). It should be recalled that much of Selye's evidence comes from animal subjects exposed to a sequence of stressors where control was totally restricted behaviorally. The experimental animal's plunge into the ice water bath was not optional.

Perhaps best known stress-related changes in feedback regulation are the short term baroreceptor sensitization changes that occur with the switch of organism from normal response to heightened arousal. This stress response adaptation allows the blood pressure to rise to abnormally high levels to combat an environmental demand. With restoration of equilbrium ("rest") however, there would need be no longer term adverse effects. The baroreceptor sensitivity changes of due to "mental arithmetic," for example, represent about two-thirds the sensitivity of a rest state (10.0 m/sec vs. 13.9 msec/mm; Conway, et al, 1984). An individual working two jobs and with young children at home would almost always be in such a "diminished sensitivity" state. In the longer term the consequences of diminished effectiveness of blood pressure regulation could accumulate and contribute to multiple noted adverse effects of high blood pressure. The observed association between low external control at work and drop in vagal cardiac response by Collins, et al, (2005- above) could reflect baroreceptor sensitivity changes.

"Down-regulation" represents an attempt to cope with a loss of control capacity at one level, which results in a loss of control capacity at a higher level. One example involves Post-Traumatic Stress Disorder (PTSD) and cortisol regulation. PTSD can certainly be considered an "ultimate low external control event" (as discussed below), and feeling of powerlessness is a defining characteristic of the trauma exposure. A PTSD review article (Yehuda, 2002) notes one mechanism which involves a modification of the "feedback control structures", which adapts to the continuing difficulty involved in stable psychological and social functioning after a traumatic episode. Long-term PTSD patients have higher levels of circulating norepinephrin and lower levels of cortisol, in addition to other biological changes. This cortisol decrease occurs in spite of both an initial increase in cortisol due the trauma, and also a sustained increase in corticotrophin-releasing factor (CRF). However, in PTSD, the increase in CRF does not lead to corticotropin release, due to increased sensitivity of the negative feedback loop in which cortisol inhibits the release of corticotropin from the anterior pituitary, and of corticotrophin-releasing factor from the hypothalamus. The long-term shifting noted here might result from restricted degree-of freedom in a system affected by cortisol levels (i.e., where cortisol levels cannot continue to remain high).

Certainly long term changes in cortisol levels can reduce the degree-of-freedom in other physiological systems. For example, receptor sites for fat cells "down regulate" with respect to insulin-directed uptake of fatty acids. This condition can be promoted by long term elevation in cortisol levels (Sapolsky, 1998, p. 60-61). This is the result of sufficiency in fat storage, but can reduce the degrees-of-freedom available for maintaining blood sugar regulation. Evidence of stress-induced long-term adverse effects of cortisol are well described by McEwan (1998), and in Selye's research.

Sometimes "down regulation" appears to represent an organism attempt to find a plateau's of temporary equilibrium - representing a more easily achievable adaptation to difficult environmental conditions - but also representing a further departure from the optimal state for the organism's overall survival. Warren, in an experiment (personal communication) with body temperature regulation in turtles, noted that as the turtles were plunged into ice-cold water they would first drop in body temperature and then stabilize at a lower body temperature level. When they continued to be held in cold water, their temperature would drop again, before reaching another lower temperature plateau - where body temperature would again stabilize for a time. This succession of unsuccessful attempts to "permanently adapt" would continue until the animal would not have survived an additional time exposure. As with Selye's subjects above, the organism's lack of external control was total.

<u>Evidence II. Equilibrium Shifts</u>

The equilibrum shifts can be "costly" adaptations. Schleifer (2002) has introduced a theory of work stress and musculoskeletal disorder involving a multistage deregulation process. The first step is normal response in stressful situations which leads to a change in both the rate and the type of breathing (a switch from diaphragm to chest breathing), but later steps can involve permanent regulatory changes that lock in musculo-skeletal disorder (MSD). The breathing changes lead to a drop in blood concentrations of CO-2, and increased blood alkalosis which along with the sympathetic arousal, in turn lead to vasoconstriction. This vasoconstriction is a very dysfunctional consequence in such "high performance situations" which caused the stress. Muscles might have to "work harder" to get the job done. The long term effect of the reduced CO-2 level is blood alkalinity, with eventually leads to reduced alkaline buffering of extracelluar fluids. This "down regulation" of the acid-base body fluid equilibrium, in the long-term, makes it difficult to sustain even everyday activity physical muscle movement. In addition, muscle tension increases particularly in the shoulder muscles (trapezius) which could further aggrevate the change in type of breathing - stabilizing the unfortunate condition. The result is that ever more extreme efforts to maintain work output precipitates ever further negative consequences, until regular employed work must stop altogether.

The deregulation processes can be driven to the point of tissue degeneration - when reversibility becomes even more difficult. Recent research has shown that pigs can be affected by a "porcine stress syndrome" (Casau, NYT, Oct 6, 2003). The problem begins with incredibly stressful living environments for pigs in agricultural factories - much of which is of course related to negligible degrees-of-behavioral-freedom (proding, tight restraint, and crowding to the extent of cannibalization promotion (Peterson, NYT, Nov 15, 03)). The nervous, excitable pigs have uncontrolled muscle twitching - and high body temperature. Stressful events in this context lead to acute hypermetabolic attacks resulting in very high temperature and low blood pH. This condition, when it leads to death in the pig, causes damaged pork meat in the form of denatured muscle protein (myosin) which cannot retain water and crumbles - giving the meat little commercial value.

The condition is resolved (presumably if not too advanced) by allowing pigs to rest or giving muscle relaxants. In this context - easily consistent with stress theory and the expanded chronic disease degeneration hypotheses here - it is surprising that researchers instead focus on "undiscovered genetic variations" related to defective calcium channels that could either be the cause of, or a pathway for genetically re-breeding the hyper-reactive pigs. (The pigs had actually been originally bread to be "lean", but then were also unfortunately found to be over-excitable). Above, we noted the thermodynamic imbalances which could affect calcium channel function and the clear consequences for heart muscle arrhythmia. The simple solution of increasing the pig's chances for "control" in their social environment would appear to be obvious.

It is noteworthy that the "opposite" process, wound healing, significantly is retarded by stressor exposure in human subjects, even in the relatively benign form of dental student examinations (Marucha, et al,1998).

<u>Evidence III. A case study - a possible reinterpretation.</u>

The definition of Post-Traumatic Stress Disorder (PTSD) is a response to an extreme stressor or event which is "traumatic" in terms of the fear, helplessness, or horror it induces, and which results in three types of symptoms: re-experiencing the event, avoiding reminders of the event, and hyper-arousal for at least 1 month (Yehuda, 2002). By this definition, a traumatic event could be considered an extreme example of "loss of control" or insufficient control capacity in stressor response, and indeed "powelessness" is one of its noted characteristics.

Many events which are potentially traumatic do not lead to PTSD in subjects who experience them. The likelihood that a difficult event will lead to PTSD appears to be somewhat dependent on whether their system is already in a "control-capacity-compromised" state when the event occurs. "Patients in whom PTSD develops have attenuated cortisol increases in the immediate aftermath of the traumatic event, which may be related to prior exposure to a traumatic event or other risk factor, … and also have higher heart rates [soon after the event], suggesting that patients with PTSD have a greater degree of activation of the sympathetic nervous system (Yehuda, 2002)" - and we add: exhausted control capacity. It is noteworthy also that there is a time course of progression of PTSD consequences: for example the exaggerated startle response is not usually seen in patients with PTSD until one month after the event (Yehuda, 2002, p. 112), presumably a period of alternative system "compensation" before physiological exhaustion.

As a case example of such stressor exposure we would suggest the following re-interpretation of a clinical case study of cardiac arrhythmia (Scully, et al, 2000; case 20-2000). A 61-year old man was assaulted and suffered a partial loss of vision - which continued until his visit to the hospital one month later with nausea, vomiting, diarrhea, profuse sweating, and an extremely high resting pulse of 200. Although the case study did not gather information to prove PTSD, the timing of the symptoms suggests that they may be the stress-related aftereffects of the assault - at least the beginnings of PTSD. This patient had arrhythmia symptoms for one day in the hospital, and was normal after the third day of hospital rest. Physicians had difficulty agreeing on a diagnosis, but ultimately specified a cardiac arrhythmia-related physical heart muscle deficiency (arrythmogenic right ventricular dysplasia), after rejecting the alternative of cardiopulmonary sarcoidosis, a fatigue related, diffusely-defined cardiac condition, also without known cause.

Our alternative interpretation is that this is an example where the physiological system's control capacity is exhausted - here manefested as loss of cardiac control, and digestive system control and a PTSD related loss of emotional control. This occurred after the man continued to sustain normal function in a weakened conditioned because of emotional load of the trauma and continued personal coping with the event's seriousness, in terms of a vision problem. The "typical one month delay" noted in the PSTD review above may reflect the duration that the average individual can mount a defense of the "sustained" consequences of such an assault episode, without hospital visit-inducing symptoms. He also had a family history involving traumatic events which along with physical injury is a potential PTSD predisposing factor (Yehuda, 2002).

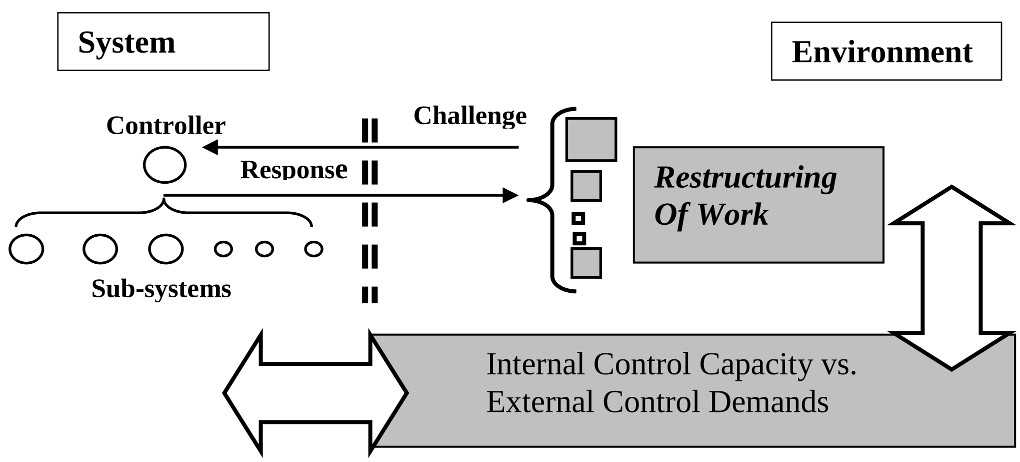
The accepted physician's diagnosis in the case review ultimately identified a "physical lesion" in the heart muscle: some fatty and fibrous tissue in one of three heart muscle biopsy locations obtained from this patient, albiet noting that such fatty tissue occurs often in older patients, and that typical electrographic finds were absent. While such heart irregularity could indeed be the consequence of a physical heart muscle defect, several noteworthy issues support an alternative explanation of a stress-related depletion of cardiac control capacity. Epidemiological literature also supports such a suggestion (Liao, et al, 1997; Greene, et al, 1972).

(1) The patient recovered to normal response with three day rest, before any major clinical intervention. Thereafter a defibrillator was implanted and he had one re-hospitalization with arrhythmia soon after and one other defibrillator event, but then no more cardiac symptoms during monitoring for another year and a half. If the underlying cause was a physical muscle deterioration, it might have been unlikely to spontaneously resolve itself so quickly. (2) The primary problem of this "dysplasia" physical defect is it is a quite diffuse diagnosis which is primarily identified after arrhythmia and sudden death (Scully, et al, 1996, case 34-1996, p. 1382) in some subjects, but our explanation of cardiac arrhythmia fits the "social trauma" and its exhausting consequences of the case in a tighter time sequence. The one month period before symptom onset is similar to other such time courses as the PTSD literature above shows, and a physical lesions of a muscle deterioration or an atherosclerotic processes could take longer to develop. (3) Finally, the main problem was the arrhythmia and elevated heart rate, but the literature has shown that it is difficult to identify clearly physical heart defects which definitively "cause" sudden death arrhythmias, notwithstanding that this is the largest single mortality category in industrialized counties (review by Huikuri, et al, 2001 NEJM). However, a Second Law-based exhaustion of control capacity explanation fits easily.

PART V

A. The Linkage between Internal Organization of Work and Worker's Health, Figure 2-F

The nature of work in modern society's social institutions is to create order out of disorder (as opposed to satisfying biological needs) - and thus could directly create uncontrollable internal physiological demands for individuals - and make them sick. Figure 2-F shows the internal organization of the work activity itself - on the environmental side. Rather than being an indivisible whole - like a predatory attack by the wolf - current environmental demands now are often built up out of components - which come from human organizations. Indeed human beings now create most work demands. Work demands are now disorganized components of work processes whose order is to be supplied by the human being - direct NegEntropy drains of our self-regulatory capacity. Our complex organizations generate further levels of social complexity to challenge the Control Capacities of our central controllers. This complexity of the "social organizational problems" also occurs with less regular break time, in a 24 hour a day 7 day a week economy with all adult family members often focused first on their work.



Since these demands are designed for some human beings by other human beings - there are now potentially social and political possibilities for modulating the nature of demands in a manner that could reduce the risk of chronic of overwhelming healthy, homeostatic balances and improve health. The worker could pursue the healthy strategy of maintaining its maximally effective response equilibria, by exercising control over the work demands in such a manner as to protect against overwhelming control capacities. This could be done by for example, allowing the human being to work after recovery periods (after "refreshing"), or allowing the worker social authority to group subtasks and social coordination so as to maximize fit with his/her particular skills (possibly trading or sub-contracting tasks to another worker), or allowing a worker to build a platform of long-term stability (as in the recent past). . Clearly, this is the most effective approach to avoid chronic disease when the demands come from social organizations - far easier than treatment of chronic disease where physiological equilibria have been already shifted in a quasi-permanent manner.

<u>The Wrong Forms of Work Organization</u>

However, it should be noted that many human work- organization philosophies, designed from the perspective of producing maximum output surplus for the organization, have made work more difficult - not less - than it was it the time of our genetic adaptation to the natural environment as hunter-gathers. For example, Frederick Taylor's Principles of Scientific Management, introduced at the beginning of the 20^{th} century manufacturing era, focuses on increasing work actions that involve sympathetic arousal to increase work output, while eliminating periods without apparent production - i,.e., rest - which are often periods of parasympathetic balance to sympathetic arousal.

Current Just-in-Time and Critical Path Method work organizational philosophies have as their central principle that whenever one segment of the work process is proceeding without difficulty more than another part, that the smoothly operating segment should have its resources removed until it just begins to fail - to avoid organizational waste - and increase overall surplus and profit. For example, worker's buffer stocks on assembly line, which are organized by them precisely for the purpose of increasing their possibility of control over their own physiological resource expenditures - are eliminated in both of these Lean Production philosophies - in hopes of reducing production costs, even if only by a few percent.

Mike Parker (1993) describes new Lean Production systems which attempt to reduce all "waste" but cutting the margin of worker's recovery even further. Parker describes an auto assembly plant which had a "score board " (andon board) on top of the assembly line with three colored lights indicating whether production was going smoothly (green), was stopped (red), or was about to experience delays (yellow). One might have expected, certainly according to the older (i,.e. mid-20th century) production organization models, that the most desirable condition from a manger's point of view was to see the production line running "green" - implying no problems. But in the Lean Production management approach, called by Make Parker "Management by Stress, "the goal of managers was to avoid green because it indicated that the work system is "wasting valuable resources" by not pushing itself the very limits of breakdown - into "yellow," and bordering on "red." Thus, if the line is running "green," management would cut workers resources or speed-up the line. All possibilities of worker's rest and recovery are being sought out in this system in a ingenious manner - and then eradicated.

The adverse physiological consequences of such work would seem hard to overlook, but because the work is often temporary (yet another stressor) it is hard to track employees for "scientifically credible" studies of the likely health costs.

B. Conclusions: Several Broad Political - Economic Speculations

1. The Grand Misfit? Man as a "cog-in-the-middle-of-the machine" does not fit.

Certainly human organization grow in a manner which has some similarities to our list of Principles in Table 3. Some organizational process might be likened to creation of a new level of physiological structure according to our Principles from section (#9) Implication IIb). This inference implies a different, more constructive, effect (also section IV, stage 2-B) than the main point in the paper that external social constraints could destructively limit the self-regulatory capacity of human beings - under other Principles (4, 5 and 8 Implication IIa). This contrast leads us to re-examine the scope of applicability of these principles.

For example, Henry Ford's creation of the automobile mass production assembly line process creates a new high-level structure - above that of hand-craft manufacture. This requires huge investments in stored energy - NegEntropy - the labor of producing the tools, jigs, and conveyors of the assembly line - where each "stored work component" is the output of some skilled craft operation on the level below (the "tool shop"). However, when this cost is spread over a 100,000 vehicles it becomes small and the mass produced car results in a major savings in production "cost" compared to craft production (if you accept the market pricing of human labor that is part of the center of the cost assessment) and the vastly expanded new revenue intake will make the new organization self-sustaining, according to capitalism's operating principles. Self-sustenance has surely occurred in this case - and caught on around the world, assisted by the personnel management techniques of Fredrick Taylor's Scientific Management. This new labor "ordering idea" has now, eighty years, later created a new level to modern civilization (or new sub-level on top of the factory system itself - the perhaps even more momentous innovation of the late 1700's).

The source of such work organization idea is no less that the primer for all of our modern global economic policy: Adam Smith's principle of the Division of Labor from his first Chapter of The Wealth of Nations (1776). The productivity advantages of human division of labor were said to come new forms of from machinery which could be used with specialized tasks (powered equipment is a separate form of explanation), saved movements, but the major savings was to come from avoiding the "learning losses" where a worker wastes time mastering many tasks as opposed to one narrow one (in fact the savings come from the reduced labor cost involved in using less skilled labor). Furthermore, a central principle of mass production is interchangable parts, based on the "constraint" of precision manufacture of each sub-component so that it will correctly fit into a larger assembly built completely independently. There is no room for variability from either workers or components in the well-designed assembly line.

A "Discontinuity" of the Stress-Disequilibrium Principles at a Higher, Social Level? -

But from the worker's perspective - based on our new Second Law understandings - this is also precisely where the problem comes: all possible orderings of tasks, usages of tools, rest times etc. which may be optimal from the perspective of the worker physiological and mental health have been foreclosed by the production process's rigid structure. While we have argued that internal "constraint's" create an anabolic structure for taking complex physiological action, the effect of external constraints is to disturb this possibly.

Human beings do not seem to adapt to being "cogs-in-the-machine," like the molecules at Level Two of our evidence table, when these organizations expand to a range where much of the activity is beyond our personal behavioral control. Thus, there appears to be an emergent property of organism's with the most complex central controllers that "maintenance of the flows" evolves to actions that are self-protective. This self protection is sought in "social organization" with other complex organisms (human beings). Protective social structures seem to be a necessary element of our social homestatsis." (Lysgaard, 1960). We can form large protective organizations as well, but even within these we can not appear to yield a needed sphere of "autonomous function," where we resist integration into a larger structure. Perhaps this is an emergent property in organisms as complex as animal life. Whatever the explanation, it would seem to imply a "break" in the validity of the principles we have outlined at lower physiological levels, as we attempt to carry them beyond family-scale social structures.

2. The Current Challenge of theThe Global Economy

In this light it is unfortunate that the impact of neo-liberal changes in labor markets and international production organization in the last several decades have meant that workers have lost the protections of paternalistic companies and national labor relations programs and are more exposed to pure market forces. Companies have outsourced jobs, and internal production processes relinquish control to environment-driven inventory chain systems (lean production), sometimes worldwide in scope. The resulting threats to workers are in overlapping areas: loss of company-level decision influence, loss of job security, loss of small-scale production control to new work systems and monitoring, a less protective social environment threatening workers basic security platforms and undermining trust.

The primary issue is the growing concern that the work situation no longer provides a stable platform for life and family development - something that in earlier times was provided in a package along with skilled performance and a wage - as a "job." The "job" is a support for starting and raising a family; it is a support for personal development in a career; it is the basis of a meaningful identity and social role in the society; and, related to all of these, the job is a daily platform of stable, manageable, and sustaining activity. This is the equilibrium of flows that our Central Controller of our Second-Law based model is charged to maintain. If the worker can maintain an easy equilibrium is his/her context, work can be used as the platform for further growth (family, career, etc.). The central question remains closely linked to the themes of this paper: how much "long-term, broad-ranged control" the worker has over his life, via his/her employment.

The exposure to market forces inherent in the neo-liberal political-economic paradigm implies that it is not just a particular organizational context that determines the level of job-insecurity now - for each individual - but global market forces and all their variability. A new, more general notion of control is needed than that employed in much of the "Job Stain" epidemiology (Section I) of the past two decades. An example of a broader formulation, still reflecting the Stress-Disequilibrium and Demand/Control principles, but addressing the larger scale social challenge might be: "'control' is the freedom to act using your repertoire of skills, within the social structures where you have made your social investments and where your get your major life-sustaining rewards."

Reflecting on political economic implications of the work organization comments above, it is hard to dismiss the most strident criticisms of sociologist and cultural critique Pierre Bourdieu (1998) who asks: " What is neoliberalism? A programme for destroying collective structures which may impede the pure market logic. … In this way, a Darwinian world emerges -- it is the struggle of all against all at all levels of the hierarchy, which finds support through everyone clinging to their job and organisation under conditions of insecurity, suffering, and stress. (p. 3, 1998)." Our control/health thesis simply represents one more critical new negative dilemma, to balance against the obvious effectiveness of the industrial organizations which for two centuries has supported the explosive growth of the species. The implication is that we need a very broad search indeed for new economic and political solutions. For example, even if company ownership were nationalized, the consequence of retaining the type of hierarchical, and destabilizing production structure above could create the same pressures during the central, "work time" part of our lives.

One quasi-alternative to reorganization of our workplaces and economic institutions is the growth of the modern pharmaceutical industry to provide more chronic disease "cures." Drug industry advertising promotions, health care viewed as consumer economic demand, and priority shifts away from the moral requirement to provide care for needy individuals are the path that have been so far prioritized as a cure for the chronic disease which we have discussed above in the US economy, and increasingly in other industrialized economies also. However, our understanding of system dynamics show that the risks of pharmaceutical interventions to restructure complex physiological dynamic processes that are attempting - with difficulty - to adapt to environmental demands, could not infrequently only complicate the overall dynamics of adjustment, which are often not understood in detail. Like a "turning up the flute" as a panacea for a dull sounding orchestra, it is a uni-dimensional and unvarying cure which fails to adjust to the complex harmonies of other instruments, and could spoil a concert.

Our global economy is rapidly creating new levels of social organization, with complex implications that could be reducing overall possibilities of maintaining stable life platforms for large groups of people. There is no question that historically new forms of social organization which have created surpluses have sustained themselves - even when initially based on simplistic hierarchical organization - and this is occurring now. However, it is also historically true that these structures have often had to be tempered with new revolutions in human moral and cultural development to find the "equilibrium" for human beings that these structures had failed to provide.

If mankind cannot now grow its hierarchical organizations without limits in the global economy because of the impossible costs for its lower status members, then what is to be done with the creative "organizing" drive that seems to have propelled the species thus far? Vanderberg (2004) speaks of stopping the development of "man in the image of the machine, " and recommends "Conducive Economy:" - a non-hierarchical mode of creative coordination in social production which constructs a form of social value based on human skills and capabilities (Karasek, 2004) rather than continued mass -production of physical goods on global scale. Perhaps this suggests a solution. While the change would be vast, so are the costs of overlooking the problem, and thus some solutions which embody similar social protections must be sought - to preserve the integrity of our -self-regulatory capacity. The payoffs and costs for internal self-regulation are of course supreme in Homo sapiens sapiens: the platform of our mental and social development. The costs must not be forgotten because the illuminate the true limitations of human adaptive capacity.