# Conceptualizing Compensatory Responses: Implications for Treatment and Research

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Many scientists approach the discovery and application of knowledge of physiological processes from a reductionistic paradigm. A reductionistic approach focuses on treating one or a few key disease-related variables but overlooks the interaction of systems and their dependency on one another to produce homeostasis. The purposes of this article are to examine the current paradigm underlying treatment and its effect on patient outcome and to present an alternative perspective for understanding the body's compensatory responses and their implications for treatment and research. Chaos theory and nonlinear methods are presented as possible ways to conceptualize and explore the complex integration of physiological patterns in response to disease, aging, and treatment.

**Keywords:** compensatory mechanisms; paradigm; homeostasis; chaos; nonlinear methods

I n recent years, scientists have emphasized reductionistic approaches to discovery and application of knowledge of physiological processes. Integration of this knowledge in clinical practice, however, has not always yielded the expected outcomes. For example, in a double-blind clinical trial in patients with acute congestive heart failure (CHF), patients whose cardiac output (CO) was normalized had poorer short-term survival than those treated with a placebo (Cuffe et al., 2002; Felker & O'Connor, 2001). Other scientists have also reported that normalization of a few key variables produced negative results in the treatment of CHF (Rathore, Curtis, Wang, Bristow, & Krumholz, 2003) and battlefield/trauma injuries (Cannon, Fraser, & Cowell, 1918; Champion, 2003; Wangensteen & Ludewig, 1969). The treatments examined in these studies were aimed at bringing a key physiological parameter back into normal range. One possible explanation for the negative outcomes when patient values were normalized,

at least in some cases, may be that treatments blocked the initiation of the patient's compensatory mechanisms and thereby adversely affected the homeostatic response. Treating one or a few key disease-related variables, a reductionistic approach, overlooks the fact that systems interact and depend on each other to produce homeostasis. Failure to consider the body's interconnected systems may initiate collapse of the compensatory response and lead to potentially lethal complications.

When advancing science, Heitkemper and Bond contend it is necessary ". . . to think comprehensively about variables contributing to a phenomenon, and . . . to consider not only single variables but the dynamic interaction of those variables as well" (Heitkemper & Bond, 2006, p. 153). Central to this paper is the common assumption in science that the body responds to disease (i.e., alterations in normal physiological processes) using compensatory mechanisms. The compensatory responses are likely controlled by a large number of different feedback loops of varying temporal quality, which need to be considered when planning treatment. Thus, the purpose of this article is two-fold: first, to examine the current paradigm underlying treatment approaches and its effect on patient outcome by using empirical evidence from the research literature, and second, to

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present an alternative perspective for understanding the body's compensatory responses and their implications for treatment and research. In the concluding section, we draw attention to ways of examining complex phenomena and compensatory responses with examples using chaos theory and nonlinear methods.

## Current Paradigm Underlying Treatment Approaches

The prevailing reductionistic paradigm focuses on the body's response to disease and treats the response by correcting one or a few major physiological variables without considering the expansiveness of the body's reaction. In shock, for example, hypotension is a primary sign that is pharmacologically managed to "normal range." This approach ignores the totality of the body's response to shock and treats one outcome of the problem without addressing the cascade of events that produced hypotension, such as the release of inflammatory mediators, changing volume, and hormonal and chemical responses initiated by the baroreceptor reflex.

This approach to treatment is also apparent in studies of trauma/battlefield injury and CHF. In trauma/ battlefield-induced hemorrhagic shock, treatment focuses on fluid resuscitation to maintain critical organ perfusion assessed by level of consciousness, pulse rate, blood pressure (BP), and urine output. An important variable treated in hemorrhagic shock is BP, but normalizing BP as an end-point of resuscitation has been questioned (Bickell et al., 1994; Capone, Safar, Stezoski, Tisherman, & Peitzman, 1995; Shoemaker et al., 1996). Normotensive resuscitation can cause increased bleeding, severe hemodilution, decreased blood viscosity, and disruption of newly formed clots (Wangensteen, Eddy, & Ludewig, 1968). An alternative resuscitation strategy, permissive hypotension (whereby the mean arterial pressure [MAP] was maintained between 40 and 60 mm Hg instead of being normalized to 80 mm Hg or above) was developed during World War II for patients with multiple injuries and active or uncontrolled bleeding. Permissive hypotension has yielded better survival rates for both animals and people experiencing hemorrhagic shock (Bickell et al., 1994; Capone et al., 1995; Gross, Landau, Klin, & Krausz, 1989; Kaweski, Sise, & Virgilio, 1990; Kowalenko, Stern, Dronen, & Wang, 1992; Stern, Dronen, Birrer, & Wang, 1993). These findings suggest that normalizing BP may be less than

ideal for treatment of uncontrolled hemorrhagic shock. In contrast, permissive hypotension may support homeostasis by allowing the body's compensatory response to unfold naturally.

Treatment of hypotension with aggressive resuscitation posthemorrhage has been linked to poor clinical outcome. Two possible explanations have been cited: the amount and timing of volume replaced and the type of fluid used for replacement (Bickell, Bruttig, Millnamow, O'Benar, & Wade, 1991; Bickell et al., 1994; Burris et al., 1999; Rhee, Koustova, & Alam, 2003). Survival was improved when prehospitalization fluid resuscitation (90 minutes posttrauma) was targeted at maintaining a MAP of 40 mmHg in contrast to no fluid resuscitation during this phase or resuscitation with a targeted endpoint of MAP 80 mmHg in a rat model (Capone et al., 1995). Treatment success may depend on implementing strategies that not only do not turn off compensatory mechanisms but also support these mechanisms. Crystalloid intravenous fluids used to replace blood loss may induce neutrophil-mediated tissue/cellular injury leading to acute respiratory distress syndrome or multiple organ failure (Alam et al., 2000; Kermarrec et al., 2005; Rhee et al., 2003). In contrast, the use of natural products, whole blood, or albumin has not been associated with negative outcome (Alam et al., 2000; Rhee et al., 2003; Sun et al., 1999). It may be that natural solutions support the body's compensatory responses and preserve key organs until equilibrium is restored. However, further research is needed to test these hypotheses using larger, more rigorous, blinded control studies.

During CHF, a decline in CO results in the initiation of three major compensatory mechanisms: (a) sympathetic nervous system activation to increase pumping and constrict the blood vessels that increase BP; (b) activation of the renin–angiotensin–aldosterone system (RAAS) resulting in increased preload to maintain circulating volume; and (c) the final, more long-term compensatory mechanism, hypertrophy of the left ventricle to manage the increase in workload. This combination of compensatory mechanisms maintains normal or near normal CO early in the disease course, but with progression, compensation becomes less effective and a destructive cycle begins. The compensation-to-decompensation response obeys a given set of rules in a specific natural order at both the macro and micro levels, with changes at the macro level appearing to enfold those at the micro level in nonlinear ways. At the macro level, a change may involve altered function of an organ or

system, while at the micro level a chemical or hormonal signal may result in the initiation of a second messenger response and subsequently the upregulation or downregulation of a protein leading to an alteration in cellular response. From a research perspective, this integrated response creates difficulty in teasing apart changes at the macro and micro levels. To systematically study the integrated response, baseline data need to be investigated for individual cases, examining how various mechanisms interact within individuals, before proceeding to study commonality in responses and interactions across groups of participants.

Treatment of chronic decompensated heart failure provides insight into the need for an alternative treatment paradigm that considers more than the primary disease-defining factor and the myriad of compensatory responses. CO can be normalized in acutely hospitalized decompensated heart failure patients using natriuretic peptide, vasodilators, or positive inotropic drugs. Analysis of data from the Acute Decompensated Heart Failure National Registry (ADHERE Study) revealed that while these three categories of drug therapy all improved CO, contractility, and dyspnea (disease-defining factors), patients had a longer length of stay and a poorer one-month survival when using the positive inotropes dobutamine or milrinone (Abraham et al., 2005). Increased mortality was also reported in studies comparing positive inotropes (milrinone, digoxin) to placebo (Cuffe et al., 2002; Felker & O'Connor, 2001; Packer et al., 1991; Rathore et al., 2003). The mechanism for increased mortality was linked with increased myocardial oxygen demand and presumably the increased arrythmogenic effect associated with inotropic therapy (Abraham et al., 2005). An elevation in circulating levels of aldosterone, norepinephrine, and endothelin-1, along with an increase in adrenergic stimulation, have also been implicated (Zineh, Schofield, & Johnson, 2003). Thus, short-term outcomes of treating CHF by placebo, vasodilators, or natriuretic peptides promoted favorable outcomes, while treating with positive inotropes decreased survival.

Considered collectively, these findings suggest that varying outcomes are obtained when treating CO by targeting different components of the compensatory response. As a result, changes in practice have been initiated. For example, rather than using traditional medications that ameliorate the gross hemodynamic manifestations of decreased contractility and CO, agents that modulate neurohumoral derangements are now being used to obtain more

positive results (Yancy et al., 2004). Continued research identifying other body networks that participate in the CHF process will lead to further improvement in patient outcomes. Although the above research has yielded valuable clinical information, this research has not expanded the depth of understanding about whole body response. Research using analytical methods designed to obtain data about the ongoing cross talk among multiple systems would provide a view of the whole body response and make a valuable contribution to the literature.

In summary, the current paradigm underlying treatment approaches has focused on correcting the disease-defining characteristics and bringing these values back to normal range. Although examining and correcting key variables have promoted great advances in understanding and treating disease, outcomes of treatment are variable. Empirical findings suggest that the tendency to fragment the body into parts and overlook the dynamic interconnection of the whole may lead to untoward outcomes including death. At this crossroad, researchers are challenged to examine physiological processes underlying compensatory responses for their complexity of interaction and the resultant implications for treatment.

## Compensatory Response

Our understanding of compensatory mechanisms in health, disease, and aging is incomplete. The body's response is signaled by internal and external environments and is mediated by a myriad of compensatory mechanisms that have a synergistic effect to restore homeostasis. Compensation involves adjustments by processes/systems not involved in the primary process that triggered the problem. Thus, compensatory mechanisms promote homeostatic balance until the problem can be corrected or modified, or decompensation occurs. Compensatory mechanisms are not likely to turn on and off, but rather operate over a range, increasing and decreasing when needed to maintain environmental stability as patterns change. Central to the operation of homeostatic balance is variation, cooperation, selection, and reinforcement by compensatory mechanisms to achieve dynamic equilibrium through incessant replacement and exchange of physiological resources. Precise regulation requires effective communication among cells, tissues, organs, systems, and the whole body. The more important the variable for whole body response,
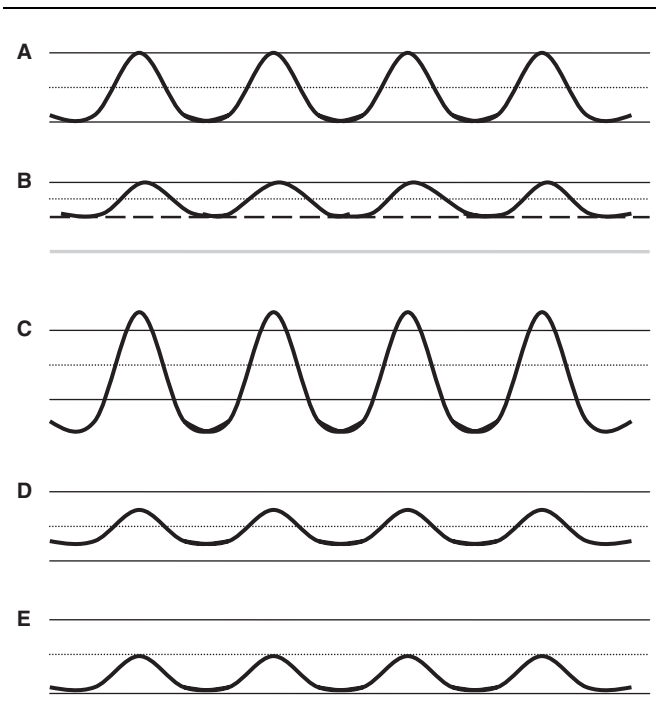
**Figure 1.** Hypothesized changes in compensatory response and effects on homeostasis under normal, aging, and disease conditions. For each of the diagrams, the outer lines represent the boundaries of homeostasis. The undulating line represents the body's compensatory response. The perforated center line represents the center of the range—ideal balance. (A) Normal fluctuation in body response by compensatory mechanisms to maintain homeostasis. (B) An upward shift in the boundaries (represented by the heavy dashed line) and center, resulting in a more restricted range indicative of resetting the homeostatic range. The lighter bottom line indicates the previous boundary that has been reset. This shift may be seen with aging. (C) Exaggerated response by compensatory mechanisms that results in fluctuation outside of the homeostatic range as may be seen with disease. (D and E) Underactivation or failure to activate the full range of the compensatory response may compromise homeostasis when shifts in the internal and external environment occur. (D) Shows the restricted response around the center line, while (E) shows a downward shift and failure to reach a maximal response.



**Figure 2.** Impact of treatment (Tx) on compensatory response. (A) Treatment corrects the body to homeostatic range. With discontinuation of treatment, an abrupt decline outside of homeostasis occurs suggesting compensatory responses were insufficient to restore balance. With resumption of treatment, balance is restored. (B) Treatment corrects the body to homeostatic range, but with cessation of treatment, there is a gradual decline in response over hours to days. Eventually homeostatic response falls outside the range.

waste, cell membrane receptors), or secondary messenger systems, resulting in physiological distortion of the internal environment, which can negatively affect survival.

Variation is expected in health. Homeostasis, while remaining an integrative process throughout the life span, changes with disease and aging. Interventions that fail to consider these changes in concert with the holistic and dynamic nature of the compensatory processes may interfere with restoration of the body to the evolving, functioning range. When balance is altered, as in disease, compensatory mechanisms acting singly or in concert are triggered at all levels (cell, tissue, organ, system, whole body) to stay within the range boundaries. Each process that contributes to the compensatory response is likely to have its own rhythm within the whole response, initiating and ending at different times. Thus, there are complex interactions among multiple macro and micro regulatory processes that operate over different time frames. Both time frames and boundaries can be altered by disease and aging.

The hypothetical diagrams in Figures 1 and 2 show normal and evolving homeostatic balance in response to disease, aging, and treatment. These diagrams aid in the conceptualization of the body's compensatory responses as it strives to attain and maintain homeostatic balance. Figure 1 (A through E) shows postulated changes in the compensatory mechanisms under a variety of conditions such as health, disease, and aging.

Although slightly different, Figure 1A and B illustrate normal variation in the upper and lower limits that define the range of homeostatic balance. The difference in Figure 1A and B is that Figure 1B has a more restricted range, which is typically seen with aging. Aging (Figure 1B) alters the range not only

the more numerous and complicated are the mechanisms to keep the value within the desired range. For example, pH is one of the most precisely regulated variables in the body. Some evidence exists that acidosis is protective during illness and facilitates the release of oxygen at the tissue level (Tombaugh & Sapolsky, 1993). Responses to correct tissue acidosis are not independent mechanisms but multilayered, part of an indivisible system response that suggests wholeness. Interfering with or blocking compensatory responses by normalizing pH may turn off key systems (e.g., capillary exchange of gasses and
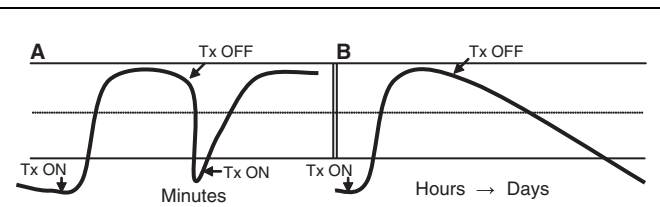
by shifting it upward but also narrowing the range boundaries. Variation in homeostatic boundaries with aging suggests that the range of response by compensatory mechanisms is similarly altered.

The loss of adaptability and feedback control seen with aging and disease (brain death, postmyocardial infarction) may be linked with autonomic nervous system (ANS) dysfunction. With aging there is a shift in the predictability of the system and resetting of the regulatory range (Lipsitz, 2002). In the elderly, for example, the normal range of BP is increased, thus, "normal" is reset. Homeostatic mechanisms become less effective and the individual is less able to tolerate disturbances in the internal and external environment, which may lead to illness and death (Lipsitz, 2004). Additionally, heart rate variability is greatly reduced or absent, simplified, and more cyclical in adults over 70 years, as well as in adults with heart disease (Goldberger, 1991; Kuusela, 2004; Lefebvre, Goodings, Kamath, & Fallen, 1993; Sugihara, Allan, Sobel, & Allan, 1996). These changes in the complexity of the cardiovascular system may be reflective of the breakdown or decoupling of integrated physiological regulation and may signal impairment of the system's ability to adapt to internal and external environmental stimuli. Lending further support to the ANS hypothesis of changes with aging, a reduction in heart rate variability is seen in premature infants, but with ANS maturation, an increased complexity in heart rate variability is found (Sugihara et al., 1996).

Figure 1C reflects a response which at times falls outside the homeostatic range. In sepsis, for example, there may be an overexaggerated response to the infection leading to immune system collapse (Sharma & Eschun, 2004). Another example is the increased vulnerability to excitatory neurotransmitter substances following trauma in the aged brain, which leads to an overexaggerated response to stimuli (Hamm, Jenkins, Lyeth, White-Gbadebo, & Hayes, 1991).

In contrast, Figures 1D and E reflect an underreaction and limited variability to baseline stimulus, which may lead to the inability of the body to mount a sufficient response if challenged. Although both figures are depicted in the normal range, failure to cover the full range of response may result in the failure to activate the totality of the compensatory response necessary for health. In wave analysis of electrocardiogram (EKG) traces, for example, the notable lack of variation in the 24-hr pattern, despite increased periods of activity, has been linked to mortality (Bigger et al., 1992; Kleiger, Miller, Bigger, & Moss, 1987). Similarly, less variability or an underactive response has been associated with patients with gastroparesis in regard to the amplitude and shape of duodenal contractions (Michoux et al., 2000). Both under- and overexaggerated responses, when occurring in disease or trauma, may cause the response to more easily fall outside of the homeostatic range (not depicted in Figure 1C through E).

The key points about homeostasis and compensatory mechanisms are summarized below

- Systems interact and depend on each other to produce homeostasis.
- Precise regulation requires effective communication among cells, tissues, organs, systems, and the whole body.
- Compensation involves adjustments made by systems not involved in the primary problem.
- Compensatory mechanisms promote homeostatic balance until the problem can be corrected or modified, or decompensation occurs.
- The more important the variable for whole body response, the more numerous and complicated are the mechanisms involved in maintaining homeostasis.
- Regulatory processes operate over different time scales.
- The body responds to aging and disease using compensatory mechanisms which evolve.

## Implications for Treatment

The above descriptions of homeostatic response, if accurate, have important treatment implications. Clinicians need to be sensitive to these variations in patterns of compensatory mechanisms so that interventions are supportive of both the body's normal initiation and sequencing of compensatory response. Interventions that interfere with the cascade of cellular through systemic responses may prematurely disrupt or halt processes vital for positive outcomes. There may be instances where it is inadvisable to treat back-to-normal range. As previously described with battlefield trauma, when transport is delayed by hours or days, aggressively returning the BP to normal may actually increase mortality from hemorrhage due to reversal of the vasoconstrictive compensatory response and the negative cascade of events that follow (Rhee et al., 2003). In recognition of this, practice under battlefield conditions has been modified to avoid interfering with the body's compensatory response until patients reach the surgical theater.

We conjecture that allowing the body to initiate a broader array of compensatory response to insult by allowing the range of key variables to remain abnormal (not corrected to |absolute| normal) could be beneficial to recovery. However, empirical research is necessary to establish the ideal range over which compensatory mechanisms are effective. Supporting the body's compensatory response to internal and external environmental insult may have implications for a wide range of clinical scenarios. Implications for treating out-of-range variables are shown in Figure 2A and B. Treatments can have variable impact on compensatory cycles. In the diagramed scenarios, pharmacologic intervention may quickly restore homeostatic balance to normal range while turning off or blunting seemingly unneeded compensatory mechanisms. With discontinuation of treatment, the body's ability to maintain homeostatic balance may be rapidly lost, precipitating an abrupt drop in the monitored variable and requiring the immediate resumption of therapy (Figure 2A). For example, when moderate to severe hypotension occurs and intravenous norepinephrine administration is interrupted, an immediate fall in BP occurs and treatment must be reinitiated. This scenario may reflect the need for additional time to upregulate muted compensatory responses to reestablish balance. Figure 2B shows temporary stabilization in the monitored variable followed by a gradual decline over hours to days rather than a sudden decline. The delayed loss of equilibrium may result from an initial ability of the compensatory mechanisms to hold the monitored variable in range; later, due to fatigue effect or being overwhelmed by additional changes in the internal or external environment, decompensation occurs. The danger of the scenario depicted in Figure 2B is that the critical decline likely occurs postdischarge, resulting in early posthospital morbidity and mortality.

## Timing of Interventions

Treatments need to be titrated by monitoring disease-defining variables as well as the body's compensatory responses and by adding or subtracting additional therapies based on clinical responses. The timing of the intervention may be important to synchronization of multiple compensatory processes. If several processes are synchronized, they may need to be tackled comprehensively in the treatment plan. Long feedback loops may serve to time other feedback loops

linking the systems, and poorly timed interventions may interfere with the body's ability to achieve a fully compensated response and homeostasis.

One piece of evidence on how timing of treatment withdrawal can negatively impact outcome may be the rebounding effect noted when oxygenating premature infants. At birth, oxygen ($O_2$) regulation is not fully operational. In the presence of reduced oxygenation, increased vascularity is noted in the retina. Oxygen therapy which provides excess $O_2$ produces the cessation of vascular growth in the retina. However, when $O_2$ is removed, one response is an overgrowth of retinal vessels, resulting in the extrusion of vessels into the eyes' vitreous humor causing blindness and the condition known as retrolental fibroplasias (the end stage of retinopathy of prematurity; Guyton & Hall, 2006). This response suggests the type and initiation of treatment may be as important as the timing of withdrawal of treatment.

Another piece of evidence to support the value of timing of treatment relates more broadly to the developmental age of the patient. Vascular development and adaptive metabolic response of tissue change with age. Tissue vascularity in neonates will adjust almost exactly to match the needs of tissue for blood flow; whereas, in older individuals tissue vascularity frequently lags behind the needs of the tissues (Guyton & Hall, 2006). Variability of response at different developmental ages may reflect the evolution of the complex body system. Age-adjusted treatment that takes into account the changing complexity of response must be considered to avoid eliminating or placing added strain on functioning compensatory mechanisms.

New ways of conceptualizing and understanding what is happening within the body in response to aging and disease are needed for achieving the best outcomes following treatment and intervention. Consideration of alternative paradigms and models that recognize the complexity of the body's response to disease and aging as it changes over the life-course may be useful for designing treatments that complement and support compensatory mechanisms.

## Examining Integrative Systems

An evolutionary framework that elucidates the complexity of the physiological system will enable scientists to characterize the salient features and rhythms that define disease and aging. Chaos theory

is only one example of a conceptual framework within which to examine multilayered responses. Chaos theory moves away from the deterministic and mechanistic worldview toward examining the nonlinear effects that manifest complexity, dynamical processes (changes with time), and evolving systems. This worldview fits well with the body. In the body, the whole system is undergoing a coordinated movement such that seemingly unrelated changes in organ response may give the appearance of disorder/chaos, when, in fact, an underlying order exists. Properties cannot be deduced from the parts composing them but rather the transformation of these structures that delineate the complexity of the response (Gleick, 1987).

A conceptual framework, organized by the whole instead of behavior of the parts, recognizes the complexity of the body, which is capable of learning and reacting to changes in internal and external environments. Chaos occurs in any system where unpredictability suddenly increases to the point that order disintegrates. That very chaos gives birth to new order. Chaotic systems exhibit self-organizational properties or the capacity of the system to reorganize itself internally (Hardy, 2000). This self-organizational capacity is observed in the body as it adjusts to new and evolving conditions. Using research methods that acknowledge this overarching complexity may contribute to the science of understanding compensatory response with disease and aging. This knowledge has the potential to form the foundation for designing and testing new approaches to treatment.

## Using Nonlinear Methods

Nonlinear methods may offer a more direct and sensitive way to assess and understand physiology of dynamic systems involved in homeostasis. Linear, rule-driven statistical processes are not powerful enough to deal with the flexible, evolving, and interactive capacities of physiological systems. Nonlinear and possibly chaotic processes are important mechanisms underlying physiological variability. They are useful to discriminate patterns of the networks involved during a compensatory response, even when those patterns are hidden behind normal values. Nonlinear dynamics have been used to explain heart rate, (Sugihara et al., 1996) QT wave, (Raghunandan, Desai, Mallavarapu, Berger, & Yeragani, 2005), and gut motor variability (Michoux et al., 2000). Michoux and colleagues reported a different organization of mortoric bowel responses in patients with gastroparesis using nonlinear analysis, which showed randomness or phase responses missed by conventional statistical methods (Michoux et al., 2000). In participants with gastroparesis, there was a lower flexibility and variation of contraction shapes when comparisons were made to normal participants. In heart rate variability studies, neither mean nor variance of R-R intervals were as successful in discriminating age comparisons as using nonlinear analysis (Sugihara et al., 1996).

Control at the cellular level also involves nonequilibrium processes where nonlinear methods can be useful. Mitochondrial function is dependent on adjustments made by multiple enzyme networks to maintain the internal cellular environment. A signature pattern of free radical generation/removal has been linked to mitochondrial dysfunction, an occurrence associated with aging and disease processes (Ramanujan & Herman, 2007). Evaluating the physiological response to stressors via nonlinear analysis techniques could provide new insight into the complexity of the body as it interacts with a fluctuating internal and external environment (Glass, 2001). Furthermore, these techniques may offer a more direct and sensitive means of assessing physiological systems and provide more powerful prognostic information than traditional indices. Findings from research using these methods may assist the practitioner to identify high-risk patient populations likely to develop negative outcomes, such as those developing malignant cardiac arrhythmias (Armoundas et al., 2002). Once pathological rhythms within a disease are identified, we may find that there are subsets of patients who respond more favorably to one specific therapy.

At present, the understanding of the interrelatedness of compensatory processes is incomplete and not ready for clinical application. However, predictions generated by the continued empirical investigation of compensatory responses and sustained research programs that expand understanding of oscillating behavior in normal health conditions and aging as well as disease states will provide a basis for translating research into clinical practice in the future.

Based on current knowledge and extant evidence, implications for practice and research follow.

- Clinicians need to be sensitive to variations in patterns of compensatory mechanisms so that interventions are supportive of both the body's normal initiation and sequencing of the compensatory response.

- Use of nonlinear analytical methods to discover the ongoing cross talk between multiple systems would provide a view of the whole body response.
- Age-adjusted treatment that takes into account the changing complexity of response must be considered to avoid eliminating or placing added strain on functioning compensatory mechanisms.
- Empirical research is needed to test the ideal range over which compensatory mechanisms are effective for varying scenarios associated with disease and aging.

## Conclusion

The traditional view, which conceptualizes alterations in health as deviations from normal of one or a few key variables and seeks to correct these variables to normal, is limited and may be associated with adverse patient outcomes. Evidence suggests that normalizing key disease-related variables may not be beneficial in all cases. Although transient improvement in a target variable may occur, this improvement does not guarantee positive patient outcomes. To presume that the adjustment of one or a few variables will completely correct the problem is inconsistent with an integrated view of the body. There is a dynamic interaction of compensatory mechanisms that cannot be fully understood or appreciated from a reductionistic point of view. Rather, the totality of the body's response needs to be examined to understand interactions on multiple system levels and how these interactions affect short- and long-term outcomes for the patient.

The integration of diverse mechanisms to produce a concept of homeostasis may be difficult because of the challenge inherent in finding coherent patterns in seemingly chaotic interactions. Nevertheless, the work is essential for developing more effective approaches to treatment. Convincing hypotheses need to be tested against data collected on the basis of a theoretical schema to move bench science to clinical applications. Studies across time focusing on long-range processes as well as one-point-in-time studies of conditions are necessary to expand understanding. Practitioners, and ultimately patients, may benefit by shifting to a broader perspective to see more clearly the approaches needed to address the dynamic response to disease, aging, and treatment.

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