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current as of October 1, 2008.

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JAMA. 2008;300(13):1580-1581 (doi:10.1001/jama.300.13.1580)

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The Conflict Between Complex Systems and Reductionism

Henry H. Q. Heng, PhD

DESCARTES' REDUCTIONIST PRINCIPLE HAS HAD A PROFOUND influence on medicine. Similar to repairing a clock in which each broken part is fixed in order, investigators have attempted to discover causal relationships among key components of an individual and to treat those components accordingly. For example, if most of the morbidity in patients with diabetes is caused by high blood glucose levels, then control of those levels should return the system to normal and the patient's health problems should disappear. However, in one recent study this strategy of more intensive glucose control resulted in increased risk of death.¹ Likewise, chemotherapy often initially reduces tumor size but also produces severe adverse effects leading to other complications, including the promotion of secondary tumors. Most important, little evidence exists that more aggressive chemotherapies prolong life for many patients.²⁻⁴ In fact, chemotherapies may have overall negative effects for some patients.

Most medical treatments make sense based on research of specific molecular pathways, so why do unexpected consequences occur after years of treatment? More simply, does the treatment that addresses a specific disease-related component harm the individual as a whole?

To address these questions, the conflict between reductionism and complex systems must be analyzed. With increasing technological capabilities, these systems can be examined in continuously smaller components, from organs to cells, cells to chromosomes, and from chromosomes to genes. Paradoxically, the success of science also leads to blind spots in thinking as scientists become increasingly reductionist and determinist. The expectation is that as the resolution of the analysis increases, so too will the quantity and quality of information. High-resolution studies focusing on the building blocks of a biological system provide specific targets on which molecular cures can be based.

While the DNA sequence of the human gene set is known, the functions of these genes are not understood in the context of a dynamic network and the resultant functional relationship to human diseases. Mutations in many genes are known to contribute to cancers in experimental systems, but the common mutations that actually cause cancer cannot yet be determined.^{5,6}

Many therapies such as antibiotics, pacemakers, blood transfusions, and organ transplantation have worked well using classic approaches. In these cases, interventions were successful in treating a specific part of a complex system without triggering system chaos in many patients. However, even

for these relatively safe interventions, unpredictable risk factors still exist. For every intervention that works well there are many others that do not, most of which involve complicated pathways and multiple levels of interaction. Even apparent major successes of the past have developed problems, such as the emergence and potential spread of super pathogens resistant to available antibiotic arrays.

One common feature of a complex system is its emergent properties—the collective result of distinct and interactive properties generated by the interaction of individual components. When parts change, the behavior of a system can sometimes be predicted—but often cannot be if the system exists on the “edge of chaos.” For example, a disconnect exists between the status of the parts (such as tumor response) and the systems behavior (such as overall survival of the patient). Furthermore, nonlinear responses of a complex system can undergo sudden massive and stochastic changes in response to what may seem minor perturbations. This may occur despite the same system displaying regular and predictable behavior under other conditions.^{7,8} For example, patients can be harmed by an uncommon adverse effect of a commonly used treatment when the system displays chaotic behavior under some circumstances. This stochastic effect is what causes surprise. Given that any medical intervention is a stress to the system and that multiple system levels can respond differently, researchers must consider the stochastic response of the entire human system to drug therapy rather than focusing solely on the targeted organ or cell or one particular molecular pathway or specific gene. The same approach is necessary for monitoring the clinical safety of a drug.

Other challenging questions await consideration. Once an entire system is altered by disease progression, how should the system be restored following replacement of a defective part? If a system is altered, should it be brought back to the previous status, or is there a new standard defining a new stable system? The development of many diseases can take years, during which time the system has adapted to function in the altered environment. These changes are not restricted to a few clinically monitored factors but can involve the whole system, which now has adapted a new homeostasis with new dynamic interactions. Restoring only a few factors without considering the entire system can often result in further stress to the system, which might trigger a decline in system chaos. For many disease conditions resulting from years of adaptation, gradual

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medical improvement rather than drastic intervention might be the best way to correct the problem. In cancer research, system behavior has been monitored during cancer progression, demonstrating that cancer evolution is driven by multiple cycles of transition between genome system stability and instability.^{9,10} Chemotherapy, by and large, induces a relatively stable system to enter into a chaotic phase. This drastic treatment might be more harmful at the individual level than had been expected. Clearly, understanding the entire system response in the context of any specific treatment is key.

Another layer of complication affects the design of clinical trials evaluating the risk and benefit of a given medical intervention. Traditionally, many diseases have been thought to be caused by common factors including environmental insults and common genetic loci. It is thus logical to validate medical benefits vs risks using large patient populations. However, increasing numbers of recent reports illustrate that some highly penetrant and individually rare genetic alterations contribute to many common diseases, including autism, schizophrenia, and hypertension.^{11,12} These findings suggest that many common diseases are not caused by common shared genetic alterations. This challenges the common disease–common variant hypothesis as well as the strategy of validating common benefits or risks using a large heterogeneous patient population.

In a heterogeneous population, patients may display a variety of genetic variations that respond differently to a given medical intervention. The same treatment could be of benefit to some patients yet harmful to others. Thus, validation of risk and benefit using a large heterogeneous population will likely produce conflicting data. Based on recent findings that most patients with cancer display drastically different patterns of genetic aberrations rather than the long-assumed common genetic alterations^{5,6,9} and that heterogeneous genetic alterations also contribute to other types of common diseases,^{11,12} it is logical to predict that patients with variable genetic alterations will display different clinical profiles and have different responses to the same treatment. Therefore, it is essential to reconsider the current strategies of validation, diagnosis, and treatment.

Analyzing the common links behind failures in the treatment of diseases is of great importance. Such analyses will promote the important realization that the key obstacle to future medicine is the conflict between the reality of complexity and a reductionist approach. Despite previous approaches to address the issue of complexity,^{7,8,13} limited medical research has been conducted within the context of complex systems. Clearly, only such realization will lead to the correct strategies that integrate information, approaches, and concepts from both low and high levels of a system.

Critical analysis of established medical concepts is needed, as is reinterpretation of the clinical significance of failed therapies from the perspective of complexity. In particular, 2 key features of a biological system, multilevel complexity and heterogeneity, need to be seriously considered when developing new medical interventions.⁶ When considering multilevel systems, the higher organizational level often domi-

nates, suggesting that benefits at the higher level should be a priority—thus the need to focus more on an individual's phenotype rather than on the molecular level. In the case of somatic cell evolution of cancer, higher-level genome alterations play a more dominant role than lower-level gene mutations.^{6,10} This information is useful when considering diagnostic and treatment strategies in cancer.

Multilevel interactions also provide an opportunity for evolution of cooperation between levels so that game theory can be applied to assess and achieve medical benefits. For example, in cancer treatment, alternative strategies need to be developed that not only focus on destroying the cancer cells but also achieve the most possible cooperative and beneficial relationship to patients.

The unpredictable nature of heterogeneity will force the consideration of the significance of clinical exceptions, because complex disease results in highly diverse responses that include many exceptions to the general rules. Furthermore, heterogeneity is not simply “noise” but a key component of evolution directly related to human disease conditions and must also be considered when designing interventions such as cancer therapies.^{6,9,14}

Clinical therapies must be individualized, balancing the parts of the system and the response of the patient as a whole. Clinical research involving pharmaceutical agents needs to focus more on the differential responses within diverse patient populations. This philosophy should be extended to the public to encourage healthy lifestyles rather than depending on the quick fix of drugs as panaceas.

Financial Disclosures: None reported.

Additional Contributions: I thank Gloria Heppner, PhD, for continuous encouragement and Steve Bremer, MD, Lesley Lawrenson, MS, Joshua Stevens, PhD, Markku Kurkinen, PhD, Christine Ye, MD, and Barbara Spyropoulos, PhD, for discussion and help in editing the manuscript. None of these individuals, all of Wayne State University, received compensation for their contributions.

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