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Complexity Science to Conceptualize Health and Disease: Is It Relevant to Clinical Medicine?

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Clinical sciences are based on several implicit and explicit concepts, assumptions, and beliefs. The current discourse on clinical medicine is dominated by a mechanistic, deterministic, and reductionist world view and has much to gain by embracing the concepts in complexity science (CS). This article sets out to achieve 3 objectives: describe the evolution of models or frameworks used in clinical medicine, outline the application of CS to conceptualize the human body in health and disease, and briefly explore how CS sheds light on our understanding of clinical conditions, using severe sepsis as an example.

Origins of the Mechanistic Models in Medicine

It has been argued that the current views and concepts in medicine had their origins in the broad process of rationalism that began in Europe in the 16th century.[1] A major influence in this process of thinking was René Descartes (1596-1650), who enunciated dualism, proposing that the body followed principles of physics and mathematics, as explained in mechanical terms, whereas the mind was limited to willful, rational, or self-conscious behavior.[2] Accordingly, the world was believed to follow a clockwork mechanism, and a reductionist approach was required to understand it: a phenomenon or the existence of an object can be explained by identifying its components and investigating them individually; reassembling them recreates the whole. An often quoted example is the ability to understand the functioning of a mechanical clock by separating its parts into individual components and investigating their functions. A landmark development in this mechanistic view of scientific thought was the work of Sir Isaac Newton, especially *Philosophiæ Naturalis Principia Mathematica*, published in 1687, and his theories of motion, optics, and gravity. This furthered the view of a "clockwork universe" that was deterministic and predictable, because it followed laws of motion, gravity, and mass.

Some researchers have included linearity and hierarchy as other features of the Newtonian mechanistic system.[3] Linearity indicates 2 features: proportionality, which means that the output from the system is proportionate to the input, and superposition, in which the effects of the combined action of different inputs can be projected by dissecting the input-output relationships of the individual components.[4] Linearity gives the system a degree of predictability and therefore is closely related conceptually to determinism. Hierarchy points to a relatively stable situation seen with mechanical devices with a central control mechanism, or a source of power, from which control or energy consistently flows to other parts of the system.[3] An example is the flow of power from a battery to the components.

The mechanistic paradigm was extended to natural sciences when in the 18th century the French philosopher Julien Offray de La Mettrie proposed the metaphor of the human being as a machine, which was aptly illustrated by Fritz Kahn's figures of the body as a "man machine."[5] These were probably the origins of a mechanistic biomedical model, in which health professionals and the public equate the human organism to a machine and the doctor to the repairer of the defective machine.[6]

The mechanistic biomedical model has continued to influence health sciences, though in an increasingly sophisticated manner. In contrast to previous attempts to equate biology to mechanical clocks, the metaphors have become closer to electronics, information technology, and computers. Terms such as *biological programming* to describe fetal influences in adult life or *programmed cell death* in the case of apoptosis illustrate this trend. However, these views are essentially variations of the "body as a machine" paradigm and therefore implicitly accept the principles of Newtonian mechanistic thinking and reductionist approaches. The latter have progressively dominated our approach to scientific inquiry and medical research, and medical advances have increasingly focused on identifying genetic or molecular markers for diseases and molecular-level interventions (eg, drugs acting on specific cell receptors and the advent of personalized medicine). Reductionism may have also contributed to "superspecialization," in which teams or individuals have specialist knowledge in a particular organ system (eg, cardiologists or neurologists) or specific aspects of an organ system (eg, cardiac electrophysiologists). Linearity brings a degree of predictability (ie, a known input ought to repeatedly produce a similar effect) and assumes that the cause-to-effect pathway can be known and predicted. This is a commonly used and almost intuitive principle in clinical medicine. A clear example is provided in the principles used in drug development. Animal studies, and the different phases in clinical trials (phases 1 to

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3) in humans, are based on the premise that each step is a predictor of the next stage of sophistication. Thus, toxicity and metabolic features in animals are assumed to predict the drug effects in humans, and in turn the effects in healthy humans are used to predict the effect on those with the target disease. A hierarchical view of organ systems is a less visible feature in modern medicine, as scientists readily acknowledge the relative importance of different body systems depending on the clinical context.

Origins of Complexity Science

The origin of CS can be traced to the systems theory developed by von Bertalanffy in the 1920s.[7,8] Systems theory has some features of mechanistic thinking in that it includes an implicit acceptance of determinism, stable hierarchies within the system, and linearity. The major point of departure relates to reductionism: systems theory states that properties of the "whole" cannot be predicted by dissecting out and exploring the properties of its individual constituent parts alone. An example is the presence of complicated colony structures of termites as a result of interactions among termites. These interactions are governed by a few simple rules, and the observable outcome (the termite colony) is more than merely the sum of its parts. Of the systems in the universe, biologic and other natural systems have another feature that makes them "open" systems. These systems are influenced by the environment and have to interact with it and exchange matter and energy to sustain their existence. The human body can be viewed as an open system that is dependent on oxygen, food, heat, and light in order to live, grow, and reproduce. All these components have to be obtained from the environment and interact with the body, which in turn adapts to them and exhibits emergent properties, such as growth. In contrast, a material system, such as a vehicle, is a more "closed" system with fewer external influences and abilities to adapt.

Closely allied to systems theory is cybernetics, which explains the autonomy and apparent stability of systems from circular coupling of events via positive and negative feedback loops. Thus, influences from the external environment that lead to perturbations of the system are compensated for by the negative feedback loops, and the system maintains a "preferred" state of affairs, or adapts to the influences.[6] Thus, the rise in environmental temperature will change the behavior of the cold-blooded animals to reduce heat production. This idea of open systems with feedback loops has been extended to describe the earth's ecosystem (eg, the Gaia hypothesis) and population health.[9]

Complexity science emerged in the 20th century, postulating a new paradigm that integrates systems theory and cybernetics. Complexity science has several key concepts that distinguish it from the mechanistic approach: adaptation, lack of hierarchies, self-organization, and emergence.[10,11] Adaptation allows the system to modify its structures (ie, self-organization) and cope with forces or influences from the environment. Since these systems are not passive and adapt by a process of reorganization, they are known as complex adaptive systems (CASs) and defined as "a collection of individual agents with freedom to act in ways that are not always totally predictable, and whose actions are interconnected so that one agent's action changes the context for other agents."[10] As a result of the self-organization and adaptation, the system may yield novel properties (ie, emergence). A CAS also exhibits multiple levels of "heterarchical" interrelations, rather than a hierarchical mode of control, and demonstrates nonlinear relationships among the subsystems.[8,12] Although the broader system is perceived to consist of a collection of open subsystems, the interrelationships among the latter do not have stable hierarchies.

The Human Body as a Complex Adaptive System

I propose that the human body can be viewed as a CAS, that is, as a system within which several closely linked organ systems or subsystems are embedded. These organ systems interact with one another through a range of diverse pathways: chemical interactions (eg, lactate production in peripheral tissues being metabolized by the liver), diffusion of chemicals through tissue planes (eg, proinflammatory cytokines released from a subdiaphragmatic abscess leading to a sympathetic lung effusion), neuronal connections (eg, autonomic nerves), hormones (eg, procatabolic cortisone), immune pathways (eg, antibodies), and cytokine pathways (tumor necrosis factor [TNF], interleukins), to name a few. The subsystems do not have stable hierarchical structures and instead have multiple levels of heterarchical interrelations and interactions.[8] Their pathways of control or influence flow from several agents (eg, via nerves arising from the brain, from blood flowing through the vascular system, from immune cells that secrete cytokines, and from endocrine organs that secrete hormones), and their relative importance changes with time, that is, the hierarchical paths of influence evolve constantly. For example, cardiovascular, musculoskeletal, and nervous systems would predominate when there is a fear response, rather than, say, the urinary system. Not that the urinary system is completely inactivated, but reduced urine output is of relatively less importance for the response. There are numerous local feedback loops linking the interacting agents. The increase in heart rate and blood pressure mediated via the autonomic system will be dampened by the baroreceptors

that sense a rise in blood pressure. The processes in the body demonstrate nonlinear relationships even in the physiologic state (eg, heart rate variability, which demonstrates nonlinearity dynamics).[12] These characteristics violate the principles of proportionality and superposition, that is, the linearity of mechanistic systems. The subsystems (organ systems in this instance) also demonstrate indistinct and fuzzy borders and overlap with one another. One can consider the examples of the immune system or the nervous system, in which almost the whole body is reached by way of body fluids or peripheral nerves, respectively.

Complex Adaptive Systems and Disease States

Emergence is a key feature of CASs and indicates the arising of properties that did not exist previously.[13] They arise because of interactions within the subsystems and the environment that lead to self-organization and adaptation. We can conceptualize clinical features of disease states as emergent properties of the human body (ie, a CAS). Since several subsystems are interacting simultaneously in a combination unique to that human being, the manifestations too are unique, which accounts for the subtle differences in presentation with a "similar" disease process. Thus, one person may have autonomic features such as sweating and nausea with a myocardial infarction and another, with a similar territory of myocardium affected, may have minimal autonomic features. Personalized therapy should take into account this aspect and not be limited to identifying solely the genetic constitution of the patient, which is only one of the many variables determining therapeutic efficacy.

Septic Shock: An Example of an Emergent Property

The pathogenesis of septic shock is used here to illustrate disease states as an emergent property of a CAS. It is important to note that the intensive care unit setting is probably one place that appreciates CS implicitly.

Septic shock is defined as a state of acute circulatory failure with persistent arterial hypotension despite resuscitation with adequate fluids or a state of tissue hypoperfusion manifested by a lactate concentration greater than 4 mg/dL (to convert to mmol/L, multiply by 0.111) that is unexplained by other causes.[14] Its pathogenesis is extremely complicated, and almost all organ systems in the body are affected.[15-17] Septic shock begins with the invasion of normally sterile tissues by pathogenic microbes. Virulence of bacterial pathogens plays a critical role in the unfolding events.[15] This virulence is enhanced by several mechanisms: evading host defenses (eg, by encapsulation to avoid opsonization and thereby phagocytosis; surface antigenic variation to prevent recognition; intracellular survival and replication; induction of immune cell apoptosis), increasing cell adherence (eg, production of adhesins to attach to collagen fibers), and delivering bacterial products into the extracellular matrix or intracellularly through specific transporter systems.

At cellular and subcellular levels, receptors (eg, platelet-activating factor receptor, leukocyte–endothelial cell adhesion molecule, and kinin receptors) are expressed in varying intensities.[18] These patterns of expressed surface proteins are in turn determined mostly by networks of genes that are differentially activated during infections and sepsis.[19]

The interrelated and dynamic response by the host during septic shock could be well described from the viewpoint of CS. Septic shock could then be viewed as an emergent property of a CAS (in this instance, the human body) in which a complex interplay of nonlinear interactions with feedback loops has occurred in a number of subsystems with fuzzy borders.

Innate immunity is an example of a system with fuzzy borders. After recognition of invading pathogens through pattern-recognition receptors, a whole cascade of events takes place: intracellular signaling (ie, signal transduction) followed by synthesis and release of mediators (ie, cytokines and kinins) into the systemic circulation. The cytokines (interleukins and TNF), kinins (eg, bradykinin), and other mediators released to combat local infections have widespread effects on other organ systems, such as impairing myocardial contractility and inducing endothelial damage, which in turn triggers the extrinsic coagulation cascade, microthrombi formation, and disseminated intravascular coagulation (ie, the coagulation subsystem).[20,21] Other crucial events include the adult respiratory distress syndrome and acute kidney injury.[22,23]

Evidence suggests strong coupling effects of some of the organ dysfunction. For example, the cardiorenal syndrome seen in sepsis demonstrates "organ cross-talk" between myocardial and renal functions.[16] The pathways of interactions include fluid overload from renal hypoperfusion, which adversely affects myocardial function; renal ischemic injury leading to increased myocardial levels of messenger RNA for TNF-α and interleukin 1; infiltration by leukocytes, their activation and subsequent myocardial inflammation; and reduced renal clearance of cytokines, which worsens myocardial inflammation and injury.[16,17] Some of these interactions lead to feedback loops and impact in a cyclical fashion; for example, TNF released from ischemic acute kidney injury induces cardiac muscle apoptosis, and the resulting hypotension promotes lactic

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acidosis and depresses the myocardium further.[17] Links with feedback loops are also shown between the parasympathetic nervous system and cytokine pathways: vagal stimulation reduces the production of proinflammatory TNF-α via acetylcholine binding to the nicotinic receptors on mononuclear phagocytes of the reticuloendothelial system, and in turn TNF-α affects heart rate variability.[24]

Clinical Implications

A CAS has multiple subsystems, and they interact with one another, adapt to the changing context (ie, co-evolve), and give rise to the emergence of new properties in the bigger system (ie, the body in this instance). A feature of CASs is nonlinear dynamics. Septic shock demonstrates this feature, and clinicians are well aware that a minor insult (eg, a minor gastric bleed from stress ulcer) can have catastrophic consequences for the patient. Such states are known as demonstrating chaos; that is, the system is highly sensitive to the initial condition, and a small difference in the initial condition can lead to widely divergent outcomes, including catastrophic outcomes under circumstances reminiscent of a "perfect storm." In these dynamic situations, long-term predictions are nearly impossible. This difficulty has led to new approaches in describing pathophysiologic states in critical care, in which attempts are made to let "the data themselves define densely populated regions of physiologic state space that collectively represented a clinical condition" in contrast to having clinicians define diseases and insert data to fit diagnoses.[25] The advancement of bioinformatics and computing has enabled further advances in this approach. Observation of thousands of real-time data points from a range of physiologic parameters has begun to reveal clusters of physiologic states that could not be explained by expert clinicians.[26] At a less sophisticated level, observations from organ system dysfunction demonstrate inherent sensitivities of the system to external insults and the interrelatedness of the subsystems to one another. For example, odds of acute kidney injury in noncritically ill adult patients are significantly higher ($P<.001$; odds ratio, 3.5) with 2 or more comorbidities than without such comorbidities, and prognostic scoring systems for sepsis suggest that involvement in more than one organ system carries a poorer prognosis.[27,28]

Interventions to change a CAS (with its numerous subsystems) ought to be multipronged and act on the different subsystems. The threshold for these multiple interventions ought to be lower than conventional criteria. The "multiple interventions at lower threshold approach" is increasingly being used in septic shock, as evidenced by early goal-directed therapy, which consists of multiple interventions at an early stage aimed at improving tissue perfusion.[29] The protocol includes a central venous catheter capable of measuring central venous oxygen saturation ($ScvO_2$), aggressive fluid boluses to achieve central venous pressure of 8 to 12 mm Hg, vasopressors to maintain mean arterial blood pressure above 65 mm Hg, transfusion of red blood cells to achieve a hematocrit value of 30% if the patient has an $ScvO_2$ of less than 70%, and early antibiotic therapy. Early goal-directed therapy reduced mortality when compared with standard care.[29] The second thread of evidence came from the recommendation to use septic care bundles in shock. Use of these bundles, which seems to have revolutionized management of sepsis, is based on the hypothesis that implementing several selected, evidence-based interventions together may result in better outcomes than if the interventions were implemented individually.[30,31] The bundles include early broad-spectrum antibiotic administration, achieving $ScvO_2$ above 70% (using early goal-directed therapy), rapid lactate clearance, administration of corticosteroids, tight glycemic control, low tidal volume ventilatory strategies, and administration of recombinant activated protein C.[30]

The dynamic nature of a CAS requires that the interventions and corrective actions be based on changes to the system. Thus, it ought to be more effective to intervene on trends of dysfunction, in contrast to a particular cutoff value. This hypothesis finds some resonance with the current recommendations of the Acute Kidney Injury Network criteria for prognostication and renal replacement in acute kidney injury, which are based on rates of increase within 48 hours: an increase in serum creatinine above 0.3 mg/dL (to convert to μmol/L, multiply by 88.4) (an absolute cutoff value) and a percentage increase in serum creatinine of 50% (1.5-fold from baseline) or more.[32] This approach to management of shock is increasingly being debated in critical care, because of the availability of real-time monitoring of physiologic dysfunction (eg, oxygen saturation, pH, heart rate), powerful computing, and complicated mathematical techniques (eg, variability analysis).[33] The approach allows the data to define physiological states that represent clinical conditions.[25] This will shake the very foundations of teaching clinical medicine, which is based on defining diseases, their etiology, pathogenesis, and clinical features.

The ability of laboratories to do arrays of analyses and advances in bioinformatics have contributed to the rapidly expanding fields of "-onomics," beginning with genomics, proteomics, metabolomics, and immunomics.[34-36] These fields are based on the principle of assaying large numbers of compounds (eg, proteins in the case of proteomics, metabolites and other compounds in metabolomics) and analyz-

ing for patterns in relation to diseases and healthy states. Although the fields are currently working compartmentally, there is a need to combine efforts in relation to disease states such as sepsis, in which genomes (via susceptibility to particular gene expressions), immunogenic proteins, cytokines, and metabolites play a role. The key is to observe the variations in the parameters, rather than absolute values, and to see emerging patterns from the interacting subsystems (eg, proteomics, metabolomics). As with the approaches used in the sepsis syndrome, we ought to let the variability indices of data themselves define disease states in dynamic physiologic and anatomic state spaces. Precisely defined diseases will become less important as we see patterns representing clinical spectrums or conditions emerging from the data. The clinician would then intervene in a multipronged manner to modify the paths taken by these patterns. Such discussions no doubt will lead to novel conceptualization of what a disease is and the interventions to prevent and treat diseases and promote health.

Conclusion

This article views the body as a CAS and a disease state as an emergent property of a biologic system. Using the example of septic shock, one finds certain attributes of a CAS being observed or being practiced in recommended therapies for the condition, such as multiple early interventions (eg, septic treatment bundles) and use of variability analysis to predict outcomes and interventions. The implications of using CAS in other, more "stable" disease states (eg, uncomplicated essential hypertension or diabetes) need to be explored.

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