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How we become ill

Investigating emergent properties of biological systems could help to better understand the pathology of diseases

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There are many causes of illness. One could get hit by a car, and the mechanical forces of the impact damage soft tissues and fracture bones. An analogous concept could be established for infectious diseases: a pathogenic microorganism "hits" the body and causes infection and inflammation along with fever, pain, and reduced physical fitness. Akin to the mechanistic forces that break a bone, the cause of infection is a virus or bacterium, and medical practice therefore tries to diagnose the causative pathogen in order to prescribe the correct therapy, be it an antiviral or an antibiotic. Moreover, in analogy to physical forces that cause injury, it is the number of microorganisms that have entered the body, which determines whether an infection will cause disease.

Different ways to become ill

But if we look at infection patterns in whole populations, it becomes obvious that not everybody who is infected by a specific "infective dose" of a particular pathogen becomes ill and shows clinical symptoms. In some cases, people appear immune even against high infective doses, whereas in other circumstances, even non-pathogenic microorganisms can cause severe infections, which often affect leukemia patients or patients suffering from immunodeficiency. This highlights another crucial factor that determines whether we become ill or not: the immune system.

In contrast to an accident, infection depends on more than just physical forces. The immune system, involving numerous specialized cells, receptors, cytokines, antibodies, and so on, adds a layer of complexity that makes it more difficult to establish causality. Its efficiency in clearing the body of pathogens not only depends on its internal state—for instance the presence of memory B cells to produce specific antibodies—but also on external factors, such as the state of nutrition, climate, or stress levels. The relation between exposure to microorganism and infection is therefore not linear but complex or even chaotic [1].

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There are also patients who become ill without any obvious external causes, such as physical forces or pathogens. This is the case for so-called complex diseases, such as many forms of cancer or cardiovascular or neurological diseases. Although risk factors have been identified, general causal models are still missing. How can we arrange these different ways to become ill—from mechanic forces, from pathogenic agents, or without any obvious external factors—into a consistent concept?

The reductionist approach

Contemporary biomedical research follows a clear strategy: search for a part of the body, which is altered and/or which can be causally linked to a pathological mechanism. This search starts at the level of organs, goes to tissues and cells, and ends at the molecular level of proteins, metabolites, and genes. This approach to explain an entire whole, such as an organism, by reducing it to its constituent parts is called reductionism. It groups phenomena into hierarchical levels, such as multicellular organisms, organs, tissues, cells, and attempts to explain the function of higher levels by the parts and function of lower ones down to the sub-atomic level of elementary particles. Reductionism has been discussed mainly in the context of the unification of science: the explanation of the laws of higher-level sciences by the laws of the underlying physical microstructure [2]. Although a reduction of complex systems, such as an organism, down to elementary particles has not been successful, it is possible in particular disciplines. The most common example is the reduction of classical thermodynamics to statistical mechanics—for example, the temperature of an ideal gas can be explained by the mean kinetic energy of its molecules.

However, reductionism has certain limits [3]. First, as complexity increases dramatically with higher levels, even from atoms to molecules, it becomes an enormous challenge to reduce phenomena to physics; this is possible only by accepting radically simplified assumptions. Since complexity increases from chemistry to biology, physical reduction seems to become impossible. The different sciences therefore have developed their own laws and theories: Laws of chemistry describe molecules, whereas laws of biology describe inheritance or the function of organisms [2].

In the medical context, reductionism is not a metaphysical or an ontological question but a methodological one: Does a treatment that targets a specific molecule improve the patient's situation or can the

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detection of a particular gene variant facilitate a diagnosis?

Here, reduction of clinically heterogeneous diseases to common molecular mechanisms helps in diagnosis and prescribing the correct treatment.

Emergence to explain higher-level properties

The complement of reductionism is emergence. The classic concept was described by C. D. Broad, who stated that the properties of a whole cannot be deduced from the knowledge of their constituting parts in isolation or in less complex wholes. This is an important constraint for biomedical research, which often studies its molecules in simplified model systems.

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It is important to distinguish between different notions of emergence. The strong version asserts that the gap between levels of organization cannot be bridged by scientific explanation. Common examples are the perception of colors or other qualities and the state of the brain: The mental presentation cannot be deduced from the nerve cells of the brain. The weak version of emergence argues that the constituents of a system are still physical parts, which allows determining the microstructure of the system and the function of individual parts therein. However, complex systems such as biological organisms are able to reorganize their constituting parts to gain new properties (organizational properties) in response to environmental changes. This dynamic process, which is in principle independent of the corresponding microstructure, cannot be explained by microreduction.

The question of reductionism and emergence can be discussed in the context of medical science as system properties and their underlying microstructure: Are diseases and their appearance—as system properties—reducible to the parts of the body, or can diseases and their clinical development be understood as emergent or organizational properties?

Systems theory provides a framework for understanding the emergence of new properties in complex systems. It characterizes biological systems by the flow of material from and to the environment; as the flow changes, biological systems reorganize themselves in response and change the organization of their parts and interactions, which may result in new properties independent of the properties of the isolated parts. Could we use systems theory to explain the development of pathological states in complex diseases as such a reorganization and the emergence of new properties?

Cancer as an emergent disease?

By way of example, there are many different types of cancer, often based on specific diagnostic tests and with different therapeutic approaches. Some forms of cancer have a higher frequency in affected families, which can be explained on the molecular level by genetic risk factors, such as the BRCA1 and BRCA2 genes for breast cancer or familial adenomatous polyposis (FAP), a condition in which intestinal polyps transform into colon cancer. In contrast, the vast majority of colon cancers are sporadic, and no clear genetic basis has been found so far. Another causal factor for cancer is infection, mainly by viruses such as hepatitis B (HBV) or human papilloma virus (HPV), but also from bacteria, notably *Helicobacter pylori*, or parasites such as *Schistosoma* [4]. In addition, many external factors play a role in the development of cancer: low physical exercise, low fruit and vegetable intake, high body mass index, alcohol use, and smoking [5]. Many molecules and internal factors that increase cancer risk and that drive its pathogenic development have been identified and their function elucidated.

In addition, it becomes evident that cancer development goes along with the reorganization of particular tissues and their functions. A preliminary step for cancer development is chronic inflammation, which causes invasion of immune cells and secretion of pro-inflammatory cytokines, which leads to chronic changes in tissue structure. The interaction of pre-cancerous cells with the immune system is considered a primary step in cancer development [6]. Finally, cells turn into tumor cells and trigger the generation of new blood vessels to support the histologically distinguishable tumor that is a new, emergent part of the body.

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Cancer development assumes a "vertical" emergence—that systemic properties cannot be deduced from the properties of the system's parts. This could help to understand cancer development: Infective agents together with/or external factors such as high-caloric nutrition create a pro-inflammatory milieu in the body. The inflammation eventually becomes chronic which enables rare mutations that inactivate cell growth control to accumulate over time, which again allows cells to proliferate and grow into a tumor [4,6].

Shifting properties

There is obviously a shift from one emergent property to another along with the establishment of new interactions of the systems' part. An invading pathogen and its interaction with the immune system cause a shift to an inflammatory response. A second shift takes place when the acute inflammation becomes chronic, which generates a permissive environment for the emergence of tumor cells [7]. Another shift from pre-cancerous cells to tumor cells causes the disease to manifest. Finally, another systems shift causes cells to break away from the tumor and travel through the blood or lymph system to other parts of the body where they grow into metastases.

These shifts could be caused by purely random processes that finally lead to the appearance of new, emergent system properties. It is also possible though that those shifts are actively driven by intrinsic mechanisms and/or external factors that govern the shift from one property of the system to another by generating new interactive relationships. Those emergent principles might help to explain the development as well as the perpetuation of a disease and its symptoms.

In the context of inflammation, emerging principles might be executed by particular

molecules such as cytokines or prostaglandins, signaling pathways, or enzymes. Although they seem to be merely a reaction to an external factor, such as a pathogenic microorganism, they, in fact, organize the organism's reaction to the infection. These are not just theoretical considerations; clinical medicine can diagnose these reactions and interfere on an empirical basis. In patients with FAP, for instance, treatment with anti-inflammatory drugs can prevent the development of cancer by suppressing chronic inflammation. Treatment of inflammatory bowel diseases with immunosuppressive drugs, such as the glucocorticoid prednisone or inhibitors of tumor necrosis factor, has also been shown to reduce the risk of colorectal cancer.

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In conclusion, knowledge of the system's parts is important for understanding diseases. While some diseases or clinical situations are more strongly determined by specific parts, for instance gene variants in monogenic hereditary diseases, most diseases arise as a result of a complex interplay of several parts and subsystems with the environment. Lastly, a biological system is able to generate different states—including emergent, new, and unforeseen ones such as diseases—by reorganizing its constituting parts.

In the clinical context, the pathophysiology of many diseases fulfills the definition of emergence: The environment—pollution, nutrition, noxii, microorganisms—enables or forces the system to reorganize and develop new properties [8,9]. This is not an anti-reductionist position since the new properties, when established, can be explained by the parts of the system and their—new—interactions. Most tumors and many other complex diseases thus emerge seemingly spontaneously. As the burden of complex or functional diseases is much higher than monogenic syndromes, emergence has a great impact on medicine, in particular the upcoming field of preventive medicine.

Applications in diagnosis and prevention

To come back to our introductory examples, medicine has become extremely successful in preventing, identifying, and treating infectious diseases, and in treating severe trauma. Antiviral and antibiotic substances, vaccines, and hygiene have significantly reduced the risk posed by pathogenic microorganisms. Better surgery and clinical care have drastically increased the chances of survival after a severe accident.

However, we still need equally efficient approaches to deal with complex diseases, and the key is early diagnosis and prevention. Thus, we have to study the system properties of the human body, because changes in these properties at various levels, such as chronic inflammation, can reveal a disease in its early stages and inform therapeutic or preventive measures. Colonoscopy, for instance, is used to identify precancerous lesions, which, at this stage, can be further monitored or easily excised before they develop into colon cancer.

To recognize changes in system properties that indicate various stages of a complex disease, we need to investigate and understand the emergent principles behind it. Even if the medical history of an individual patient may differ along with the molecules and cellular subsystems involved, the guiding emergent principles that govern the shift between system states should be the same and therefore essential for diagnosis and efficient treatment. We could influence common systems and molecules involved as well as the system's environment by diet, lifestyle, or drugs, for example, to dampen inflammation and thereby decrease cancer risk. Identification and analysis of emergent principles would also be very helpful to better understand, diagnose, treat, and manage clinical situations.

Generally, understanding the system's state and influencing its environment would be important for all diseases without a clear clinically identifiable pathological mechanism, which is the case for many patients who see their doctor. Yet, a taxonomy of diseases that reflects the developmental history of a biological system and its emergent principles may not be easily integrated into current concepts of diagnosis. It would not provide simple or even monocausal explanations but more complex and flexible concepts for diagnosis, therapy, and prognostics. Moreover, detailed knowledge of property shifts and emergent principles is not indispensible for all medical practice: A surgeon fixing a fracture after a car accident or conducting a bypass operation needs first of all anatomic knowledge and experience.

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Nonetheless, medical disciplines that deal with complex diseases such as oncology, endocrinology, or microbiology would profit enormously from investigating and understanding emergent principles and how these govern system shifts. It would help clinicians to diagnose complex and slowly developing diseases much earlier and thus prevent malignant transformations more effectively. In addition, teaching concepts of emergence and self-organization in medical education might improve students' understanding of complex diseases more generally and thus enable physicians to look for telltale signs of system shifts that could eventually develop into a disease.

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Conflict of interest

The author declares that he has no conflict of interest.

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