A Novel Definition and Three-Stage Model for Health and Sickness

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Abstract

Current definitions of health and sickness are too vague for application in bio models of disease processes. We propose a three-stage model identifying the boundary between the two states. Model Stage one is health, when multiple patho-physiological processes may occur but do not progress to disease due to host immunity. Stage two is subclinical disease, when pathophysiological processes may still be altered by medical diagnosis and treatment, and stage three is overt clinical disease. There is a critical threshold between the first and second stages at which the innate immunity is overcome, leading to the appearance of clinical symptoms. This model has important implications for interventional and preventive medicine.

1. Introduction

The use of bioinformational data to model and predict disease processes requires a clear definition of sickness and health. According to the Constitution of the World Health Organization, adopted in 1948, health is "a state of complete physical, mental, and social well-being" and not merely the absence of disease.[1] However, this definition is not based on scientific theory and is too broad for practical application. Subsequent attempts also yielded vague descriptions disconnected from contemporary medical knowledge.[2,3] Some authors viewed disease as the opposite of health, caused by an impairment of normal function that could be identified by distinct signs and symptoms.[4] Others considered health and disease arbitrary and changeable qualities that defied definition.[5,6] Further studies of human biology suggested that disease represents a lost battle between external pathological vectors and internal defense mechanisms.[6-9] However, the features of the battle that determine the disease were not characterized. For example, in Xeroderma Pigmentosum, the genetic lack of certain enzymes leads to irreparable sun-related nuclear damage. So, is the disease in effect the mutations that lead to the enzymatic disturbance or the skin cancer that develops as a consequence of ultraviolet radiation?[6-9]

This work presents a novel model of health and sickness which is based on the rationale that every physiological disturbance has a specific starting point: a genetic mutation, penetration by a virulent organism, or exposure to a toxic material. However, the mere presence of a starting point is not enough: For disease to develop, a complex series of events needs to occur at multiple sites, each involving both the causative agent and the body's defense mechanisms. When this course reaches a critical threshold, it becomes a "disease process" which, if unchecked by internal or external forces (body's immune system, medical screening), progresses to a potentially irreversible stage. Clinical symptoms are manifested at this point and may prompt diagnosis and treatment, if possible. Recent progress in the field of bioinformatics and genome sequencing has suggested that by combining genomic information with multiple monitoring of physiological states, physicians can formulate "Omics" profiles for individual patients.[10] These studies may shed light on the manner in which health converts to clinical disease and aid physicians in identifying the specific tipping point at which the switch between the two states takes place.

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2. Three-Stage Model of Health And Disease

The proposed a three-stage model of human pathophysiology defining the spectrum and boundaries of health and sickness.

Stage 1. *Health.* In the first stage, host defense systems are strong and operative. If any potential pathological starting points are present (mutations, microorganisms, environmental toxins, etc.), the host defense mechanisms prevent their triggering the chain of events to clinical symptoms.

Stage 2. *Subclinical disease*. In the second stage, internal or external disturbances to the immune system occur at various sites. This is the stage that represents the start of the chain reaction of the clinical disease. However, clinical symptoms are not yet manifest, and the process can still be altered if it is identified by medical screening/diagnosis followed by early treatment. Otherwise, the process progresses to stage 3.

Stage 3. *Clinical disease.* In the third stage, clinical symptoms appear. This is the stage at which most diagnostic measures are taken. Its magnitude and duration depend on the nature of the disease and the state of the host immune system. The clinical disease may be self-limiting or may require external therapeutic intervention. Ultimately, the disease process either resolves or progressively worsens, even to termination of life.

Because the number of pathological events steadily decreases as the disease reaches higher and higher levels, the three-stage process can be graphically depicted as a pathophysiological pyramid (Figure 1).

3. *Disease Threshold*

The critical threshold is crucial to the model, representing the tipping point between health (stage one) and disease (stages two-three). It is the culmination of the complex set of events that leads to an “all or nothing” standoff between the internal defense mechanisms and ultimately irreversible pathophysiological changes. In accordance with the increasingly widespread use of mathematical models of pathological processes in the fields of mathematical biologics and biological informatics, the critical threshold can be simplified as the sum of several functions:

$$\mathbf{X \times Y + X^1 \times Y^1 + X^2 \times Y^2 + X^3 \times Y^3 + ... = 1}$$

where 1 refers to disease (0, no disease); X, X^1, X^2, X^3, etc. refer to internal biological and pathophysiological events, such as bacterial growth, anti-oxidant enzyme activity, or T-cell activity; and Y^1, Y^2, Y^3, etc. refer to the specific activity of these events.

The host defense variables have a negative value in this equation. The chances of a pathophysiological process passing the disease threshold can also be represented as a basic probability function. The more we learn about the processes leading to clinical disease,[10] the greater the number of variables entered into the equation, and the narrower the probability error for specific diseases. Conversely, the more we improve the mathematical model, the more precise our understanding of disease development. Both collectively and for individual diseases, each of which has its own specific pathway depending on the causative agent(s), the defense mechanisms activated by the host, and their various combinations. Waddington[11] described the robustness of such processes in nature in relation to genetic mutations. However, given the current state of knowledge, the course of most diseases can be identified only by "reverse extrapolation".

4. Application of the Model

4.1 Disease Types Intervention and Cure

Inherited genetic diseases all have the same starting point: a gene mutation. The simplest ones are the single-mutation, autosomal dominant (with full penetrance) Mendelian diseases. Every person with the mutation has the disease, but multiple factors determine its clinical presentation. For example, in Achondroplasia, the presence of the mutation (disease threshold) induces an early and sure biological chain reaction. Thus, according to our model, there is no stage 1 and stage 2 is extremely short. By contrast, in Huntington's chorea, the interval between appearance of the mutation and the clinical symptoms may be decades. Thus there is no stage 1, and stage 2 is very long.

Environmental diseases occur as a consequence of exposure to external factors, such as chemicals or radiation. Their final clinical presentation involves, according to modern concepts, an interaction with the individual patient genome, making both the environment and the genome part of the structure of the subclinical stage In some cases, clinical signs and symptoms manifest years after the disease process has begun, yielding a very shallow angle on graphic presentation of the disease course. However, the exact function on the graph is very complex because not all the protective mechanisms to each exposure are known. It is possible that much of the environment-related damage can be corrected by the body before the critical threshold is reached.

Aging is associated with a time-dependent cumulative weakening of the body's defense systems, which has an additive effect on the cumulative exposure to toxins over time.

Cancers are characterized by a change in cell properties, accelerated cell growth, and absence of cell-growth regulation. Contemporary belief is that most neoplastic processes are halted in the health stage by host defense mechanism and only a few pass the critical threshold. The rate of development varies. For example, skin-cancer-related Xeroderma Pigmentosum appears soon after the cancer cells reach critical mass, whereas in basal cell carcinoma of the skin, this interval may extend up to 20 years. Sometimes, as in environmental diseases, the damage can be corrected by internal mechanisms. Therefore, using our model, cancer can be viewed as both a separate disease and an outcome of a disease process.

4.2Screening

Theoretically, patient screening before the appearance of clinical signs of disease belongs to the subclinical stage, when the medical community can better deal with the disease process. However, in patients at high risk of a specific disease, screening may also be part of the health stage. For example: Routine mammography can detect early breast cancer lesions for earlier and better treatment, improving prognosis. By contrast, testing for the BRCA gene can lead to preventive mastectomy in the health stage, potentially lowering the chances of breast cancer developing.

4.3 Intervention and Cure

Curative measures are usually undertaken after clinical diagnosis of disease and belong in the third, clinical disease, stage. The shorter the interval between the threshold and the intervention, the better the chances of reversing (or halting) the disease process. In many cases, late-term treatments may slow the process but can no longer halt it. Thus, measures taken early in the disease process will be simpler and less costly than targeted therapy given later and will result in less morbidity.

4.4 Preventive Medicine

True preventive medicine operates in the health stage. It eliminates factors that potentially lead to disease (e.g., exposure to carcinogens) or adds factors that strengthen inherent defense mechanisms. There is some evidence that psychological support[12] can also operate in the health stage.

Although intervention before the appearance of clinical symptoms may be impossible in some diseases, usually knowing the critical the threshold will lead to the best of all worlds: cost-effective preventive medicine.

5. Summary

Disease is defined a biophysiological chain of events leading to clinical symptoms. This work presents a three-stage model of health and sickness based on a clearly defined threshold between the two states. The model is intended to improve understanding of the evolution of disease and may have applications in treatment and prevention. It may also be useful for interpreting bioinformatics data and mathematical algorithms of the disease process. Interventions in the first stages of the model, especially before the critical threshold is reached, will be simpler and more cost-effective than later-stage, focused interventions.

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Legend to Figure1: The Pathophysiological Pyramid