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Facing a Shift in Paradigm at the Bedside?*

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ABSTRACT

Our entire medical framework is based on the concept of disease, understood as a qualitative departure from normality (health) with a structural substrate (lesion), and usually an identifiable cause (aetiology). This paradigm is loaded with problems, some of which are discussed in the text. Nevertheless, we study, diagnose and treat diseases, and while often painfully conscious of the dysfunctionalities of this scheme, we can hardly imagine how we could practice medicine otherwise. However, most of the recent developments in basic sciences, and most notably in Immunology, Genetics and -omics, are inconsistent with this "health/disease" paradigm. The emerging scenario is that of complex networks, more in the spirit of Systems Biology. In these settings the qualitative difference between health and disease loses its meaning, and the whole discourse becomes progressively irreducible to our conventional clinical categories. As clinical research stagnates while basic sciences thrive, this gap is widening, and a change in the prevailing paradigm seems unavoidable. However, all our clinical judgments (including Bayesian reasoning and Evidence Based Medicine) are rooted in the disease/health dichotomy, and one can hardly conceive how they could work without it. The shift in paradigm will not be easy, and certain turmoil is to be expected.

Keywords: Clinical Diagnosis; Genetics; Immunology; -Omics; General Systems Theory

1. Introduction

In his influential book "The structure of scientific revolutions" [1], Kuhn argues that the swift and progressive "normal" scientific development is episodically interrupted by "scientific revolutions", characterized by a shift in the prevailing paradigm. This is not just a growth crisis: it leads to profound changes in the areas that are considered "of scientific interest", and both in the tools and the answers offered by the scientific community. Furthermore, during the period in which the old and the new paradigm coexist they remain mutually incommensurable and therefore can hardly be confronted in scientific terms.

This process starts with certain contradictions or dysfunction that the prevailing paradigm considers "minor anomalies" and tends to overlook. Gradually, these anomalies grow and partial responses appear trying to handle them. Finally, they converge in a new paradigm with radically different points of view, which can hardly be understood under the light of the previous model.

We believe something like this may be happening in medicine.

2. Sources and General Outline

Most practicing physicians have to integrate their clinical work—essentially diagnosing and treating diseases—with the ever increasing flow of bioscientific advancements. However, as discussed later, these advances are often phrased in a physiological, continuistic language that clashes with our classical, qualitative, disease-oriented mentality. This tension, as experienced by two practicing general internists, is the origin and main focus of our paper.

The general scheme will be:

- a presentation of the concept of disease as used in conventional clinical practice.
- a discussion on the problems and contradictions of this paradigm.
- the development of disciplines increasingly difficult to reconcile with the conventional disease-centered paradigm.
- a forecast of what may be some of the new conceptual lines sustaining medical practice, and some of the resulting problems.

3. The Origins: The Anatomoclinic School and the Concept of Disease

It is debatable when does the modern idea of disease start. Lain Entralgo [2] would relate it with the development of a clinical diagnosis understood as the intent of direct or indirect visualization (in opposition to imagining) the pathologic process, and he located it to the second half of

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the XVII century, mainly with Sydenham. The following couple of centuries witnessed the explosive development of Anatomopathology, and the notion of disease became rooted in the lesion. This school of thought remains hegemonic until our days, as proved by the role of "final judgment" plaid by pathological studies, and most notably by autopsies.

During the XIX century several important new threads were introduced in the medical fabric. The first was the Physiopathologic school, which tended to explain the disease not so much as the result of an anatomic lesion, but as a quantitative change in the same processes operating in the healthy subject (and conceived the lesion as its consequence). Therefore, instead of searching for specific lesions and naming clinical syndromes, physiopathologists focused on measuring these physiological processes and interpreting them as variations of the same systems operating in every subject.

This blurred the limits between health and disease, and made it more convenient for the laboratory than for the bedside. Therefore, while this has been the prevailing intellectual current in basic research, it has remained somehow peripheral in clinical practice.

The other great XIX century intellectual current was the Ethiopathogenic School. The development of Microbiology, Immunology and later antibiotics resulted in a dramatic improvement not only in our explanatory tools, but especially in our ability to change the course of disease. This, added to its easy melding with the archetypical idea of disease (a qualitative departure from normality induced by an external agent) warranted its over-whelming success. However, under its apparent indisputability lie serious problems, most notably a rather naive "cops-and-robbers-like" causal thinking**.**

4. Anomalies

Almost since its birth, the concept of disease had several drawbacks (**Table 1**):

- Since the beginning, there was a hot debate regarding diseases without an identifiable lesion [3]. Obviously, the first counterargument was that not being able to find a lesion does not prove its absence. However, this debate continues in many fields (*i.e.* psychiatry), and we often recur to vague concepts such as "biochemical lesion" or "intracellular lesion" to justify certain states in which no conventional lesion may be found.
- The standard idea of disease is highly dichotomic (either you have the disease or not), and this trends applies not only to the health/disease contradiction, but to almost every medical sign or symptom. Even obviously continuous variables (temperature, blood pressure, glycaemia, etc.) are immediately dichotomized (febrile/afebrile, hypertensive/normotensive, etc.) using an often arbitrarily drawn threshold, or "red line".
- Although conceptually dichotomic, the disease's borders are extremely fuzzy. It is often impossible to state when an ailment "starts" and when it ends. Areas like Rheumatology are perpetual battlefields between "lumpers" and "splitters" [4]. Practicing physicians often care for chronic patients with dyspnoea in whom it may be impossible to separate heart failure from chronic obstructive pulmonary disease (COPD) exacerbation. While conceptually different entities, the clinical picture is almost indistinguishable, and the final label is chosen somehow arbitrarily. Many physicians perceive a divorce between the distinct vasculitides described in classic textbooks (*i.e.* Wegener's, Churg-Strauss, etc.) and the "gray rheumatology" vasculitides that account for most of the cases seen in daily practice. The neat distinction between embolic and thrombotic stroke presented in books is often difficult or impossible to establish in real life··· the list is endless.
- This "frontier problem" is especially obvious regarding age and "degenerative" processes. The same degree of arteriosclerosis would be considered as the main disease in an elderly patient dying of a stroke, and as normal age-related atheromatosis in the same patient dying in a car accident**.** The limit between dementia and age-related cognitive impairment is arguably blurry at best, and similar observation can be made about osteoarthritis, heart failure and many other clinical entities.
- There is often a striking asymmetry between the "patients diseases" (irritable bowel disease, fibromyalgia) that are often frowned at by physicians, and "physicians diseases" (obesity, dyslipidemia) that are often hardly considered as diseases by patients.
- The disease-centered paradigm is ontological, in the sense that it considers disease as a real entity with proper existence. In this framework one can easily perceive the echoes of the old pre-scientific idea of possession: something that pushes the subject away from natural order (thus becoming a *patient*), and require that Nature acts to restore health. If this is not

Table 1. Problems with conventional clinical categories.

• Diseases without an identifiable lesion
• Artificial dichotomization
• Fuzzy borders
• Ageing
• "Patients diseases" (e.g. irritable bowel syndrome) vs. "physicians diseases" (e.g. nicotine addiction)
• Ontological conception: disease as a possession
• Stigmatization
• Processes evolving in time

enough, we physicians will try to exorcise the ailment. All the metaphoric discourse of Medicine is full of this idea of fight against evil (and we have a therapeutic armamentarium, an antibiotic strategy, or a concept of the Immune System as a "home police"). However, this conception is not harmless, and it often results in dangerous stigmatization. Once a physician has labeled a patient as suffering of psychosis, dementia or COPD, it is extremely unlikely that this diagnosis shall ever be removed, and all further care will be decisively conditioned by this label.

- The lesional bias inherent to the conventional notion of disease is an important limitation in processes evolving in time (*i.e.* dysplasia and "pre-neoplastic" syndromes). This is even more obvious in essentially functional disorders. For example, it is generally accepted that perfusion/ventilation mismatch is an essential feature of COPD; however, since there is no obvious structural alteration to be seen, this cardinal variable is generally overlooked and hardly ever measured.

5. Drifting Fields

The last two centuries have witnessed the development of several areas born under the auspices of the classical paradigm, but that have drifted to become its worse enemies.

The first example is Immunology [5]. It started as an appendix to Microbiology, dealing with the "specific" responses to infectious agents and acting as a "home police" in charge of the "self/non self" dilemma, in perfect harmony with the classic notion of disease. However, in the last decades it has become a complex regulatory system, in which any attempt to separate "healthy" from "un-healthy" functions is naive at best. Nowadays the Immune System is the prototype of a complex network: the precise subject of General System's Theory.

Another example is Genetics. At its beginning, when dealing with hereditary diseases, it seemed just the right example of disease: a qualitative change with a clear cause (either you had the mutation or not). Soon, things became muddy: penetrance had to be considered, mutations in the same gene produced radically different clinical syndromes and the same syndrome could be caused by different mutations. Furthermore, some quantitative characteristics had to be included (*i.e.* number of triplets in heredodegenerative diseases). However, this could be handled as long as the field of interest was restricted to typical Mendelian (and rare) hereditary diseases. The real problem started when dealing with the much more frequent hereditary (non-Mendelian) traits such as hypertension, diabetes or obesity, and it became absolutely out of control when studying somatic mutations (cancer, ageing, etc). Furthermore, the initially "clean and tidy" mechanism of point mutations in specific genes so friendly to the conventional causal mentality was soon disrupted. Although the human genome was finally sequenced [6], processes such as alternative splicing, DNA methylation, protein-DNA and RNA-DNA interactions or changes in the three-dimensional structure of DNA [7,8] made the the classical "one gene-one protein" theory untenable and shattered the conventional agenda of classic Genetics.

Furthermore, and in addition to conventional genetic cross-talk and regulation, there is a new "mesoscopic" level of increasing importance. The behavior of a cell cannot be isolated from its environment [9,10], and the influence of the mesenchymal stroma is crucial in many processes, most notably in cancer. The conventional somatic mutation theory of cancer seems clearly insufficient: tumorigenesis cannot be analyzed at the cellular level, and needs be considered at the level of the tissue.

This mesoscopic level is also missing in functional pathology. Usual pathology operates in two distinct scenarios: a three-dimensional macroscopic level (*i.e.* brain abscess) and a two-dimensional microscopic range (*i.e.* glomerulonephritis). However, certain structures are characterized by a delicately woven fractal structure, often involving several networks (alveolar/capillary in the lung, hepatocytes/sinusoids/biliary ducts in the liver). Classic pathology has no instrument to visualize these structures, and therefore we remain blind to the unfolding from the two-dimensional microscopic to the three dimensional organ level. Nevertheless, it is at this midrange level that some of the most prevalent functional pathologies operate (*i.e.* portal hypertension in cirrhosis, alveolo-capillary mismatch in chronic bronchitis).

The "omics revolution" witnessed during the last 30 years has been yet another nail in the coffin of the conventional idea of disease. Omics are usually understood as the disciplines involved in analyzing the interactions of biological information objects in various omes including genome, proteome, metabolome, expressome, and interactome [11]. By means of new techniques such as DNA microarrays and mass spectrometry, huge amounts of information are collected and organized, opening new windows on the cell's biology. This has changed dramatically our way of understanding and classifying tumours [12]. Gene expression profiles have improved our classification of breast tumours [13] and enhanced our prognostic assessments [14]. The same stands for lymphomas [15], esophageal tumours [16] and lung tumours [17], to cite just a few. Meanwhile, conventional pathology agonizes struggling with its morphologic categories, trying to keep pace with these changes.

Once and again, the scenario that appears is that of intricate networks, complying with the standard requirements of a complex system [18], namely: 1) possessing

information, 2) being neither strictly ordered (as a crystal) nor fully disordered (as a gas), 3) being thermodynamically open, 4) displaying emergent collective properties and 5) having a "history" (meaning that its present behavior is in part determined by its past behavior).

In this context, the classic dychotomic "physiologic vs. pathologic" reasoning becomes utterly meaningless.

6. Complex Networks and General Systems Theory

Medical development during the last centuries has followed the conventional reductionistic agenda: to understand a system one only has to study thoroughly each of its parts. Therefore, the microscope has been one of the most successful tools, and the cellular theory one of its milestones. This program has been extremely successful, and its consequences need not be commented.

However, the reductionistic paradigm has several important limitations: it requires a closed, isolated system, and it has problems handling multiple causal links, or mutual or recursive influences. Elements such as non linear terms or feed-forward loops are also difficult to manage within this model. Most notably, it is unable to deal with emergent properties, that is, properties that are due to the functioning of the system as a whole and can not be understood in terms of its parts (e.g. the characteristics of water can not be predicted analyzing oxygen and hydrogen).

Most of the recent developments in basic medical sciences (genetics, -omics, immunology or cell biology, to cite just a few) clearly fly in the face of the classic reductionistic agenda and are prototypic examples of complex systems.

We still don't have a full-blown alternative paradigm to handle complex biological systems. Some areas such as nonlineal dynamics or fractal geometry [19] are introducing new insights both in basic and clinical sciences, while -omics, Genetics and Immunology are the perfect breeding ground for System Biology [20,21]. In general, the whole topic could be included in the broad field of General Systems Theory.

A full discussion of General System Theory falls out of the scope of this paper, but in short, Systems thinking is the process of understanding how things influence one another within a whole, emphasizing on the properties that appear because of its wholeness. While almost trivial at first glance, the consequences of this approach are often disquieting. Its insistence on links, rather than on objects clashes with our object-centered mentality. Furthermore, given that a strictly isolated system is impossible, it forbids a comprehensive and precise description (or prediction) of any system. As in quantum theory, uncertainty is not just the consequence of our technical insufficiencies, but is built-in in the system. Our knowledge is inevitably limited to a time and space window, and a "complete understanding" is impossible.

7. Conflictive Issues

This may seem remote to our daily bedside activity. But we are constantly faced with the inadequacies of our disease-centered paradigm, while at the same time it is increasingly difficult to keep path with the technical progresses in basic sciences [22]. These developments usually follow the physiopathologic discourse, and its translation to our conventional "health/disease" categories is ever more challenging. As long as basic, rather than clinical, sciences remain the motor of medical progress, this cultural gap is only going to increase.

Naturally, several efforts have been made to bridge this gap. Some postulate that a meaningful clinical categoryzation should stand on solid physiopathologic roots, and thus propose a deductive, "up-down" process [23-26]. Others authors try to avoid any *a priori* bias and propose an inductive, "down-up" course that starting by an open-minded observation of clinical facts would try to relate these data to well-established genetic and physiologic processes [27-29]. In any case, all these approaches rely heavily on new scientific disciplines, most notably network theory, that are not part of our usual medical *curriculum*.

Although this is arguably a non-return process, at present there is no full-blown alternative model to our classic disease-centered paradigm, and all these attempts keep using conventional clinical syndromes as their roadmaps (often tempered by nuances such as "disease phenotypes") while keeping the core problem (the health/disease dichotomy) off the table.

Paradigm shifts are laborious and painful, and often, the old paradigm seems much simpler and friendlier. For instance, the old Ptolemaic geocentric model was much easier and precise than the new Copernican heliocentric model in order to predict the movement of the sun, and its use persisted for decades. However, several inconsistencies could not be resolved within this model, and it finally had to be abandoned.

Of course, it can be argued that the idea of disease is a conceptual crutch used to assist in decision making, and that we do not need to accept the existence of disease as a proper entity per se. On could even claim that the problematic notion is not disease, but rather the concept of health. However, whatever term we use, the problem lies in the dichotomy (health/disease, normal/abnormal) and this scheme is so prevalent in our culture that we can hardly imagine how to care for our patients if we drop this tool. This is the backbone lever empowering Evidence Based Medicine and conventional Bayesian reasoning, and it is difficult to conceive how can they work without this dichotomy.

Therefore, although we believe the change in paradigm is already in its way, in several areas it will face a strong resistance.

In the first place, we will still need "red lines" to make decisions and unleash certain actions. Of course, continuous variables have been with us for long time [30] and one can always draw cut-off points in them, but we will need to be ready for variable limits, heavily depending on the context, and radically different to the "health/disease" scenario.

Most of our conventional tools, and most notably the theoretical corpus of Evidence Based Medicine, shall need a profound refurbishment if we want them still alive. The basic philosophy of EBM (most notably its focus on empirism) needs no change, but its present conceptual machinery is rooted in the idea of disease, and will not survive the classic paradigm.

And probably, the strongest resistance will come from patients (or whatever they become). Not only is the concept of disease deeply rooted in the lay public, but its superseding will require considerable scientific skills. It will be hard to conciliate sound (and technically complex) decision making with the principle of autonomy.

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