A historical review of the concepts of normal/pathological and health/disease

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ABSTRACT

Introduction and objectives. The concepts of normal/pathological and health/disease have been the pillars of the history of medicine and of ideas, in a mutual interaction. These concepts are mutable and have been strongly influenced by cultural and arbitrary factors, both in the past and today. This article presents a historical review of key moments in this evolution, followed by an analysis of key sources and interpretation.

Methods. The concepts in question are analysed first from an etymological and semantic perspective, and subsequently following a strictly historical approach, addressing relevant works in the history of medicine and the history of thought; we shall also consider their role today, analysing reports from the recent literature. Excerpts related to these concepts are placed in their historical context, and their medical and social implications are analysed.

Results. Normal is derived from the Latin *norma*, carpenter's square; therefore, normal would be that which fits or belongs, always in accordance with a predetermined rule or criterion. Thus, the concept of normality has evolved over time to fit the ideology of each era. Pathology or disease was defined by a lack of balance or by external invasion. It was the absence of normality, characterised by the existence of various morbid species. Only in the modern age was the patient's *pathos* or pain accepted as a criterion for disease; now, the concept also encompassed subjective experience, with patients beginning to decide the meaning of disease. Scientific medicine in the time of Comte, Claude Bernard, and Leriche understood health/disease as a continuum that could be explained in both directions. Canguilhem emphasised health as a biological luxury, in a struggle to maintain internal constants in an adverse environment, ideas clearly influenced by the theory of evolution. His disciple Foucault was able to unravel how health came to be possessed by power from the 18th century, as a result of direct productive interests adjusted to the expanding liberal model.

Discussion. After the excesses of the concept of normality from 1857 (Morel and degeneration theory) until 1945 (eugenics), the World Health Organization (1948) created a new concept of health, still valid today, based on a loosely defined status of multidimensional well-being. Marinker characterised new public perspectives of disease based on linguistic nuances (1975); almost at the same time, Lalonde included healthcare systems and lifestyles among the determinants of health (1974). Currently, biomarkers and predictive medicine, exploiting big data and artificial intelligence techniques, have been used to stratify levels of differential risk into bands delimited by clinical criteria. These new models of health/disease are subject to outstanding issues around equity, liability, and privacy. There is a need for collective debate and reflection to avoid repeating the mistakes of the past.

KEYWORDS

Normality and pathology, health and disease, degeneration theory and eugenics, Claude Bernard, Canguilhem, Foucault, biomarkers, predictive medicine

Introduction

Physicians in general, and neurologists in particular, use the terms normal, abnormal, anomaly, healthy, good health, pathological, and disease on a daily basis. An initial reflection on these terms raises questions about whether "pathological" is equivalent to "abnormal" or "not normal," about the criteria for normality, or about who decides whether a person is sick: the individual in

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question or the physician. Clearly, "not normal" does not signify disease, as the norms or rules defining what we call normal are mutable and arbitrary; and the concept "pathological" (from the Greek *pathos*, suffering) does not always overlap with disease because, among other reasons, in modern society, it is patients (and not only healthcare professionals) who are drawing the line between health and disease. These concepts have changed over the course of history, with their mutable features demonstrating how medicine has always been a part of history,[1] shaping it from both a conceptual and a linguistic viewpoint.

The scope of this debate is particularly relevant in our times, in which we have seen an unending emergence of new disorders of essentially cultural character, whose status as entities is debatable; age and longevity are considered as biologically manipulable entities; and we are on the cusp of seeing the availability of procedures for improving healthy individuals that, with bioprosthetics technologies and artificial intelligence algorithms, may lead to the creation of new species, as some leading experts have recently suggested.[2] This subject raises important bioethical questions around the identity of the individual and issues related to equity,[3] liability, transparency, privacy, and explicability, which now represent a challenge for the scientific community.[4,5]

Material and methods

For the reasons outlined above, I thought it beneficial to write this study on the historical evolution of the concepts in question, as they have not always been static. Understanding these changes may be useful in current debates, which once more are raising questions around what health and disease are, and where we should draw the line between the pathological and the healthy. To that end, the concepts in question are analysed first from an etymological and semantic perspective, and subsequently with a historical approach, in works considered relevant in the history of medicine and the history of thought; we shall also consider their role today, analysing studies from the recent literature. Subsequently, excerpts related to these concepts are placed in their historical context, and their medical and social implications are analysed.

Results

Linguistic, etymological, and semantic considerations

The word normal is derived from the Latin *norma*, meaning carpenter's square.[6] Therefore, the concept alludes to something ruled, fitting, belonging, not deviating from the spatial set on which it acts. This is an idea of fit within a pre-established concept. Definitions of normal in the dictionary of the Royal Academy of the Spanish Language also include that of a line perpendicular to a plane, as well as non-geometrical concepts such as "an object being in its natural or habitual and ordinary state."[7] Therefore, abnormal would be that which departs from the norm, the extraordinary, unusual, or unnatural.

Another relevant term related to abnormality is anomaly. The word is derived from the Greek *homalos* (even or equal) with the prefix *an-* (not), and would therefore refer to unevenness, roughness, or irregularity, particularly with reference to a surface, such as the land.[6,7] However, as explained by the French medical historian Georges Canguilhem[8] (1904-1995), this sense has been ignored due to contamination from a similar Greek word, *nomos*, meaning law (hence, for instance, autonomous, "having one's own laws"). Thus, for our purposes, the meaning of anomaly was (wrongly) attributed to *a-nomos*, with the Greek *nomos* or law having been associated with the Latin *norma*, mentioned above. In a strictly semantic sense, anomaly is a descriptive term to describe a fact, whereas abnormality is a normative or appreciative term, referring to a comparison against a value. However, these meanings have been cross-contaminated, with abnormal becoming the descriptive term and anomalous being based on evaluation against a norm. Canguilhem criticises this contamination himself with a reference to Geoffroy Saint-Hilaire; both in zoology and in anatomy, questions had been raised since the pre-Darwinian era about whether the unusual or extraordinary should be considered an error or disorder of nature. Thus, anatomical anomalies, and by extension functional anomalies, refer to the fundamental issue of inter-individual variability and the significance of being a carrier of that variability. It is precisely as a result of this variability that life is able to adapt to new situations and resources, with humans being no exception.

Therefore, anomaly should not be considered equivalent to pathology. Whether or not an anomaly is pathological is a matter of its severity and of the perception of the individual in question, whose mental experience will be decisive in establishing the clinical relevance of the anomaly. Therefore, it is expressivity, tolerance to variation from that considered normal or standard, that determines whether or not an anomaly should be considered pathological. This complicates the issue, as

symptom expressivity depends in turn on cultural factors, which subjects live and experience in their mind under environmental influences that may be intense and cause suffering. Generally, suffering is the decisive factor for that expressivity and the subsequent consideration of the "anomaly" as pathological. For instance, body image disorders or eating disorders are discussed today in these contexts. Ultimately, it is due its *effect* that an anomaly (or abnormality, where the two overlap) is assigned the value of pathology or disease. In essence, the decisive factor will be the value attributed to health and its limits in a given time and place. As noted by Paul Valéry, power without abuse loses its charm.[9] Using the terminology of Canguilhem, the abuse of power lies at the bottom of the love of power or, in our case, the possible abuse of health gives rise to values and limits established for health.

If this results from the lived experience of anomaly as suffering, then it is worth analysing the meaning of the latter term. According to Corominas'[6] etymological dictionary, the verb to suffer is derived from *sufferre*, which in turn is derived from *ferre*, "to bear." It should therefore be no surprise that the first definition of the term in María Moliner's[10] *Diccionario de uso del español* is: "To endure, to support, or to accept without complaint, protest, or struggle an unbearable pain or discomfort": in other words, the sense of enduring that is implicit in the Latin *ferre*. Thus, we may say that a person is long-suffering, that another knows how to suffer, or suffered without blinking the disdain of their peers. This original sense of suffering has been contaminated by that of illness or pain. This sense, *pati* in Latin (*padecer* in Spanish), in which to suffer is to experience a suffering or a feeling, subsequently contaminated the concept of bearing or tolerating, mentioned above, which was the original meaning of suffering, derived from the Latin *ferre*. This sense of suffering originates from the Latin *pati*, which is directly reflected in the Catalan *patir* and the French *pâtir*. Another interesting derivative of the term is patient, which refers to the individual who suffers, the subject of suffering or disease, but which is also used as an adjective in the original sense of suffering (*ferre*): one who is able to wait, to tolerate, and to bear discomfort or pain, suffering in silence. Other familiar derivatives are the antonym of the second sense of patient, impatient, meaning those who are unable to wait or to endure pain or suffering; and compassion and the related Spanish term *compadecer* (sympathise), expressing how the speaker shares and endures the suffering or pain of the patient. The Greek term for suffering is *pathos*, signalling dramatic tragedy; a derivative of *pathos* is pathetic, and the original meaning of the term is just that, to suffer or endure pain, hardship, or feeling. By adding to *pathos* the suffix *logos* (knowledge), we come to the term pathology, so familiar in medicine, which alludes to the treatise or compendium of diseases. By extension, and as a scholarly term, the word pathology has also come to mean disease, as observed in healthcare settings, where we may say that "the patient suffers multiple pathologies" ("pluripathological") or hear such phrases as "multiple sclerosis is a pathology studied by neurologists."

Therefore, from an etymological perspective, the term pathological is not the precise opposite of normal, or the absence of criteria defining the norm. Rather, it would refer to the presence of suffering, a universal mental experience in humans of numerous causes, including the consideration of variability and anomaly, which in turn are frequently influenced by social or cultural factors.

With reference to the other pair of terms, health/disease, the etymology of the former (in Spanish, *salud*) is derived from the Latin *salus*, which means both health and greeting (*saludar*). And indeed, to greet means simply to wish good health. The root of *salus* is *salvus*, meaning intact or sound, hence the expression "safe and sound." Thus, healthy would be that which is whole (the Greek *holos*), intact, complete, and sound.[6,11] This sense of intactness is the origin of the sense of the healthy subject as one who is not aware of the functioning of his/her organs, free from damage and therefore free to act; this is the essence of vitalism assimilated in the strong, healthy, whole subject, an ideal of the vitalist schools of thought that culminated in the 19th century with Nietzsche as its leading exponent. These ideas even persisted into the 20th century, with Pío Baroja writing in his *Memorias de un hombre de acción* (Memoirs of a man of action) that "action for action's sake is the ideal of the strong and healthy man."[12] Therefore, the healthy subject is one who is strong, whole, free of unpleasant sensations, who may fully deliver themselves to their project or action. As we shall see, this concept has evolved since the WHO's definition of a more holistic concept of health, speaking of well-being (a subjective, almost phenomenological concept) in both the physical and the mental and social domains. Once more, social and cultural factors play a decisive role in the semantic change or evolution of the original etymological concept, as above with *pathos* and pathology, and in this case with health.

The sick (infirm) subject would be *infirmus*, lacking firmness, strength, or resistance, having a tendency to fall. Clearly, this term recalls weakness, the need for support; thus, in this case, it is indeed the opposite of the healthy, sound, intact individual who enjoys freedom of action and will, so characteristic of Baroja's thought. This etymological concept of disease as weakness connects well with Hippocratic medicine. That harmonious, balanced society consisted of three orders. The cosmos, responsibility of the priests, the polis, domain of the magistrates, and the body, the sphere of the physicians. The ideas of order and measure (it is no coincidence that the Greeks were great mathematicians and geometers) were expressed in the classical theory of humours. Health was defined by the stability and equilibrium of the humours, and disease by the loss of these characteristics.[13] Given their weakness, the infirm needed a protector or guardian, who would make the necessary decisions on their behalf to recover the balance between the humours and, consequently, their health. As a result, medicine was necessarily paternalistic. As we have seen, this is much in keeping with the etymology of these terms.

Auguste Comte, Claude Bernard, and René Leriche: three conceptions of health and disease

The classical Greek concept of disease as an internal imbalance contrasts with that of possession or invasion by parasites (in a metaphorical sense). This concept of dominance by an external force was the idea held by ancient Egyptians and by hunter-gatherer and pre-Neolithic civilisations. Greek physicians imitated nature and its order to restore the lost internal equilibrium; whereas healers, mages, and pre-Neolithic witchdoctors sought formulae to expel the invading ailment, nearly always through complex rites of exorcism.[13] Surprisingly, Pasteur's germ theory is related to the concept of external agents as the cause of disease, despite its having been developed in the scientific era of medicine; the same may be said of poisoning or diseases of deficiency. In turn, Greek humoural theory found its place in the scientific age with pathologies prefixed by dys-, hypo-, or hyper- (dysfunctions and endocrine alterations with hypo- or hyperactivity, disorders of homeostasis, etc). As a result, curiously, medicine has not ceased to oscillate between these two paradigms of the causes of disease. In both, the subject feels the disease through lived experience. Disease is the result of a confrontation, either with an intrinsically modified internal environment, or with an external invader. The goal of the therapist is to recover the previous, healthy state, defined by absence of the other states. Thus, two qualitative conceptions are at play, those of healthy and infirm, whose limits are less precise than may theoretically appear to be the case. This is due to the need to define the multiple morbid species (a task that has been ongoing since the pioneering work of Thomas Sydenham [1624-1689]) and the relationships between the organs of the healthy and of the diseased body or, rather, the physiology of the diseased body and organs, which would constitute a part of that discipline. Claude Bernard even proposed that the physiology of the diseased body could be understood through understanding that of the healthy body; thus, the physiology of the diseased body would be part of that unique discipline, physiology, which could in turn describe pathology. This may sound unorthodox to neurologists, who have been accustomed to the opposite approach since the first case of motor aphasia was reported by Paul Broca, confirming the localisation of language in the brain.[14]

The normal-pathological continuum has actually been conceived as that of a single quantitative phenomenon. This idea becomes clearer if we take into account the physiological ideas of William Harvey (1578-1657). These reached Morgagni (1682-1771), the founder of anatomical pathology, and resulted in an animation or vivification of anatomy, which became a physiology, expanding that discipline. Thus, pathological phenomena were seen essentially as prolongations or quantitative variations, in one sense or another, of physiological phenomena. The corollary of this is that health and disease were no longer, in consequence, qualitatively opposed. Therefore, the concept of disease became less clear-cut. Science was becoming increasingly powerful at the time, eventually leading to the conviction that the normality that characterised the healthy could be restored through understanding of normal physiology, based on research by health scientists. However, this knowledge was fundamentally drawn from pathology studies. It would be this discipline that would describe the essential physiological traits of the healthy body, in the same way as ideas emerged from the darkness in Plato's cave allegory.

The idea that health and disease exist on a continuum was widely accepted in culture in general and in literature in particular, with a clear impact on naturalism and realism, both in Spain (Pérez Galdos) and abroad, particularly in France (Zola, Renan).[15] Descriptions of the lame, deformed, and sick were numerous, and the pro-

posed treatments were often characterised by methods for returning to the natural and the salutary. Regarding this point, Nietzsche,[16] mentioned above as the philosopher of vitalism, wrote that "The value of all morbid conditions consists in the fact that they magnify certain normal phenomena which are difficult to discern in normal conditions"; for Canguilhem,[6(p20)] these words could have been borrowed from Claude Bernard.

Auguste Comte (1798-1857), the father of positivism (the doctrine that truth is the result of observation and experimentation, rejecting speculation), was an influential author not only on social issues, his main area of interest, but also in life as biology. The objective of this discipline was to reinforce the central concept of progress as the development of order. For Comte, the idea of normal and pathological was that of a shift from a normal to a pathological or exaggerated excitation, which he considered irritation. Disease phenomena essentially coincided with the normal status of health, from which they differed only in degree or intensity; thus, pathology belonged within the set of biology and, conversely, it was possible to transit from pathology to natural physiology. This principle, which Comte adopts from Broussais,[6(p52)] also extended to intellectual, moral, and social functions, using disturbances in these to deduce their normal or ideal natural state. By extension, Broussais' principle could perfect social laws, as social bodies are more complex than individuals and their problems, more severe and more varied; analysis of these bodies would likewise lead to a transition toward the normal or essential state of a society considered ideal.

Examination of the pathological would be richer and more varied than examination of the normal, and could be considered a series of natural experiments, accessible through the study of pathology. It would offer unquestionable advantages compared to experimental or forced studies, in which transitions are sudden and do not resemble the natural course of disease, whose progression and recovery conceal the keys to understanding health. Pathological examination would therefore be richer than experimental studies, as defended years later by Claude Bernard, who would propose a reverse approach, seeking to understand pathology through deep understanding of physiology. Comte's arguments collide with a paradox for positivist thought, based on observation: he proposes no practical example of that which he defends, and therefore ends up in the same position as that which he criticises in pre-positivist thought, speculation. In fact, this limitation is even greater, as he presents no argument explaining how to approach or recognise the normal. Comte shows an aversion to measurement procedures, which he considers applicable only to physical/chemical phenomena and to their laws and mathematical equations, which are greatly different to the essentially qualitative variations that characterise biological phenomena. Normal states would be defined as such with reference to a norm considered valid and desirable, away from which pathology and the different extremes would expand. However, these can only be understood with the language of quantification, which is able to explain homogeneity and variation. In turn, Comte conceives of a physiology/pathology or a normal/disease continuum as parts of a single phenomenon, a kind of expanded physiology (or expanded pathology, if we may), with significant limitations, as we shall see. To justify this speculation, Comte searches for more arguments supporting his sociological theory. Asserting that diseases do not essentially alter vital phenomena, he also lays down the foundations of his political doctrine. Thus, his biological ideas on the oneness of normality/pathology permit him to explain that the treatment for social crises consists in leading societies to what he considers their essential, permanent structure, and not to tolerate changes or progress exceeding the limits of variation from the natural order defined by sociology, a discipline created by Comte himself.[6(p40)] Therefore, we face the problem that normality is defined arbitrarily, according to criteria designed to satisfy ideological or other interests in a given historical moment. Later in the article, this foundation will be exposed as an abuse of normality, beginning in the second half of the 19th century, in 1857, coincidentally the year both of Comte's death and of Morel's publication of the highly influential book *Traité des dégénérescences physiques, intellectuelles et morales* (Treatise on physical, intellectual and moral degeneration).

The thought of Claude Bernard (1813-1878; Figure 1) ran in parallel to Comte's propositions about health/disease, seeking a correlation between them. This led him to conclude that there was indeed a continuum between the two states. However, he took the opposite path: firstly, Bernard considered that physiology should be the starting point to explain disease (in contrast to Comte's approach, reasoning from disease to physiology); secondly, whereas one of Comte's weaknesses was his lack of specific examples and experimental data, Claude Bernard is considered the father of experimental medicine. His

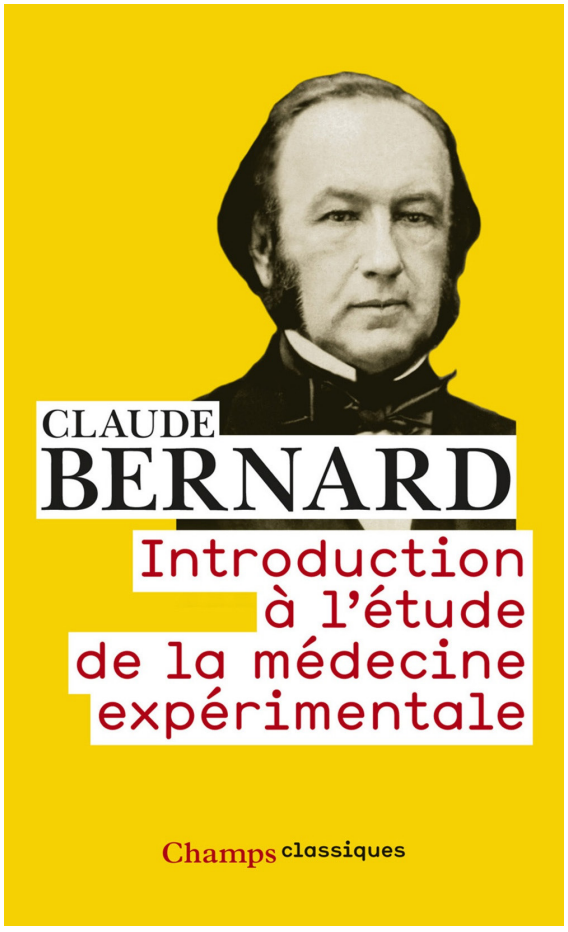


Figure 1. Claude Bernard and the cover page of the edition of his magnum opus used for this article. Bernard's fundamental contributions were in the field of physiology, where he proposed a conception of health/disease as a quantitative continuum enabling disease to be explained on the basis of the normal physiology of the healthy body.

book *Introduction to the study of experimental medicine* is one of the founding treatises on the scientific method in medicine, thanks to its analysis of experimentation and the presuppositions of validity.[17] In this work and in another, *Leçons sur la chaleur animale* (Lessons on animal heat),[18] he sets out his hypothesis that pathology is a physiological state that has surpassed the limits of the natural or normal.

For this distinguished physiologist who experimented with method, complete understanding of a physiological phenomenon would offer insight on the mechanisms of associated pathological states; thus, "physiology and pathology are mistaken for one another; ultimately, they are one and the same."[18(p56)] They differed only in degree, in a context of homogeneity and continuity. Pathological states were situated between two extremes. Bernard questions the ideal of the perfection of health, and recalls that this is merely a normative type and ideal, and should be defined according to experimental data to prevent its becoming an artificial or vacuous concept.[8(p77)] Explaining this concept, Canguilhem calls attention to iatrocracy or medical power, due to the risks involved in defining health as an ideal from a medical perspective, which would naturally refer to the medicalisation of various situations in life, as occurred in the comedies of Molière. The work was published in 1943 (an expanded edition, consulted for the present study, appeared in

1963), five years before the WHO published its definition of health (1948) and nine years before the first edition of the *Diagnostic and statistical manual of mental disorders* (DSM-I, 1952).

The most classic example is that of glycaemia and glycosuria, our understanding of which we owe largely to Claude Bernard, who described hepatic glycogenesis and quantitatively analysed glycosuria, concluding that healthy individuals with normal kidney function presented values of zero. Defining limits for one and another parameter was sufficient to differentiate the healthy from the sick. More remains to be said about animal heat. Bernard was roundly criticised for comparing heat before and after sympathectomy, and for his studies of hepatic glycogenesis: Jaccoud, whose *Traité de pathologie interne* (Treatise on internal pathology) was published in numerous editions, with its translation into Spanish also having a literary impact,[15] even asserted that "the transformation of glycogen into sugar is either a pathological or cadaverous phenomenon."[8(p71)] Bernard even considered there to be a continuity between the chemistry of inert bodies and that of living beings, all of which were subject to universal laws of chemistry and physics, or between life and death.

Logically, pathological and physiological states cannot always be explained through quantitative continuity. This postulate requires abstraction of the effects or consequences of the phenomenon of continuity, as well as its origin: the long-term effects of *different* levels of glycaemia, or the cause of hyperthermia, which determines prognosis, to give some examples. Bernard's theories fit well into the general model of disharmony or imbalance in classical Greece. From this perspective, it is difficult to understand infectious diseases or their effects as a continuum. It was also unable to explain mental functions and alterations to them, at a time when the work of Hughlings Jackson (1835-1911) was leading the way to a new conception of these.

René Leriche (1879-1955) was an unusual surgeon, taking particular interest in pain, which he considered to be a sign of pathology or disease, not a fate for man, a position that had been held for centuries by monotheistic religions asserting that pain possessed symbolic and narrative value of central importance in the essence of humanity.[19,20] Leriche is a significant figure in the history of surgery, partly due to his affirmation that "health is life lived in the silence of the organs" (sometimes erroneously abbreviated as "health is the silence of the organs").[21] This concept implies that, to the contrary, disease would be that which individuals notice in their normal life and activity, and especially that which makes them suffer. This definition confers a central role to the awareness of the disease, due to the limiting mental experience of suffering that this implies. This factor leads Leriche to differentiate between the condition of pathology, or disease as perceived by the physician, and disease proper, or the patient's mental experience. He accepts the existence of asymptomatic lesions as real entities, although the condition of disease always results from the patient's conception, the first condition without which pathology would not exist, as medicine exists thanks to patients and their demand for care.[8(p91-93),21] The patient would literally be a "man in action," as his body would be affected in a new pathological physiology, determining the body and its global manifestations. Curiously, a century after these proposals of Leriche, brain areas have been described that are responsible for so-called sickness behaviours, which overlap with disease in Leriche's man of action (withdrawal, lethargy, anorexia, adipsia). These are considered a form of adaptive response to damage of various origins, which would excite neuron clusters in the solitary nucleus and area postrema.[22]

The distinguished surgeon was also a pioneer in analysing pain as a disease in itself. This was the study model according to which he considered disease from the perspective of its effects, rather than its causes. It should be noted that it was not for another half a century, in the 1970s, that pain came to be defined according to Melzack's concept of a multidimensional mental experience. With this paradigm, Leriche proposed that understanding could be reached from pathology and symptoms, which would elucidate physiology by way of retrospective abstraction from clinical and therapeutic knowledge.[8(p99)] This is reminiscent of Comte's thought, although the differences are greater than the similarities: for Comte, pathology is equivalent to an experiment in a healthy individual, whereas Leriche considers it to be a physiology in itself, that of the patient in action mentioned above, as a discrete entity, as healthy individuals, given their capacity for response and adaptation, could never achieve the responses of the sick individual.

Canguilhem, Foucault, and the abuses of normality

Therefore, it is becoming clear how the historical sources, encompassing a period of nearly a century between

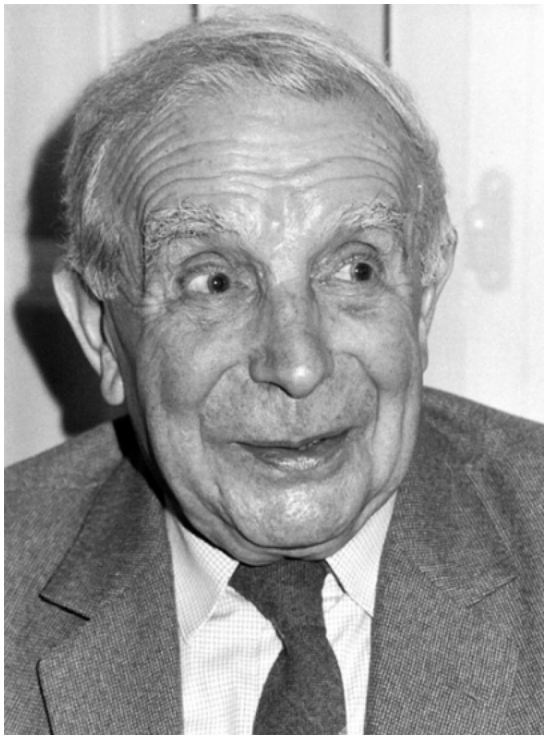
Comte and Leriche, invoking different theories of continuity between health and disease, quantitative variations in one sense or another, are insufficient to define and understand these ideas in conceptual terms. At this juncture, we should discuss the thought of Georges Canguilhem (Figure 2), who served as our guide in the previous section. For Canguilhem, health was a luxury, man's excess in his environment, in his interactions with which he is always vulnerable to disease. For instance, he said that "to be in good health is being able to fall sick and recover; it is a biological luxury," and characterised health as the truth of the body in a situation of exercise[8]; with the latter idea, he recalls Leriche. He conceives of life as a polarity, a struggle between the inner environment of the body and the external or vital environment in which it develops. Thus, "life, as not only subject to the environment but also as an institution of its own environment, thereby posits values not only in the environment but also in the organism itself. This is what we call biological normativity."[8(p227)] The pathological state may be considered normal insofar as it expresses a relationship with the normativity of life, which, naturally, is different than physiological normativity; the two are similar in that rules (though different) exist in both. Strictly speaking, abnormality cannot be defined as the absence of normality, as there is not life without norms; thus, "the morbid state is always a certain mode of living."[8(p228)]

The pathological state is no more than a reduction of the norms of life tolerated by the living subject, which Canguilhem calls a precariousness of norms determined by disease. For these purposes, he considers the other extreme, that of the healthy subject, to be a physiological state rather than a normal state. This is the case insofar as a transition to new norms is tolerated; thus, properly speaking, "man is healthy insofar as he is normative relative to the fluctuations of his environment."[8(p228)]

This ability to respond or to react to the environment, enabling the inner environment to remain within a given range, with flexibility to adapt, represents the essence of the theory of evolution. Canguilhem does not mention it, but his proposed responses of the inner environment (which he terms biological normativity) in the context of an environment with limited resources, which will inevitably lead to a biological struggle, is no more than the concept of fitness or adaptability to the environment. The fact that this is more the case for individuals than for groups constitutes a theoretical difference between medicine in the traditional sense and the theory of evolution. Thus, the objective of medicine is health, hence the fact that it targets individual cases or patients (with the exception of public health/medicine), whereas evolution focuses on populations. Evolution is not "interested" in health, but rather in the aforementioned adaptation or fitness, the multiplication of individuals as a result of their survival and reproduction. In the case of medicine, health implies above all the stability of the internal environment (biological normativity, to use Canguilhem's term) through homeostasis; the external environment may represent a threat to the maintenance of this stability, causing disease when the limits of acceptability are surpassed. In contrast, in the study of evolution, the focus is not on the internal but rather on the external environment and on adaptation to it in ecological terms; as a result, fitness or adaptability to different environments is the defining trait of this discipline, and also has a key role in the success of a population in terms of growth. Continuing this line of argument, medicine often characterises cases with an idealising tendency, drawing a dichotomy between the healthy and the sick, whereas the basic trait in evolution is variability within and between populations. As a result of adaptation and the struggle for existence, evolution is defined by diversity. In medicine, on the other hand, we tend to catalogue or to establish nosographic scales with reductionist thresholds between normal and pathological, according to fluid, debatable criteria.[23] We shall return to this subject in the following section.

Despite the differences between the two disciplines, evolution and medicine, their convergence has been fruitful. For these purposes, and with respect to the mechanisms of the transition from healthy to sick in interaction with the environment, a historically relevant development was the appearance in 1991 of the foundations of Darwinian medicine established by Williams and Nesse,[24] who for the first time integrated evolutionary biology and medicine. This work describes five basic mechanisms enabling an evolutionary approach to any disease or syndrome group (see Table 1 for a summary with illustrative examples). In today's medicine and neurology, the same mechanisms can be used to interpret the epidemiology and mechanisms of the diseases treated in everyday practice.[25,26]

This conception of health almost as a luxury of biology, as described by Canguilhem, is reminiscent of the well-known phrase of Dr Knock, the titular physician in Jules Romain's 1923 play: "healthy people are simply people



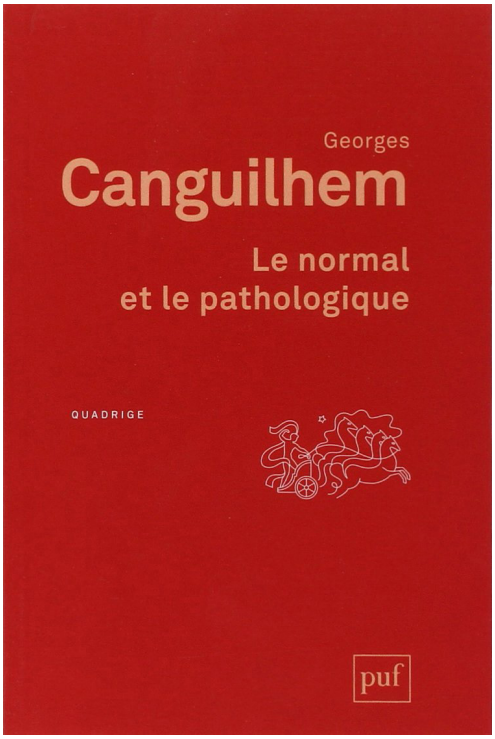


Figure 2. French philosopher and medical historian Georges Canguilhem (1904-1995). Source: ©CNRS Photothèque/OROP. To the right, the cover page of the edition of his work used for this study, which combines the 1943 and the expanded 1963 editions.

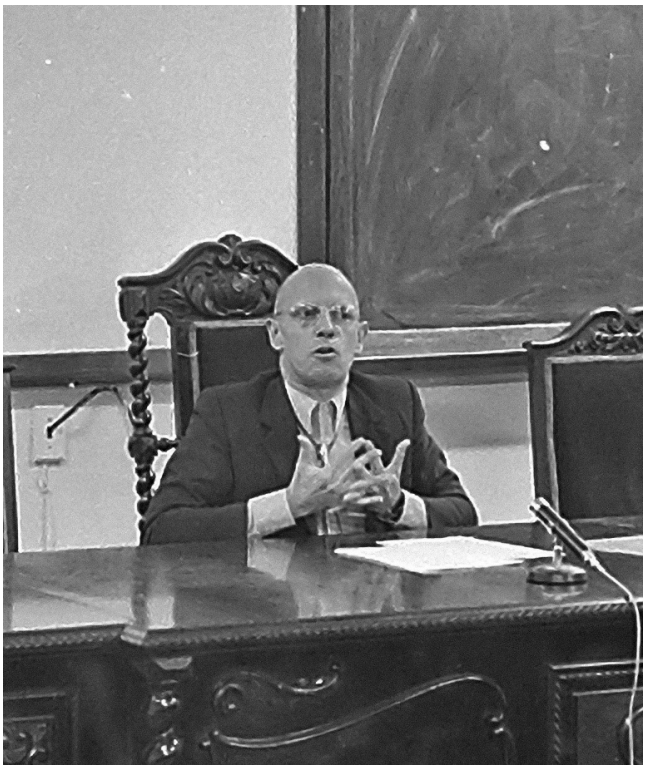
who don't realise they are ill. […] Health is no more than a word whose removal from our vocabulary would have no disadvantage."[21] The same historian of medicine underscored this point in 1943 in a discussion about iatrocracy, mentioned above. This is the context in which we must interpret the work of Michel Foucault (1926-1984, Figure 3) and his interpretation of the medicalisation of pathology in modern society. Foucault, a disciple of Canguilhem,[27] proposes in his work *The birth of the clinic*[28] that health became public from the 18th century in particular, coinciding with several historical sociological phenomena, especially the early days of population statistics and monitoring, with reference not only to epidemics but also to regulations governing cemeteries, food, public hygiene, inspections, and healthcare norms. This resulted in a demand for individuals to be aware of their own health, leading to the nationalisation of medicine in France, with physicians coming to receive similar treatment to the clergy[27]; from that time, the profession was organised "like the clergy, and invested, at the level of man's bodily health, with powers similar to those exercised by the clergy over men's souls."[28(p36)] The physician was a kind of lay healer, who released illness from the body, rather than from the soul (as was the case with priests), and was subject not to the dictates of the church, but rather to those of the state, which thereby watched over the bodies of its citizens as the first stakeholder in their health, as a means of production. Biopolitics had been born. The term, coined by Foucault,[29] applies perfectly to the healthcare policies we experienced recently in response to the COVID-19 pandemic. According to Foucault, medicine took on an essentially normative character with the onset of the modern age. Its field of influence would include what had until then been private, such as morality, liberation, and celebration: "it takes its place in that borderline, but for modern man paramount,

Table 1. The five types of evolutionary mechanisms with direct clinical applications.

TYPE	ORIGIN	EXAMPLE	ADVANTAGE	RISK
Defence (evolutionary root)	Physiological defensive responses	Fever, pain, cough, anxiety, emotions	Homeostasis	Deficit: increased mortality Excess: specific syndromes
Conflicts with other organisms	Evolutionary coexistence	Microbiome Nematodes	Prevention of infectious diseases	Deficit: autoimmune diseases Excess: virulence
Trade-offs	New evolutionary traits	Thalassaemia	Malaria resistence	Increased mortality due to haemolytic anaemia in homozygotes
		Ageing (antagonistic pleiotropy)	Longevity	Age-related diseases
Confrontation with novelties	New environments	Modern society: surplus of foods	Decreased mortality due to famine	Diseases of affluence (diabetes, hypertension, stroke)
		Acces to drugs	Mental experiences	Drug addiction
Limitations of the organism	New anatomical trait	Connection of upper respiratory/digestive tracts	Segregation of the two functions in vertebrates	Aspiration
		Standing erect	Increased visual field Hands free for other tasks	Spinal overload Long femoral neck (fractures)

area where a certain organic, unruffled, sensory happiness communicates by right with the order of a nation, the vigour of its armies, the fertility of its people, and the patient advance of its labours"[28(p40)]; this is also stressed in an influential article by Esteban García.[27(p40)] It seems obvious that the normal and the pathological are a late development in the history of medicine, with a normativity based on biopolitical interests, which are responsible for that healthy/sick dichotomy that would mark the evolution both of medicine and of such social sciences as anthropology and sociology, which in Foucault's view were born of an extension of man as a potentially sick subject.[27(p41)] Disease also affected the mind, giving rise to other forms of normativity and the enormous power of the sciences of the mind, particularly psychiatry, which Foucault anticipated no less than 50 years ago.[30]

Normativity, which as we have seen throughout this article is of cultural (and therefore arbitrary) nature, has historically been associated with certain risks. By this, I refer to degeneration theory and eugenics. Both ideologies were born of the definition of normality based on social norms that became a biopolitics of "public hygiene" through the purging of those considered to have deviated from the accepted definition of a healthy individual. In the case of degeneration theory, Morel's original theory from 1857 established that mental and physical defects were determined through heredity in entire lineages of subjects, who were doomed to disappear due to the hereditary transmission of degeneration.[31] These subjects were marked by and destined to live with crime, alcoholism, intellectual disability, epilepsy, such infectious diseases as syphilis and tuberculosis, or epidemics arising from poor hygiene.[32,33] Poverty was the common environment in which all of these subjects lived (or rather, survived), in extremely harsh settings and a struggle for existence. According to Morel's original theory (Figure



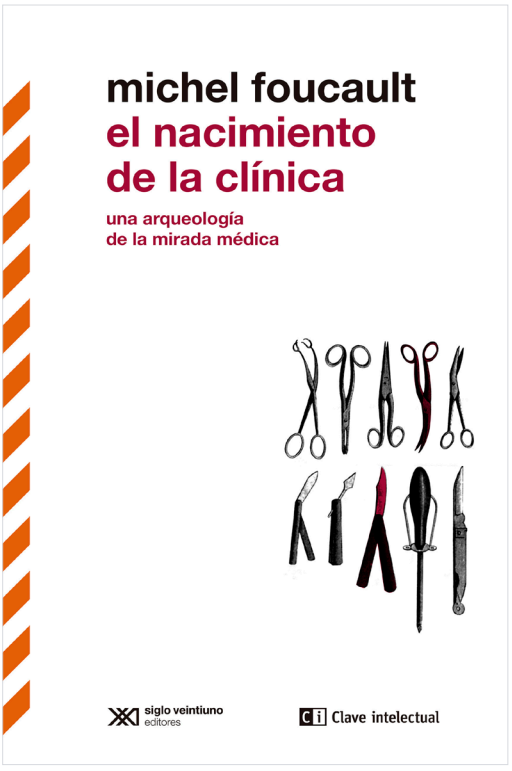


Figure 3. Michel Foucault (1926-1984), the French philosopher who developed an archaeology of knowledge with a profound sense of critique towards traditional social institutions, including medicine and psychiatry. The work shown on the right is the most relevant for the purposes of this article.

4), these individuals and their offspring were destined to die early, and moreover were a scourge to society, which was a potential victim of all their defects, whether crime-related or infectious diseases (syphilis and prostitution were common among so-called degenerates), and even improper mixing with lineages unaffected by these defects. In conclusion, these individuals represented a deviation from the normal primitive or original type of humanity, which had become degraded and was capable of genetic transmission.

The social influence of this theory in the second half of the 19th century was enormous, both in medicine and in such disciplines as anthropology and criminology, and in literature. Degenerates were considered to present certain physical traits, particularly in the cranium and face: microcephaly, flattening of the skull, turricephaly, snout-like facial prominence, etc. These features were connected with Lombroso's criminology, phrenology, and phreno-psychopathology, which were extensively developed in Spain.[34] This theory contributed to the development of expert legal testimony, with well-documented descriptions that enabled characterisation of the typical mental and physical traits of criminals, one of the applications of phrenology. This had practical implications for judicial decisions. Lombroso's proposal was even bolder: he advocated preventive social hygiene, whereby a subject's defining traits would enable the identification of such defects, and consequently the preventive isolation of the individual.

Degeneration theory can be interpreted in the context of a deviation from normality in the sense used by Morel; in other words, the human origin, established as an ideal, which without a doubt was the dominant ideal of the upper classes in the Second French Empire. This deviation was characterised by degradation, defined by a drift towards abnormality. The terms pathology and disease

were not used; rather, degeneration was considered as a pure abnormality or anomaly with social and even political implications. It was no coincidence that Hitler exploited the same theory, above all in art, in which context he referred to avant-garde works as degenerate. Hitler believed that if the authors saw the world in that way, the cause was a deformation of the mind, which was sick and disordered due to degeneration, that stain that he so desired to cast out of the ideal normality of his people. Degeneration served as a didactic argument for the population, which he praised and compared against the purity and the virtues he sought.[35]

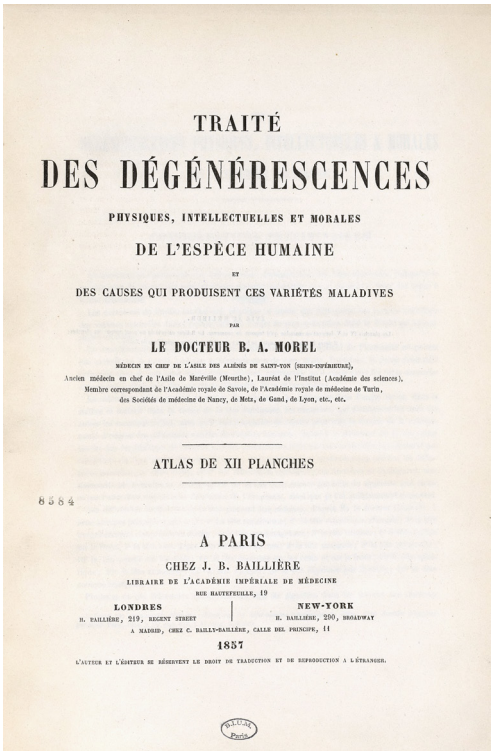
As is well known, entire races and population groups were considered to be degenerates or dangerous, deviations from the norm or ideal. This was the case because of gender or intellectual capacity. This distance from the norm was particularly the case during the heyday of eugenics, an extreme paradigm of normality characterised by sociocultural criteria aligned with the interests of the time. It was defined by Galton, the famous cousin of Darwin, as a form of exaltation of human genetic purity, which was to be preserved and stimulated. Although his objective was to define statistical patterns about the grouping of traits, his proposal to prevent the risk of perversion of the most genetically gifted had a strong societal influence in the first decades of the 20th century. That time was marked by the isolation and alienation of individuals with intellectual disability and numerous other "contaminations" or defects, considered a regression for the purity of the human race (in which, of course, the white race was considered superior). These practices were not exclusive to Nazi Germany, and are now known to have occurred in such other countries as the United States and Sweden, even before the dawn of Nazism.[35,36] In these years, the names Eugene/Eugenia were widely used, eventually becoming less popular in the second half of the 20th century. The English writer G.K. Chesterton recognised what was happening at the time, and wrote a multitude of articles attacking eugenics. This was condensed into a phrase in one of his articles, in which he asked himself the reasons why the world was the way it was, how it had gone so wrong: "what is wrong is that we do not ask what is right."[37] This phrase synthesises his view of the subject, underlining the inability to define what was and was not right in society, what was and was not normal, or what was health and what was disease; indeed, these reflections appear in a chapter entitled "The medical mistake."

From the abuses of normality to the WHO's definition

Societal abuses of normality from 1857 (Morel) until the Second World War gave way to a new concept of normality, which in reality defined health in the best-known terms since it was promoted by the WHO: "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity." The definition was endorsed by WHO member states in 1946, coming into effect in 1948, and has not been modified since.[38]

The concept of health, like that of disease, has evolved over the course of history, as we have seen. Both are closely linked to the concept of person, understood as an individual of the human species. To use the terms of Heidegger, this person, or being, makes itself in the world, in the "there," with the experience and in the care received and later transmitted. Making oneself in the care of that person involved certain rights, including the right to health, such a mutable entity. From its initial link to the concept *sound*, that is, to intactness and salvation (see the section above on etymology), with the modern industrial age health became an essentially functional or dynamic right, linked to the capacity for activity, which according to Foucault's 20th-century interpretation could be attributed to the interests of industry or production. After the perversions and atrocities of this conception in the second half of the 19th and first half of the 20th century, the end of the Second World War saw the recognition of human rights in the International Bill of Human Rights, of clear Kantian inspiration. These included the right to health, understood as a sense of complete, overall well-being of the person in question. This is closely linked to the historic universal recognition of the dignity of the person, who, precisely for this reason, bears rights, with the right to health being essential. Regarding this concept, it should be noted that all spheres of well-being must necessarily be unequivocally linked to the notion of function or activity. This recalls the silence of the organs and the capacity to act and to adapt to the environment, both of which were discussed previously. There is an obvious association with cultural issues related to economy and liberty. Furthermore, the concept of well-being also seems not to be original: we may compare it to Aristotle's *eudaimonia*, the action of being happy through virtue.[39]

In 1974, Lalonde defined a model that expanded on that of the WHO. He analysed the main determinants of individual and collective health, listing four: human biolo-



TRAITÉ

DES DÉGÉNÉRESCENCES

PHYSIQUES, INTELLECTUELLES ET MORALES

DE L'ESPÈCE HUMAINE

ET

DES CAUSES QUI PRODUISENT CES VARIÉTÉS MALADIVES

PAR

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des Sociétés de médecine de Nancy, de Metz, de Gand, de Lyon, etc., etc.

ATLAS DE XII PLANCHES

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1857

L'AUTEUR ET L'ÉDITEUR SE RÉSERVENT LE DROIT DE TRADUCTION ET DE REPRODUCTION A L'ÉTRANGER.

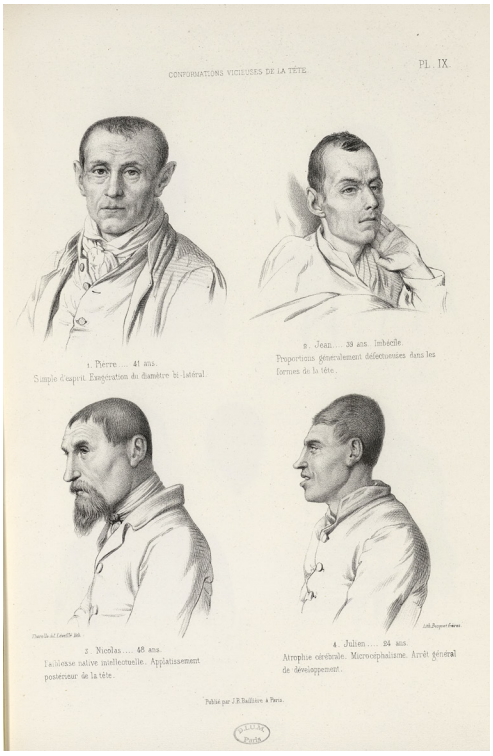

Figure 4. Title page of the original 1857 work by Bénédict Augustin Morel (1809-1873), in which he defines degeneration theory and its implications for the human race. It may be considered the result of an abuse of the concept of normality as a pre-established norm defined by the culture of the time. To the right, an illustration from the book showing the characteristic deformities of the "degenerate" skull and face. Public domain images

gy, environment, lifestyle, and healthcare systems.[40] The objective was to model variables to analyse the interaction of organisms with mental and physical capacities, in environments containing resources allowing for the well-being inherent to healthy lifestyles, in social and environmental equilibrium, all facilitated by healthcare education and systems that led the individual towards that well-being. Though this sounds obvious today, 50 years ago it represented a spectacular advance, which took a number of years to be accepted and integrated as a model of health in different regions of Canada, at the time an exemplary country, where the report was produced.

The WHO definition of health is a more or less imprecise ideal that should be interpreted as an aspiration, something towards which we should move as individuals, without precisely stating what well-being is; how its three spheres are to be defined; or whether it is the same for all individuals, moments in life, and conditions. It is no surprise that this definition, which remains in use today, has received considerable criticism, due to these limitations and others, such as its essential link with the productive nature of the individual. Similar critiques have been levelled at the consequences of the loss of health, which the WHO defines in negative terms as disease: "The alteration or deviation of one or several parts of the organism from its physiological state due to causes that are usually known, manifested by characteristic signs and symptoms, and the evolution of which is somewhat predictable."[38] Once more, the concept only addressed partial aspects of disease, from a clinical perspective, the fruit of centuries of development of nosography, particularly in the 19th century. It disregarded such aspects as the subjectivity and social consideration of suffering, which are essential to integrated healthcare. With respect to this, the proposal of Marinker[41] is particularly relevant.

Marshall Marinker was a general practitioner in the British tradition, who carefully studied the nuances between the terms disease, illness, and sickness.

This distinction is helpful as it considers the mental experience of suffering, an essential characteristic in the phenomenon of being sick. For Marinker, *disease* refers to a pathological process that is nearly always physical, such as a cancer, heart attack, meningitis, or schizophrenia. The essential identifying feature is deviation from a biological parameter or norm. These are objective processes that are empirically evaluable, either directly through the senses or indirectly using tests or instruments facilitating detection of the change in question. *Illness*, in turn, is the feeling, the mental experience of the patient. Thus, it is an intimate and personal lived experience. It may accompany the objective disease, but may also appear, Marinker explains, as a dominant manifestation of earlier or undeclared phases of disease (eg, depression or apathy), or even as a pure manifestation in the absence of objective disease (eg, premonitory manifestations or early discomfort in Parkinson's disease). An even more characteristic case is illness in patients without any evidence of disease in the traditional organic sense. Such has been the case, in a very challenging situation for patients, with disorders in which the dominant (if not the only) manifestation is pain and suffering (fibromyalgia, chronic fatigue, etc). In general, patients face a prolonged struggle to avoid relegation to the subjective territory of illness and to achieve recognition of their condition as a disease. The third term, *sickness*, refers to external perceptions of the unhealthy or sick individual, a public view of what disease is. In this exterior or public domain, disease takes on a role or status, a "negotiated position in the world," to use Marinker's terminology. It may be difficult to achieve this, even if the sickness is publicly recognised, as this does not guarantee equitable treatment or recognition of the facts; thus, its status as an entity in the consideration of others is highly variable.[42]

Moving beyond the healthy/sick dichotomy: biomarkers and preventive medicine

Society has been structured around the dichotomous concepts healthy and sick. This dichotomy facilitates understanding and classification: in simple terms, one is either A or B; thus, being A implies not being B, and not being A implies being B. True/untrue, beautiful/ugly, just/unjust, intelligent/unintelligent, sane/disordered, or healthy/sick. This dichotomous conception divides the world into opposed, mutually exclusive halves, a notion that has impregnated not only medicine but also such other disciplines as the law and social sciences; the distribution of resources and even the prevailing moral attitudes have been (and continue to be) defined by this dichotomy. These conceptions are deeply rooted in neurology and psychiatry, particularly when pathologies are described as disorders defined by symptom groups, as is the case in successive editions of the DSM or the International Classification of Headache Disorders (of which versions 5 and 3, respectively, are currently applicable).

This division between the healthy and the sick, between those with and without a disease, is not the only dichotomy. Such distinctions are also established between entities that frequently share symptoms; for instance, psychosis is observed both in schizophrenia and in bipolar disorder, or pain characteristics in such primary headache disorders as migraine, tension-type headache, and even cluster headache. These patient-reported symptoms are subject to the limitations inherent to language: inability to express the phenomenological essence of emotions and suffering, cultural limitations, biases due to inhibition and communication limitations, fraudulent use of descriptions, etc. These weaknesses constitute part of the clinical descriptions and diagnoses established. As is logical, this is often a difficult process (as demonstrated by the descriptors probable or possible), and the results are often overturned with time (for instance, cluster headache may progress to migraine, or schizophrenia may become bipolar disorder, with reasonable certainty). These terms are of undeniable practical use due to their logical implications beyond diagnosis, such as prognosis and therapeutic management.

Many diseases develop over very long time intervals, potentially over periods of years or even decades. Such is typically the case with neurodegenerative diseases, in which neuronal loss or deposition of pathogenic material is observed at late phases, manifesting as a prolonged silent course whose identification before clinical onset is critical. In the light of the shortcomings of diagnostic criteria and late diagnosis, at advanced stages of disease, in which therapeutic interventions present poor effectiveness, biomarkers have become highly relevant in recent years, especially when they are associated with the concept of risk and its probabilistic management over time.[43]

A biomarker is an objectively measurable trait or characteristic. They are typically considered indicators of a normal or pathological process or of treatment response. These markers are either dry (nearly always imaging studies or solid samples) or wet (generally body fluids, including in "omics" studies, which are currently in vogue). They may have present, future (prospective), or past (retrospective) diagnostic value. It should be noted that biomarkers do not differentiate between cause and correlation, a difference that generally requires other approaches, such as follow-up or dose-effect analysis. However, this limitation does not decrease the value of biomarkers as predictors in time, which is truly decisive due to their diagnostic, therapeutic, and even legal and moral implications.[44]

Regardless of their value as an aetiological factor, biomarkers may contribute valuable information on disease mechanisms. A classic example is phenylketonuria. In this condition, limited metabolism of dietary phenylalanine results in increased levels of the amino acid in the blood. Accumulation of phenylalanine has toxic effects for the central nervous system, and is a perfect predictor of the appearance of intellectual dysfunction (but not of the degree or clinical subtype of dysfunction). This marker enabled discovery of the mechanisms of the disease. However, phenylketonuria is only observed in 1%-2% of cases of intellectual dysfunction; therefore, its predictive value in the general population is very low. Similar situations are observed for proteomics, such a popular subject at present, and other studies analysing genetic polymorphisms in a multitude of diseases.[44] These disorders differ greatly in terms of clinical expression, with markers signalling only a small proportion of the samples analysed with sufficient predictive capacity for clinical use. This low diagnostic and predictive sensitivity could be improved through the combined analysis of multiple biomarkers, including genetic and other wet and dry biomarkers, together with demographic and clinical variables. Multiplexing biomarker analysis enables the construction of actuarial (bioactuarial) algorithms appropriate for artificial intelligence systems. We have an opportunity to translate risk quantification and management from economic sciences to biology, with the use of estimation tools no different than those used in economics or in the insurance sector. In complex disorders, such as dementia, these bioactuarial algorithms are superior to the use of genetics as the only marker.[45,46]

The pleiotropy of biomarkers implies that they present probabilistic information on a wide range of potential disorders or future situations, rather than just one. This limits their validity if we apply a binary perspective to estimation (healthy vs sick; pathology A vs pathology B), as no linear correspondence exists. On the other hand, their predictive capacity increases if estimation accounts for their true value, which is the capacity to signal multiple disorders susceptible to identification in advance through combinations of biomarkers. These concepts also explain the current tendency to stratify patients into groups according to levels of risk, rather than the clear-cut divisions between diseases or between healthy and sick, which continue to be used. Another advantage of this risk stratification is the ability to detect situations of social injustice resulting from the distribution of resources according to classical divisions. These may overlook certain strata or groups of patients (or future patients) who need the same resources at earlier stages, or even individuals whose disorders are not diagnosed as they do not correspond to those established in disease classification systems.

Discussion

Social resources and the objectives of medicine are determined according to the traditional dichotomous understanding of disease. This concept of disease may contribute to the stigma that has come to mark many diseases from a medical perspective. This almost always begins with an underestimation that subsequently takes years to revert; a good example is migraine.[47] Migraine, as well as episodic diseases in general (eg, epilepsy), and diseases with no current significance but which may have repercussions in future, even including sudden death (eg, channelopathy in Brugada syndrome),[48] are those that may benefit the most from the use of biomarkers. Their potential applications for all the disorders mentioned are currently being analysed in studies using big data and artificial intelligence techniques, and may lead to the evolution of the conception of disorder or disease to one based around probability and risk of damage. The bioprediction made possible by the aforementioned actuarial algorithms enables and will enable estimation of the magnitude and temporal profile of risk. As a result, we may see a paradigm shift in the understanding of disease, with clear benefits for individuals, large groups of whom will be reified as patients, included in healthcare maps as individuals in need of healthcare.

The validity of the concept of disorder inherent to these procedures will continue to need the same criteria as those applied in traditional definitions: essentially, disorders must be recognised (face validity), applicable in practice (construct validity), and robust in different contexts and times, including in a future in which a plethora of data are available.[43(p44-45)] Clearly, these disorders do not fit current diagnostic categories, nor the dichotomous conception of diagnosis; rather, as noted by Baum, they "[blur] the distinction between the silo of an existing disorder category and the meta-silo of non-disorder."[43(p46)] Thus, disorders will be systematised according to a key supposition, that of risk. The term is derived from the Italian *risco*, referring to dangers at sea, and signals the existence of contingency or imminent damage.[6,11] The relevant consideration here is not the presence/absence of risk, but rather its magnitude; thus, when we talk about disorders under this new conception, we describe the likelihood of dysfunction.

The conception of disease or disorder as a likelihood of dysfunction involves three conditions: variation with respect from a biological average; association with increased likelihood of damage; and the existence of an alteration that implies a particular response. Thus, rather than merely the variation between individuals, it is the direction or sense of the change that is relevant, and above all the outcome in terms of the functional limitation that, moreover, implies an alteration requiring medical attention. These three concepts were introduced by Boorse, Wakefield, and Gert, respectively,[49] in the field of mental disorders. They stand in contrast to the definitions of the DSM-5; this is particularly the case for Gert's more comprehensive definition. The latter, in addition to deviation and damage, also accounts for risk, which, as mentioned above, is critical in the characterisation of disorders that frequently present overlaps (as a result of the pleiotropy mentioned previously), which with these tools may come to be considered with present and future prognostic value. Some other points related to variability and likelihood of damage are also worth addressing.

Variability is important, as the concept is sometimes very difficult to define with regard to a natural, physiological function or trait. An illustrative example of this are disorders related to ageing, which can be very difficult to delineate. The difficulties arise from genetics, as genes are generally pleiotropic and their effects may be favourable during one stage of life (generally at young ages) and harmful at others (generally in old age). This hypothesis was proposed by Williams in 1957, with the name "antagonistic pleiotropy,"[26] and is supported by a growing body of evidence from multiple species and different aspects of ageing.[50] Dementia is one example of this. In this context, it is difficult to establish whether the dysfunction observed is the result of antagonistic pleiotropy, or a real disease. Rather than merely the effect of natural selection for variation, the decisive factor will be the consistency of the association between genetic variants and the damage defined as a disorder; in terms of risk, we would measure the unidirectionality of variation, rather than its magnitude. The imprecision of variability in characterising disorders has led to the proposal that the reference framework should be the so-called image averaging, a concept borrowed from crystallography, in which an average image is calculated from an "agnostic" position (blind to the effect), with validity for a multitude of variations, yielding replicable average image models that serve as controls. These images are used to characterise disorders and define probability functions for each type of damage and risk.[43(p54-57)]

Bioprediction would use past and present data to estimate the likelihood of future damage and dysfunction. In general, it is expected to work synergically with traditional conceptions of disease, reinforcing them rather than excluding them. This probability includes time, a factor associated with risk. Correct estimation would enable differentiation of self-limited disorders, in which the probability of damage decreases over time. The likelihood of dysfunction is represented by a set of graphs, differentiated for general and specific damage, tracing a complex landscape of that probability function. There, we may identify groups or clusters, always taking into account the fact that variations in a given biomarker may change the likelihood of damage in one or several groups simultaneously, due to the aforementioned pleiotropy of many biomarkers. The resulting landscape is made up of a series of three-dimensional wave functions capable of estimating the specific risk of damage over time. Wave functions change in line with environmental modifications, constituting the probability function. A typical example is the quantification and probabilistic representation of cardiocerebrovascular disease in relation to various events and risk biomarkers over time.[51] Dynamic changes are observed and modified as biomarkers appear and disappear over time. Establishing the point at which these probability functions constitute dysfunction requires clinical judgement. In the previously mentioned

example of cardiocerebrovascular disease, this was defined by Karlawish[52] as the point at which the probability of a cardiovascular event is sufficiently high that a clinician should recommend an intervention to reduce this risk. These types of analyses and proposals have also been studied for such other neurological conditions as Alzheimer disease.

Establishing the probability thresholds beyond which clinical judgement should indicate the onset of dysfunction requiring a response is a challenging task that turns medicine into an elaborate exercise in risk management.[43(p66)] The likelihood of dysfunction becomes the likelihood of damage, justifying an intervention to reduce the likelihood of the event occurring in the future. Estimating these risks may lead to different responses in other areas, such as law, due to issues of moral liability, or in the social sphere, due to the implications for social equity.

From the perspective of biomarkers, risk/probability, and time, medicine is rebuilding the classical nosology in terms that more accurately represent the magnitude and form of risk of occurrence of events. These are subject to clinical judgement, which must establish thresholds for a therapeutic response to different disorders. Disorders will be grouped according to risk bands, which will delineate a new nosology. This approach, based on the concept of risk/damage, will facilitate clinical decision-making and the incorporation of strategies to prevent individual and clinical as well as moral and social harm. This evolution of the paradigms of health/disease has wide-ranging implications for medical training, which must address the concepts of probability and risk, computing, artificial intelligence, and communication skills; it will also have repercussions for the general public, who must know and understand its basic foundations.

Conflicts of interest

The author has no conflicts of interest to declare.

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