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Dissecting the Meanings of "Physiology" to Assess the Vitality of the Discipline

Introduction

Physiology is one of the central disciplines on which all biological and medical sciences were historically built (63). However, questions have recently been raised concerning the relevance and vitality of physiology and its ability to make a useful contribution to biological and medical sciences. Physiology is sometimes seen as a discipline of the past that is "dying" in the era of molecular biology and high-throughput DNA sequencing (5, 50, 77, 96). However, close scrutiny would suggest a less clear-cut picture. Not everyone would agree with claims that the intellectual discipline of physiology is dying, or perhaps even already dead (97). They feel that physiology has gradually "disintegrated" precisely because it has given rise to a series of daughter disciplines, such as neurosciences, immunology, and endocrinology (45, 74, 84). According to this view, physiology is not so much "dead" as a key element underlying some of the most dynamic fields in the biological sciences of today, including the various -omics disciplines (120). Some would even defend the view that physiology remains a key field in modern-day biology and that it could perhaps inspire renewal in other biological disciplines, including molecular biology and evolution (24, 51, 84, 86).

This conceptual review aims to introduce physiologists to the philosophy of biology and medicine. We argue here that the claims made about the vitality and utility of physiology depend heavily on the definition of "physiology" adopted. We distinguish between two families of definitions of physiology found in the scientific literature. Some focus on what physiology is about—its *object*—whereas others focus on how physiology is used to study the biological reality—its *method*. Within each definition, we will examine the claims about the vitality of physiology. We will consider the specific features of physiology and whether it can continue to play the integrative role it has played in the past, with the capacity to unify diverse biological approaches and experimental data through common concepts or explanatory principles. The results of this conceptual investigation are shown in Table 1.

In a nutshell, physiology can be viewed from two different angles. If we use a line of reasoning according to which each biological science provides its own contribution to the general functional explanation, then physiology now coexists with other disciplines. On the other hand, as a science with a specific object, the normal state of the whole organism, characterized by homeostasis, physiology is constantly reinventing itself and will continue to make a crucial contribution to other disciplines.

What is Physiology? Lessons from the Historical Development of a Discipline

Physiology has very deep, rich historical roots providing important insight into the current status of this discipline. A quick glance at the history of physiology highlights three key debates:

1) Is physiology a general all-encompassing biological science, or, much more modestly, simply the medical investigation of the functions of human organs?

2) Can a single, highly general phenomenon, such as homeostasis, serve as the basis for integrating knowledge about organisms?

3) Can physiology be identified with a specific experimental method?

The first of these debates concerns the status of physiology as either the broadest biological science or, much more humbly, a domain focusing primarily on humans and their health. Physiology has a long history. It has often been stressed that the roots of physiology lie in the works of Aristotle and Galen, and the term *physiology* was first coined by the French physician Jean Fernel in his *De Naturali Parte Medicinae* in 1542 (34). However, the meaning of *physiology* has changed significantly during the course of the history of this domain. In the 18th century, in particular, physiology had a broad, not specifically medical sense, encompassing animals and plants, very much like the modern term "biology" (114). This tradition culminated at the start of the 19th century with Dutrochet's claim of the unification of the general science of physiology around phenomena such as osmosis (1). At around the same time, Schwann generalized the notion of metabolism, and both of these scientists promoted the idea of cellular physiology as a fundamental biological science applicable to all living things (28). Cuvier, through his conception of comparative anatomy based on functional correlations between organs, also contributed to this idea of a broad science (3), and "comparative physiology" developed in parallel with "comparative anatomy." However, the term *physiology* has also been used in a more restricted, medical, and human-centered sense (22, 23), which has also undergone major shifts in meaning. Physiology was long considered a branch of anatomy (54), particularly at the institutional level, but also, to a lesser extent, intellectually. However, in the 18th and 19th centuries, physiologists began to show that function could not necessarily be deduced from structure (13), thereby relegating anatomy to an ancillary role (63, 114). This development led to a large number of physiology laboratories, departments, and societies being created in a general movement of liberation from both the anatomical and medical contexts. This debate about the object of physiology and its degree of generality (i.e., is its object limited to human health, or much more broadly, the entire living world?) is still alive today.

The second debate concerns the possibility of using a single phenomenon as the unifying basis of physiology in general. Historically, physiologists endowed various phenomena with a central explanatory power in the general science of

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Table 1. ***An examination of the most frequent definitions of the discipline of 'physiology' in the scientific literature***

Definition of *Physiology* in the Literature	Explication of This Definition	Is Physiology Alive in This Sense?
	Method	
Physiology is the science of functions	Physiology focuses on identifying the causal contribution of a part to the whole organism.	Alive but complemented by emerging biological disciplines not based on the explanation of biological phenomena through the assignment of causal roles.
Physiology is the main explanatory domain of the biological sciences	In this view, many life sciences are descriptive, but physiology is distinctive in that it aims to provide explanations of biological phenomena.	Alive but complemented by emerging biological disciplines that do not provide explanations.
Physiology is the basic science of organisms	In this view, biological data become intelligible only after their integration into a physiological framework.	Alive since physiology is indeed *a* basic science based on a template of multiple layers of functions, but it is not necessarily *the* basic science in organism biology.
	Object	
Physiology as the science of physiological and pathological phenomena	Insofar as it includes pathophysiology, physiology can be defined as the science of healthy and pathological phenomena.	Alive and necessary, but not sufficient to explain how physiological phenomena become pathological
Physiology as the science of the integrity of the organism	This definition is understood in at least two senses: *1*) Physiology takes into account the organism as a whole when considering biological phenomena. *2*) Physiology investigates the role played by "unifying systems"—particularly the nervous and immune systems—in the integrity of the organism.	Alive, but often vague. Physiological integration (in a hierarchy of embedded functions) must be complemented by other forms of integration. The nervous and immune systems are endowed with the capacity to unify the organism into a cohesive whole.
Physiology as the science of a highly general, almost universal, biological process: the case of homeostasis	Physiology has focused on phenomena observable at all levels in all living beings, including homeostasis in particular.	Alive but requiring complementation when the identification of interactions between physiological systems leads to the search for non-physiological explanations. Alive and fruitful when a homeostasis-based reasoning leads to the discovery of novel, "cross-system," physiological phenomenon.

Since it would be impossible to investigate systematically all published definitions of physiology, we tried to group together consensual and common views (*left*), especially in the context of the alleged crisis in physiology. We then used the philosophical method of conceptual analysis, or "explication," to explain what these definitions refer to (*middle*). Finally, we propose a critical assessment of these definitions in terms of the vitality of physiology in modern science (*right*). One of the results of our analysis was the distinction between object-based (*bottom*) and method-based (*top*) definitions of physiology.

organisms. In the 18th century, living organisms were characterized by integrated mechanisms, systemic properties, or what was then called "living economy" and later became "animal economy" (114). This aspect was seen as the specific object of physiology at the beginning of the 19th century. By focusing on how organisms become autonomous with respect to variations of their environment, Claude Bernard defined the *milieu intérieur*, a basic phenomenon in every organism (6). Cannon stressed the importance of a dynamic equilibrium between essential parameters, which he referred to as *homeostasis* (15). These different views have in common the idea that it is possible to unify physiological processes under the banner of a single fundamental phenomenon of life. Again, as we will see below, many modern physiologists continue to share this ambition for their discipline (108).

The third debate concerns the possibility of identifying physiology with a specific experimental method. Physiology became a fully fledged experimental science in the second half of the 19th century. At the time, physiology was firmly entrenched in a hypothesis-driven approach, promoted, in particular, by Claude Bernard (6, 8), considered by many to be the "founder" of experimental physiology (29, 43, 82), although other pioneers preceded him (42). One key question concerns the extent to which physiology can be identified with the use of what were then new, cutting-edge, specific detection and intervention techniques, such as electrophysiology or experimental lesions, as in the work of François Magendie, Johannes Müller, Claude Bernard, Herman von Helmoltz, Ivan Pavlov, and Charles Sherrington (63). Were the continual, rapid changes in technology accompanied by changes in physiology? Or did physiology remain associated with technologies invented at the end of the 19th and beginning of the 20th centuries? The influence of new experimental tools, transforming the field of physiology, continues to be a matter of debate for the physiologists of today (98).

The definition of the discipline of physiology and estimations of its current relevance depend very much on which of these historical debates is considered the most important. Evaluation of the status of physiology in modern life sciences depends heavily on, for example, whether physiology is still seen as an all-encompassing discipline, whether it is seen as associated with a general phenomenon, such as homeostasis, or whether it is considered to be based on the use of specific experimental methods, such as electrophysiology. These different standpoints make it difficult to propose a general characterization of physiology, and at least some of the disagreements concerning the vitality of this discipline arise from the different conceptions of physiology held by different researchers.

Despite these uncertainties, history suggests that a possible overall definition of physiology can be devised from its *method* and *object* (Table 2; see also Table 1). Such a definition would probably also be representative of the views of contemporary physiologists concerning their discipline. Methodologically speaking, physiology is *explanatory*, its explanations are of a *functional* kind, and it is *integrative*. Thematically, it focuses on phenomena considered *normal* or *pathological*, on the *integrity of organisms* or on *general phenomena* common to many or even all living things, such as homeostasis.

Below, we provide a detailed justification of this characterization of physiology in terms of its method and object, and we show that the current vitality of physiology can be assessed with reference to this classification.

Physiological Methods

In this section, we show that the primordial goal of physiology is *explaining* a system's behavior, rather than predicting or controlling it, and that the explanations provided are based on *function*. Some recent, innovative approaches have diverged from this rationale of explanation based on function. It remains unclear whether these approaches should be seen as offshoots of physiology or of other disciplines. As we shall see, those inclined to see them as offshoots of physiology tend to view physiology as an integrative science, at the risk of reducing it to a synthesis of preexisting knowledge rather than a source of new knowledge.

In this examination of the methods of physiology, we will begin by considering why attempts to explain phenomena on the basis of biological functions play such a key role in physiological science. We will then show that the relevance of physiology has been called into question precisely because emerging biological disciplines either do not explain biological phenomena in terms of function or do not explain them at all. Finally, we examine the claim, often made by physiologists themselves, that physiological methods remain the best way to integrate biological knowledge.

The Central Role of Function in Physiology

One hallmark of physiology is its search for *functional explanations*. The identification of functions through their experimental neutralization provides information about the contribution of part of the organism to the whole, and an explanation of this function:

> *"Successful physiological analysis requires an understanding of the functional interactions between the key components of cells, organs, and systems, as well as how these interactions change in disease states" (79).*
> *"Physiology, in my view, is clearly characterized by asking the truly functional questions. These questions can only be answered by continuously integrating knowledge from other disciplines into the larger scheme of mechanisms that allow organisms to actually live" (97).*

Philosophers of science have characterized "functional analysis" as the decomposition of a causal role of part of a system into a flowchart of functions (21). Functional analyses generally consider one of the effects or outputs of a system. They consider the causal interactions between parts, called "functions," relative to the effect of interest. Each of these interactions can, in turn, be broken down into causal interactions between subparts. The result is an explanation. There is some debate among philosophers of biology and medicine as to whether this is sufficient to define a biological function (41). However, physiology has been based on such functional analyses since its inception. In our view, therefore, the most adequate definition of physiology is a *science explaining functional organization*.

If this characterization of physiology is correct, then the strongest challenge to this domain is not the appearance of other experimental sciences but the recent emergence of both *non-functional explanations* and *non-explanatory approaches* in biology.

Non-Functional Explanations of Biological Phenomena

Innovative approaches, such as systems biology, have recently provided explanations for biological phenomena that are not functional in nature. If such non-functional explanations are valid, then it would be overstretching the mark to suggest, as some have done, that systems biology, in its entirety, is just a new incarnation of physiology.

Let us begin by considering one of the many examples of a non-functional explanation. The Gomperz-Makeham equation describes changes in the probability of death over time in a living organism: $m(t) = I.e^{Gt} + E$, where I is intrinsic vulnerability, G is the rate of aging, and E represents environmental risk. G has been observed to be constant. Kowald recently proposed a simplified systems biology hypothesis concerning aging in which G is expressed in terms of mathematical functions describing the stochastic accumulation of mitochondrial defects (62).

The *explanandum* (i.e., what is to be explained) is the change in the probability of death over time. The *explanans* (i.e., what the explanation is based on) is this mathematical function expressing the stochastic accumulation of defects. This explanation must be considered "non-functional" because it is not based on biological functions. Indeed, physiological functions, or at least their loss, instead define the *explanandum*.

Table 2. *Characterization of physiology on the basis of its method and object*

Method	Object
Physiology is:	*Physiology is the science of*:
• An explanatory, as opposed to observational or predictive science	• Normal and pathological phenomena
• The science of functional explanations of living phenomena	• The integrity of the organism
• A basic science into which all the results of other biological sciences must ultimately be translatable	• General phenomena common to many specialist fields in biology

Philosophers have pointed out that systems biology sometimes resorts to explanations of *functions* by an *explanans* that is not itself a set of functions:

> *"In a first approximation, systems biology may be said to study the interactions between the components of biological systems, and how they give rise to function and behavior by using a series of 'omics' operational protocols" (12).*

Moreover, one of the aims of systems biology is to decompartmentalize knowledge about the interactions occurring within physiologically defined systems performing particular functions, to achieve generalization to the interactions of various components of various systems, as highlighted by the philosophers O'Malley and Soyer (90). In this respect, systems biology contrasts with physiology, and with the major result of a long physiological tradition: the "breaking up" of the organism into well-delineated and functional "apparatuses" or "systems." This tidy view of the concatenation of compartmentalized functional systems into a whole may, in some cases, hinder understanding of how organisms work. Along the same lines, the philosopher Philippe Huneman provided several examples of explanations of robustness—an essential property of biological systems at several levels, but not a function—in terms of topological properties (47). For instance, scale-free networks, in which a small number of nodes are highly connected and large numbers of nodes are poorly connected, are rarely disrupted by random mutations, which have an equal likelihood of striking any of the nodes of the network (4).

Functional explanation is a crucial element in physiology. However, functional explanations, although not obsolete, naïve, or inadequate, are not the only possible explanations applicable to organisms. Non-functional explanations also exist and are increasing in importance in modern biology.

Non-Explanatory Approaches in Modern Biology

There has recently been an increase in the use of approaches that do not seek primarily to provide an explanation of the phenomenon considered but rather to *predict* and *control* it. This is particularly true of approaches based on systems biology and computer models. One of the many possible illustrations of this trend is provided by research on cancer treatments. In particular, "immunoscore," expressing the degree of immune cell infiltration into the tumor, has recently been proposed as an alternative to the traditional TNM score, based on the presence of cancer cells in the tumor (T) and lymph node (N), and the presence of metastasis (M) (2). The advocates of immunoscore use have claimed that this score is superior to TNM for predicting disease outcome and treatment response for some cancers (37). This approach, which is based on systems biology, the use of complex computer models, bioinformatics, and big data (36), does not seek explanations in the way that physiology has traditionally done. More generally, approaches focusing on prediction and control rather than explanation have rapidly risen to the fore in many areas of biology and medicine over the last 10 years. These approaches can inspire, and be inspired by, physiology, but are not themselves physiological, in that they do not focus on explanation.

Is Physiology the Basic Science of Organisms?

In the eyes of many physiologists, non-physiological scientific results, such as those described above, acquire explanatory or predictive power only at the expense of clarity. According to this view, the findings of systems biology, for example, become meaningful and explanatory only when re-interpreted physiologically. The general idea is that systems biology provides tools for data collection, whereas only physiology can render the results intelligible. As Joyner put it:

> *". . . without a narrative approach that includes hypothesis testing and key concepts like homeostasis, systems biology runs the risk of becoming scientific 'Abstract Expressionism'" (51).*

According to the defenders of this view, clarity can only be achieved by placing the knowledge gathered in non-physiological approaches into a framework, by *integrating* it into a *physiological* picture (52, 78, 79, 97). Without this integration into a physiological framework, biological claims cannot be correctly understood and explained. This is one of the implications of the notion that physiology is an integrative science and has been used to support the claim that physiology should be seen as the basic science of organisms.

One argument that can be used in support of this view is that the functional template provided by physiology is not generally likely to be called into question by the results of non-physiological approaches. Indeed, in most cases, non-physiological approaches do not provide a novel functional explanation; they merely provide more detail and fill in gaps in our knowledge. This is what Noble calls the "boundary conditions" of the higher level on the lower level (82), meaning that results must be assimilated into a template at the organism level, just as the inner workings of ion channels cannot be understood without looking at the bigger picture of cell voltage.

However, we think that this argument can be taken further since, in principle, there should always be a conceivable functional explanation of the phenomenon considered. The real question, therefore, is not so much whether physiology is *a* basic science but whether it is *the* basic science. The question thus boils down to what we consider to be ultimately clear or intelligible, which remains a matter of debate. As pointed out above, some would argue that systems biology provides intelligibility through mathematical models rather than functional templates (49), whereas others might claim that chains of chemical reactions or an evolutionary perspective also provide intelligibility without being based on function.

There is no reason a priori to suppose that our understanding of what an organism does should necessarily involve the interplay of functions, or for assuming that anything the organism does could not be understood in this way. Thus physiology is indeed *a* basic science based on a template of multiple layers of functions, possibly encompassing all the knowledge about organisms collected, but it is not necessarily *the* basic science (i.e., the ultimate or most elementary science) in organism biology. As such, physiology is neither timeless nor outdated, because its descriptions of higher-level systems are not necessarily final and can, in principle, be modified in line with the results of data-intensive biology, certain phenomena may remain unexplained, and the descriptions generated are relevant for the organization of the information generated by this approach into a base of knowledge.

Thus physiology is primarily defined by a specific approach, a functional, explanatory, and integrative approach. As such, physiology is alive and well, but it cannot be the all-encompassing discipline that it once was. Over the last decade, it has become increasingly clear that physiology must coexist with other approaches because it is not the only way to explain phenomena and because explanation need not be the sole goal of biology.

Objects of Physiology

We will now turn our attention to definitions of physiology based on its object of investigation. What is the specific object of physiology, as opposed to other biological sciences? What we refer to here as the "object" of physiology is a highly general property of living beings forming a distinctive focus of interest for physiology. As reported in Table 2, this object has been defined in the physiological literature as "normal" as opposed to "pathological" processes, as the integrity of the organism as a whole, and as universal or quasi-universal biological processes, such as homeostasis. Below, we consider these three conceptions of the object of physiology.

Physiology as the Science of Physiological and Pathological Phenomena

Physiology has sometimes been defined as the science of healthy phenomena, and sometimes as the science of both healthy and pathological phenomena. This distinction, however, has been blurred by the emergence of molecular biology. Indeed, it is not always clear at the molecular level whether a phenomenon is "physiological" (normal) or "pathological" (abnormal). It has been suggested that this distinction is no longer relevant to the general science of living organisms. It has even been argued, by most philosophers of medicine (14, 19, 32, 87), with the notable exception of Christopher Boorse and some of his followers (10, 46), that this distinction is not grounded in hard science but merely reflects our values.

This argument may be robust, but it does not necessarily imply that physiology has become dispensable or is a remnant of the past. Physiology remains a basic medical and biological science. Rough physiological descriptions of mechanisms serve as operational and objective proxies for our intuition that some states are "bad." These states may be considered to be naturalized clinical entities, in that they provide a robust causal model of the basis for clinical manifestations of disease (64). When a molecular biologist scrutinizes complex processes, such as cascades of biochemical reactions, it is tacitly assumed that these processes are involved in physiological phenomena, pathological phenomena, or both, in that they can be causally linked to physiological or pathological, that is, *biological* processes, themselves known to underlie certain states or behaviors. We know what happens during fever, cardiac insufficiency, bronchial asthma, vomiting, diarrhea, cramps, fainting, headaches, and so on, although we do not always know why these phenomena occur. In philosophical terms, physiology is, in such cases, the science of the *explanandum* of molecular biology, that is, the *prima facie* biological phenomenon to be explained, rather than the science of the *explanans*, that is, the underlying processes explaining the phenomenon (see FIGURE 1).

Thus, as the science of the nonspecific phenomena explaining the states we deem normal or abnormal in daily life, physiology plays a key role in describing what requires further explanation, although the explanation is often obtained

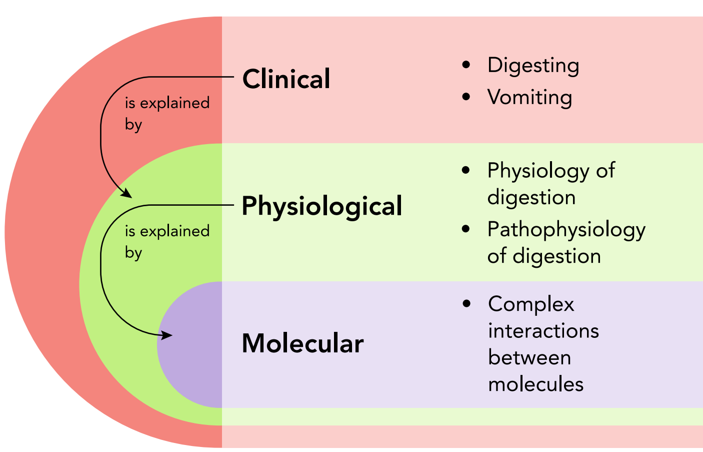

FIGURE 1. **Levels of explanation (*explanandum* and *explananda*)**
Clinical phenomena (*explandum*) are first explained by physiological phenomena (*explanans*). These physiological phenomena (*explandum*) can then be explained by molecular phenomena (*explanans*) or by phenomena described by other innovative sciences.

through other sciences, such as molecular biology.

Physiology as the Science of the Integrity of the Organism

Physiology has often been described as the science of whole organisms (15, 53, 93). According to this view, rather than being restricted to one particular biological level or organ, physiology involves the study of biological phenomena across all levels. This implies that physiological processes can occur at any level of organization in the organism, as testified by the existence of subfields such as "cellular physiology" (119) and "molecular physiology" (88). It also implies that physiology is "integrative," in that it brings together knowledge accumulated about different body compartments (107). We suggest that physiology can be seen as "integrative" in two ways: "vertically" and "horizontally" (FIGURE 2; see also Ref. 117, p. 3).

Physiology is "vertically integrative" in that it brings together knowledge about a given organ or system at different levels—genes, proteins, cells, tissues, etc, (66, 82). For example, a physiological account of the functioning of the heart requires an understanding of the roles of the entities located at different levels (genes, proteins, cells, tissues, etc.) in this functioning, and the potential influence of each level on the others (79). However, physiology is also "horizontally integrative," in that it compares and combines knowledge accumulated in studies of different body components at the same level (16). For example, physiology combines what is known about the kidney, heart, and liver (organ level), or about different types of barriers in the body [such as the gut immune barrier and the blood-brain barrier (25) (structure-type level), or about microglia in the brain and other phagocytic cells in the body (cell level)]. It also involves studies of the ways in which different body organs and subsystems interact and are regulated, such as studies of how the digestive, nervous, immune and endocrine systems communicate and influence each other (101), and how body rhythms interact and are regulated (40).

Many biologists (6, 65, 78, 96, 112) have highlighted the risks associated with trying to explain biological phenomena with "analytic" or "reductive" methods, in which the organism is broken down into isolated elements or subsystems. Most physiologists avoid conflict between the study of "parts" and the "whole." Instead, they suggest that physiology is "integrative" in that it combines and connects all the constituent parts of the organism and all the biological processes occurring within it. We feel that this "integrative" aim is still a key component of the physiology of today (81, 82, 92, 98, 117) but that it may not be as specific to physiology as physiologists generally claim. Systems biology, as we have already seen, also combines data from different levels and often adopts a holistic perspective, without necessarily trying to establish functional explanations between these components and levels in the way that physiology does. Consequently, physiology can still be seen as an integrative discipline, but it can no longer be considered the only integrative discipline. It would, therefore, be inappropriate to consider integration to be a feature unique to physiology.

However, some physiologists go further when considering the "integrity of the organism." They claim that the organism is *causally special*, since the way in which it is constructed and self-regulated renders it unique in the living world (15). Commenting on the views of Claude Bernard, Cannon explained how organisms are unique: "as organisms become more independent, freer from changes in the outer world, they do so by preserving uniform their own inner world in spite of shifts of outer circumstances." This idea was later taken up and refined by the proponents of "autopoiesis" (68, 102). The integrity of the organism is sometimes interpreted more specifically as resulting from one particular biological process or system, typically the nervous (7, 15, 17, 18, 105) or immune (11, 73) system. The nervous system integrates information originating from all body components, controls a myriad of biological processes, accounts for a very large proportion of the energy consumed by the body (100), and, in some circumstances, is given priority over other body constituents (94). The immune system constitutes a mechanism of discrimination that includes and excludes elements, thereby making a decisive contribution to delineation of the boundaries of the organism and to the constant aggregation of its constituents (99). Both the nervous and the immune systems may play a unifying role, and they may even do so in concert via the complex neuroimmunoendocrine system (44).

Are all these views still held in the physiology of today? We think so. Many authors stress the importance of taking the

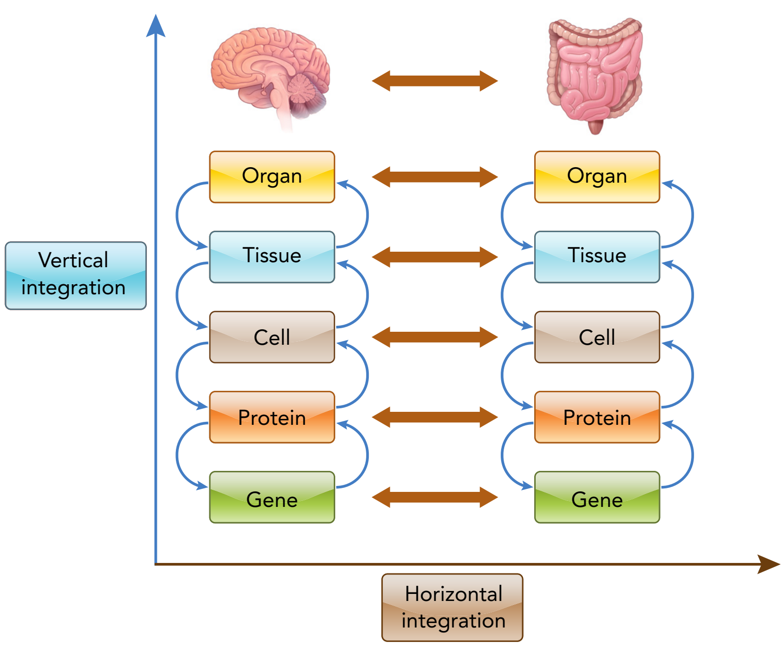

FIGURE 2. **Physiology is both vertically (between different levels within an organ) and horizontally (between different organs) integrative**

whole organism into account in biological and medical phenomena, and in investigations of the contributions of the nervous and immune systems to organism integrity. For example, recent studies have highlighted the control over many metabolic processes wielded by the nervous system (76), and the contribution of the immune system, as a whole, to the surveillance of anomalies in the organism (61, 109). Moreover, these contributions are often presented as "physiological" (61), suggesting that traditional physiological views about the nature of organisms persist in some of the biological disciplines that have arisen from physiology (31).

Physiology as the Science of a Highly General, Almost Universal, Biological Process: The Case of Homeostasis

Physiology has focused on phenomena observable at all levels, in all living beings, such as *homeostasis* in particular. Homeostasis has played the role of a central, all-encompassing phenomenon forming the principal object of physiology: "homeostasis is the process that gave birth to physiology and continues to define it" (Ref. 78; see also Refs. 20, 82, 106). This term is still widely used today in physiology and the biological domains that it has spawned, such as neurosciences, immunology, endocrinology, and stem cell biology (30, 39, 61, 67, 89). Other concepts, such as stress, could be considered here, but homeostasis has greater generality.

No precise description or assessment of the extent of the phenomenon of homeostasis is yet available. The first vague and limited description of this phenomena was humoralism, the ancient theory that health results from a general balance between blood components. Claude Bernard (7) converted this vague idea of humoralism (i.e., a balance of components in the blood) into a much more accurate description under the label of "fixité du milieu intérieur," defined as the active maintenance, in organisms, of certain values within fixed boundaries (water, nutrients, oxygen, salt, and, in some cases, temperature, etc.). Cannon gave homeostasis its name and focused on the description of physiological systems fulfilling the various functions of stability, and on the concatenation of various mechanisms resulting in stability. He also stressed the notion of boundaries for fluctuations and described other parameters subject to homeostatic regulation, such as glucose concentration and pH (15). Wiener generalized the description of homeostasis to all cybernetic systems and introduced the notion of a feedback loop (118): he pioneered a tradition in mathematical biology that culminated in the development of dynamic systems theory between the 1960s and 1980s (9).

Since the 1980s, there has been much discussion of new concepts thought to expand the explanatory power of homeostasis, such as "rheostasis" (75) and "allostasis," originally described by Sterling and Eyer as a form of cognitive anticipation of potential changes in the environment, selected during evolution due to the improvements in fitness it provides (103, 104, 110, 111). The contribution of these new concepts has been called into question (27). More recently, attempts have been made to redefine homeostasis through comparison with the concept of robustness (56–60). Homeostasis is a key concept for understanding organisms, and conceptual breakthroughs and empirical discoveries about its various forms and scope are still being made. The imperfect description and mapping of homeostasis is sufficient to demonstrate the potential vitality of physiology.

A further illustration of this vitality is provided by the observation that many newly discovered mechanisms are not exceptions to known instances of homeostasis, instead being embedded in unexpected forms of homeostasis, thereby extending the scope of this concept. An example is provided by studies of interactions between the immune and neurological systems in the onset of mental disorders (26, 33, 38). In such studies, these interactions are seen as constituting a deregulation of homeostatic processes, the understanding of which lies outside the traditional boundaries of physiological systems. For instance, physiological knowledge suggests that the immune system should not interfere with tryptophan catabolism. Accidental interactions cannot be studied by traditional physiological approaches and must therefore be studied by molecular biology methods instead. In such cases, homeostasis is background knowledge and does not play a key role in discovery.

In a second type of discovery, these interactions are themselves described as a new instance of homeostasis, calling into question the original distinction between systems. As the object of the investigation is then a new homeostatic system, the discovery legitimately counts as progress in physiology. For instance, McEwen's work on "allostasis" proposes the integration of cytokines into the normal, but enhanced balance we generally call "stress" (69–72). McEwen and coworkers illustrate this idea with the example of the "regulation" of pro- and anti-inflammatory cytokines by glucocorticoids and catecholamines and the "feedback" of peripheral IL-6 on central IL-6, contribution to regulation of the stress axis via the hippocampus. Another example is provided by the so-called "neurovascular unit," in which neurons, astrocytes, smooth muscle cells, and endothelial cells are involved in the "homeostasis of the brain microenvironment" (48): instead of thinking of the neuronal network, circulatory system, and neuroglia as generally separate coordinated systems, a neurovascular unit is defined as a locally regulated "functional unit" (48) acting in coordination and competition with other such neurovascular units.

Similarly, recent findings concerning the intimate interactions and between the nervous and immune systems and the molecular pathways common to these two systems (55, 91, 113) have led several authors to propose the concept of a "neuroimmune unit" (115) or a "neuroimmune cell unit" (NICU) (116) based on the general idea that "the nervous system and immune system have evolved to work in a concerted manner to promote tissue homeostasis and defense" (116). Ongoing discoveries about the dialog between the microbiota (the microbes residing in and on the host), the nervous system, and the immune system provide strong support for this view (35). Some have gone even further, proposing the concept of a single and encompassing "neuroendocrine-immune system" (95), which is understood to be the actual protector of homeostasis in the organism.

Discoveries of the first type may give the impression that the study of interactions extends beyond the limits of physiology into a different branch of science, because the explanations obtained are not based on physiological and homeostasis-related considerations. By contrast, discoveries of the second type suggest that, over and above what physiology has already taught us, there are still physiological phenomena to be discovered and that homeostasis remains the best conceptual framework in which to interpret them.

Conclusions

So, is physiology dead or alive? Many different defining features have been attributed to physiology, and, depending on the features considered, different answers to this question may be obtained. Most of these defining features have been inherited from the centuries-long history of this discipline. We propose here to distinguish between definitions of physiology based on its method and definitions of physiology based on its object.

In terms of its method, physiology is:

1) A quest to identify biological functions in organisms. From this point of view, physiology is one of many explanatory sciences in biology, to be contrasted, in particular, with other biological sciences seeking non-functional explanations.

2) A search for explanations based on biological functions. From this point of view, physiology is one of many possible forms of biological science, with others instead focusing on prediction or manipulation.

3) *A* basic biological science but no longer necessarily *the* basic biological science.

In terms of its specific object, physiology focuses on:

4) Physiological and pathological phenomena, no longer as an explanation for clinical phenomena but described so that they can be explained (generally at a molecular level): here, physiology is no longer the central explanatory discipline but is instead becoming the central descriptive discipline.

5) The integrity of the organism, which may now also be accounted for by different, non-functional disciplines.

6) All-encompassing phenomena, such as homeostasis, which, although not able to account for all biological phenomena, nevertheless provide useful and fruitful models for discovering new processes and understanding them.

On balance, neither the method nor the object of investigation of physiology is outdated. What seems crucial today is to acknowledge the existence of novel, wide-ranging approaches, such as systems biology, and, rather than trying to reduce them all to physiology, to construct a fruitful dialog with them (85, 112). Physiology will continue to survive, as it always has, and can only be strengthened by exchanges with other fields from which it can take inspiration. ■

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