THE PRINCIPAL STRUCTURES OF PHYSIOLOGY: WHAT AND WHERE ARE THEY? THE CASE OF BARCROFT’S ARCHITECTURE

K. B. Roberts
Faculty of Medicine, Memorial University, St. John’s, Newfoundland, Canada A1B 3V6

"Die Geschichte einer Wissenschaft ist die Wissenschaft selbst." [The history of a science represents that science.]—J. W. von Goethe [from C. Heymans (9)]

Joseph Barcroft, of the University of Cambridge, England, published in 1934 a monograph, Features in the Architecture of Physiological Function. It was reprinted in 1938. His intent when writing the book was to make explicit the general principles he had discerned during his long experience as a researcher and teacher of physiology.

He was approaching physiology from an unusual angle, "not from that of mere structure, whether the structure of organs or of chemical formulae, but from the principles of function." In that way, the monograph differed from the generality of physiological texts in which the systems are considered, for the most part, independently of each other. It differed also in that its primary object was not to convey information but to assist thinking about known physiological processes. To do this, the circle must be completed by using information obtained from experiments. In this case the experiments were often Barcroft’s own. The reader therefore gathers information and thinks about interacting processes at one and the same time. Barcroft did not make any theoretical fuss about any of this, regarding it as the obvious way to proceed.

He had already written more than 200 scientific papers and had influenced generations of undergraduates, graduates, and co-workers. He was 62 years old. He was not a medical graduate and had not written a doctoral thesis.

In this strangely named book, Barcroft identified nine features in the "noble" edifice of physiology, each of which was supported by underpinnings from his own physiological investigations (Table 1). Revisiting Barcroft’s Architecture we can readily see that the style is original and imaginative—but sixty years in the past.

In this paper I attempt:

1) to present Barcroft’s strategies for research, reflection, and review

2) to find out how this book came to be written

3) to understand the elements of Barcroft’s physiological thinking, by referring to just two of the nine principles he had considered: the physiological internal environment and teleology in physiological explanations

4) to place the book and its influence in the context of its own day

5) to consider today’s relevance of this book, particularly in relation to physiology education. How may we identify—and communicate to student colleagues—the features of current physiology?

BARCROFT’S STRATEGIES FOR RESEARCH, REFLECTION, AND REVIEW

It was Barcroft’s practice to publish his current laboratory investigations in the form of papers, often short papers, each addressing precise research questions that had emerged as he continued to investigate a topic. He was an inventive, persistent, rigorous, and...
thoughtful experimenter. When he had studied an area for some years, and after the general outlines of his inquiries became apparent, Barcroft would then write an extensive review reflecting on their significance.1

Barcroft’s early research on oxygen uptake in resting and in active tissues, “a metabolic balance sheet,” was published in an extended review of 95 pages in Ergebnisse der Physiologie in 1908. The Respiratory Function of the Blood, which included “lessons from high altitude,” was issued as a monograph in 1914. Revised extensively, and incorporating new researches on hemoglobin, it was reissued in two parts in 1925 and 1928. Features in the Architecture of Physiological Function (1934) and The Brain and Its Environment (1938) were next, reassessing his general ideas, exploring particularly concepts concerning the control of the internal environment. In 1946 came the first of two projected volumes on fetal and neonatal physiology, the product of concerted research using sheep and goats to investigate the adaptation of the fetus to intrauterine life and to its transition to an independent existence: Researches on Pre-Natal Life. Barcroft died in 1947, and the project remains incomplete.

As Barcroft explained in the Preface to Researches on Pre-Natal Life, “... [N]ot the least interesting part of the work has been the fitting together of individual items, dealt with in individual papers, into a picture from which a likeness of the organism is commencing to emerge.” The interest and excitement of doing just that is evident in each of his books.

HOW THIS BOOK CAME TO BE WRITTEN

Stimulated by a chance remark about the principles of physiology, Barcroft wondered what its principles were. He soon produced the list that finally appeared as the chapter headings in the book—the list in Table 1. It became clear to him that these features were interdependent:

The highest functions of the nervous system demand a quite special constancy in the composition of its intimate environment. The stability of the internal milieu almost compels the principle of the storage of materials and of integration in adaptation. Again an easy stepping stone to integration is the practice of the body to have more than one way of doing things. But parallel mechanisms may express themselves not only in integrative but in antagonistic processes. Moreover increased function ... may be achieved by heightening the efforts of units already functioning or by marshalling a greater number of units: and so we arrive at the “all-or-none” relation.

1 Other scientists of that generation, including other physiologists, were doing the same thing. This tradition seems to be less vigorous today, to the detriment of teaching, learning, and understanding.
The Internal Environment

This section will condense arguments in the first three chapters of his book, the section dealing with Claude Bernard’s dictum, “La fixité du milieu intérieur est la condition de la vie libre” [The constancy of the internal environment is a condition for a free life].

One thrust of Barcroft’s chapters on the internal environment was directed at the concept of the liberty of life to be attained by the constancy (fixité) of the internal environment (milieu intérieur). Two avenues were open to examination. 1) To what degree does constancy exist in lower organisms with no circulation? How efficiently are they enabled to manage their lives with variable internal environments? 2) How do higher organisms, specifically the human organism, respond to disturbed constancy?

He discussed the (relative) constancy of pH, of temperature, and of oxygen.

Regulation of hydrogen ion concentration in the internal environment (Chapter 1). Lower animals have variable ability to control their pH. In animals with circulations, pH is regulated not only by cells but also by the blood, the kidney, and the respiratory center. Regarding the buffering properties of the blood, Barcroft noted the “higher” the species the better the buffering. Hemoglobin in particular is of interest as a principal buffer of the blood. Barcroft considered the evolution of blood respiratory pigments: by the time we have reached the lower vertebrates all the elements in buffering of blood have been laid down—there is little difference in kind between frog’s blood and that of an anemic human being in this respect. The finer points of pH regulation, however, depend not on evasion (buffering), but on elimination (excretion)—the elimination of substances in solution by the kidney and of CO₂ by the lung. At the time of Barcroft’s writing it was difficult to make any quantitative statement regarding factors that regulate elimination of alkali, or acid, by the kidney. But, says Barcroft, there are good reasons to think, from denervation experiments, that the nervous system is not primarily involved. He thought that the manufacture of NH₃ was an interesting field for the comparative physiologist.

Barcroft then considered the control of CO₂ elimination, and hence pulmonary ventilation, which is, in turn, conditioned by the activity of the respiratory center. He reviews the then recently reported experiments of Lumsden (15), in which sections were made at different levels in the brain to reveal the structural organization of this center. He confirmed Lumsden’s levels from his own studies on fetal respiration and on the respiratory response to HCN. He concluded that the higher levels of the respiratory center were involved in controlling the elimination of CO₂. Knowledge of the afferent activity to the respiratory center had progressed to the point where Barcroft could quote Heymans’ work on the carotid sinus but not his research on the carotid body—this lay in the future (see Ref. 9). He recognized the specific and general importance of rhythm generation, quoting the studies of Adrian and Buytendijk (2) on the isolated goldfish brain. This showed potential changes occurring at the rhythm of gill movements.

The ability to generate rhythms at various periodicities is surely a physiological principle which was then, and is still, open to study; there is no shortage of examples.

Barcroft’s short summary of his first chapter on the constancy of the hydrogen ion concentration in the internal environment was:

Let me therefore conclude with the enumeration of the specific points I should like to stress: Firstly, there are two methods of regulating constancy of the hydrogen-ion concentration, that of evasion and that of correction.

Secondly, the former of these [buffering] is perfected, in kind, though not in degree, by the time the lower vertebrates are reached.

Thirdly, the latter [e.g., regulation by the kidney and by respiration] is common to the whole animal kingdom; but
Fourthly, its most delicate regulation [by control of breathing] only develops at the mammalian (and perhaps collateral) at the avian) level.

Fifthly, that most delicate regulation is a regulation by the nervous system, and at a level of the nervous system which is probably higher than the ordinary medullary centres.

Temperature control of the internal environment (Chapter 2). Here Barcroft considered the effect of temperature on biological reactions, from enzymes in vitro to the rate of movement of Ameba and to the frequency of the isolated and the intact frog's heart. He pointed out that if the velocity of a single reaction got out of step with its neighbors then one would expect theoretically the whole machine to jam. In reality, however, “enquiry shows to what a remarkable extent nature has contrived to circumvent any such barrier imposed by this simple application of chemical laws.” He discussed some of the ingenious ways in which this has been achieved at different levels of organization—enzymes to intact poikilothermic vertebrates. He then investigated the transition from the lower vertebrates to the mammalia by way of hibernating animals and then to the anesthetized cat and to the unanesthetized human being—himself.

In many mammals, but not people or horses, the respiratory center is a principal regulating center for the control of internal body temperature; panting allows cooling but is so adapted that, making use of dead space, shallow, quick breathing will still allow effective cooling and respiratory gas and hydrogen ion regulation. The actual fight for preservation of these aspects of a constant internal environment is carried out in the brain.

In cold-blooded organisms adaptation to variable external temperatures is in the nature of buffering, an acceptance of temperature variation, the method of evasion. This is so whether individual enzymic reactions or the response of the intact animal are being considered. In warm-blooded species there is a (partial) reversal of the process, the refusal to accept great alteration of temperature, the domination of the method of elimination—by panting or sweating to get rid of heat. It is now known, however, that some human beings as well as other mammals can in everyday life accept a considerable nocturnal drop of core temperature when exposed during cold nights (22).

Barcroft's conclusion was, “We started with a purely chemical phenomenon in a unicellular organism, we end somewhere just below the cerebral hemispheres.” It may be noted here that the broad references and the insights of Knut Schmidt-Nielsen (25) and others in the comparative physiology of temperature control exemplify, and of course greatly extend, the principles defined by Barcroft. Behavioral evasions, individual and social, also contribute significantly to homeothermy.

Oxygen partial pressures in the internal environment (Chapter 3). “When Claude Bernard put forward the principle of constancy of internal environment he instanced three substances, one of which was oxygen.” Joseph Barcroft himself was well placed to demonstrate, as he did in this chapter, the physiological significance of the sigmoid O2 dissociation curves, for he had materially assisted in establishing them and their importance. Here he explained reasons for considering that hemoglobin was “an oxygen buffer of a very complete kind.” The evolution of respiratory pigments was put in perspective; Keilin's work on cytochrome and hemoglobins had not long been published (12). Indeed, Barcroft's ideas in this section can be regarded, but in retrospect, to be approaching that of molecular biology. Perutz and Kendrew took their giant steps forward in determining the three-dimensional structure of myoglobin and hemoglobin, and the molecular alterations during oxygenation, in Cambridge in a Barcroft-inspired environment (23; see also Ref. 20). That environment has remained conducive to advanced studies of those respiratory proteins.

“What then is this free life of which the fixity of internal environment is the condition?” One approach was to see what happens to human beings when that environment exceeds or falls below the usual limits; he lists the observed effects in a table largely taken from Cannon. Barcroft pointed out that the symptoms were well known to him because of self-experimentation: “[F]ate has forced a number of these deficiencies and excesses on my own person.” In this list, he observed,
[T]here are no alterations in muscle contraction as such, or changes in the heart, kidney, liver, pancreas... The blow is to the central nervous system, and in particular higher centres of the brain. The fixity of the internal environment is in short the condition of mental activity.... To look for a high intellectual development in a milieu whose properties have not become stabilized is to seek music amongst the crashings of a rudimentary wireless [radio] or the ripple patterns on the surface of the stormy Atlantic.

Barcroft was an experienced ocean-going sailor.

The concluding paragraphs that follow these sentences must surely have been the peroration at the end of one of the Dunham Lectures at Harvard in 1929 on which this book was based. The phrasing is much broader and grander than is usual in today's physiological literature, but it represents well the conscious driving forces behind Barcroft's years of physiological dedication:

Each century, and now each decade, add emphasis to the antithesis between the complete insignificance of man when considered as part of the material universe and the astounding ascendency to which his intellect has attained in comprehending the universe in which he is placed. Of that intellectual ascendency, "la fixité du milieu intérieur" appears to be the, or at least a, condition; of that intellectual ascendency—"la vie libre" is no inapt description.

**Teleology in Physiology**

In the last chapter (Chapter 9) of the Architecture, entitled "The chance that a phenomenon has a significance," Barcroft discussed teleology—as well he might. Many studying physiology think initially in terms of purpose—"white cells stick to the capillary wall and move into the tissue spaces in order to phagocytose streptococci" or "the purpose of the carotid sinus is to regulate the arterial blood pressure." Surprisingly few physiologists writing texts have faced up to this common way of thinking (13).

Barcroft, when he was head of department, insisted that he give the series of introductory lectures to undergraduates. He spent time in student laboratories and would often have heard teleological reasoning.

His lively discussion of this usage includes a defense of a reformulation of certain elements of teleology. His general approach in the Architecture was to replace questions about "purpose" with questions of What? and How? However, considerations of evolutionary advantage through natural selection also figure implicitly in his account. And note that, in the chapter title, Barcroft phrased the question of teleology pragmatically, rather than philosophically.

He ended this chapter, and his book, this way:

Accidents happen in nature as elsewhere, but... I range myself on the side of those who regard a phenomenon as more likely to have a significance than not. Those who think with me must shoulder the burden of discovering what the significance may be, but on our opponents rests the much heavier burden of proving the phenomenon to be an accident, if indeed it be such.

This shadows Karl Popper's thinking on validation of hypotheses (21). Would it be helpful to replace the word **significance** with **context**? "The chance that a phenomenon has a evolutionary and physiological context..." seems to me less teleological, more pragmatic, largely because it appears to lead more naturally to further experiments designed to define that context.

**PLACING BARCROFT'S ARCHITECTURE IN THE MILIEU OF SIXTY YEARS AGO**

A number of his contemporaries have testified to the impact made by Barcroft's books. August Krogh, whose monograph The Anatomy and Physiology of Capillaries (1922 and 1924) had been so influential, commented: "After having read [Barcroft's] The Respiratory Function of the Blood, 1914, there came a fundamental change [in our work]. We began to conquer new fields of our science with the method of Professor Barcroft to think science." This quotation is taken from Bodil Schmidt-Nielsen (24), who has written of the deep friendship that existed between the two men—Barcroft and her father. Krogh's later view was that Barcroft's Architecture was his "most important contribution to physiology.... [It] gives an integration of physiology of such a kind that it ought to be read by everybody who is going into experimental..."
work in physiology. It gives the general ideas which cannot be obtained from any other book in existence” (A. Krogh, in Ref. 23).

Walter B. Cannon’s The Wisdom of the Body (1932), named from the title of a lecture by E. H. Starling, was published before Architecture but after Barcroft’s Dunham Lectures in 1929. That is perhaps why Barcroft makes few references in his book to the term homeostasis introduced and used by Cannon (see Ref. 14). Homeostasis expresses in one word the concept of the (relative) constancy, and therefore control, of the internal environment, a concept first enunciated by Claude Bernard and discussed in depth in the first three chapters of Architecture as indicated above.

Barcroft points to the lack of balance in Bernard’s aphorism, “the accuracy of the first clause contrasting almost comically with the vagueness of the second.” Barcroft justifies Claude Bernard’s entire sentence from the standpoint of evolutionary biology—a feature of much British physiology from Thomas Henry Huxley to Peter Medawar and beyond (see Ref. 3). In somewhat different form, the evolutionary approach was also adopted by American physiologists. Cannon, in Bodily Changes in Pain, Hunger, Fear and Rage... (1915 and 1929), emphasized the survival value of these bodily changes. In The Way of an Investigator: A Scientist’s Experience in Medical Research (4), Cannon notes two characteristics of Barcroft: his mastery of imaginative scientific writing and his generosity of spirit. Quotations from the Architecture given above demonstrate the first. Barcroft’s generosity towards other researchers has also been noted by others.

In 1920, in a public address on anoxia to fellow scientists and laypersons, Barcroft discusses his and others’ controversy with J. S. Haldane—the latter had put forward a theory of oxygen secretion by the lung epithelia by which oxygen in specific circumstances could pass into the pulmonary blood against a concentration gradient. Barcroft ends his address:

And here I come to the personal note on which I should like to conclude. In the pages which I have read views have been expressed which differ from those which [J. S. H.] holds in matters of detail—perhaps in matters of important detail. But Haldane’s teaching transcends mere detail.... The more gladly, therefore, do I take this opportunity of saying how much I owe, and how much I think medicine owes and will owe, to the inspiration of Haldane’s teaching. (see Ref. 23).

Cannon (4) quotes Barcroft on the same subject:

At times I have heard persons speak as though there was some inherent absurdity in Haldane’s theory and as though it were intellectually unworthy of the great man who pinned his confidence to it.... I am out of sympathy with such comments. It seems to me a very good theory.... The question in my mind ... was not whether the theory was a good one but whether it was really supported by the facts.

The work on animals by Marie Krogh with August Krogh (see Ref. 24), and the human studies of Barcroft and others in anoxic conditions at simulated or actual high altitude, showed that Haldane’s theory was not supported by experimental findings, that his hypothesis could not stand. Haldane, Barcroft, and other physiologists had put their lives in danger experimenting on themselves to refute, or not, the theory of oxygen secretion. McCance (16) has discussed self-experimentation in this “age of adventure” in physiology.

Barcroft’s generosity of spirit in his controversy with Haldane was deep-rooted. Related personal characteristics are remembered by those who knew him or heard him speak. It is probable that these characteristics contributed to his excellence as a teacher, as a mentor for younger colleagues, and as a writer of wide-ranging texts. His style in research is described by R. A. Peters in the Barcroft Haemoglobin Symposium (23); it was as productive as anyone’s in the first half of this century. It was the antithesis of the researcher, or the scholar, who attempts to dominate a field, to exclude, displace, or derogate those that do not support his team. Such a person is unlikely to have written, or want to write, a book of the nature of Barcroft’s Architecture.

Contemporary with the Architecture there were an number of books by physiologists—texts, monographs and other synthetic works—that attempted to
define, implicitly or explicitly, the structure of their subject or some section of it. Confining consideration to a few books in the English language, we may note first J. S. Haldane’s Respiration, published in 1922. An earlier version had appeared soon after he had given the Silliman Lectures at Yale University on which the books were based; the earlier version is called Organization and Environment as Illustrated by the Physiology of Breathing (1917); each title of the four chapters in this book contains the word “regulation.” A further edition of Respiration was issued in 1935, almost simultaneously with Barcroft’s Architecture.

L. J. Henderson’s Blood (1928) and Barcroft’s two editions of The Respiratory Function of the Blood (1914 and 1925/28) were widely read on both sides of the Atlantic. The two works complement each other. (Henderson has received insufficient attention as researcher and physiological thinker; see Ref. 19) Investigations into human respiration in the interwar period involved both reductionist studies on the properties of hemoglobin and studies on the integrated response of unanesthetized human beings to modifications in the composition or pressure of the inspired air. The books referred to, Henderson’s and Barcroft’s, achieved a synthesis between the two. Many of the other researchers in respiration were both laboratory and whole person physiologists, equally at home working at the bench or high in the mountains of Europe, North Africa, or South and North America.²

Joseph Needham in Biochemistry and Morphogenesis (17) wrote about the reducibility, or irreducibility, of biological facts to physico-chemical facts. "...The laws or regularities which we find at one level cannot be expected to appear at lower levels. The conditions for their appearance do not exist there.... These old controversies are unnecessary if we realize that we are dealing with a series of levels of organization. We must seek to elucidate the regularities which occur at each of these levels without attempting either to force the higher or coarser processes into the framework of the lower or finer processes, or conversely to explain the lower by the higher." The philosophical implications of reductionism/emergent properties that may be present in Needham’s ideas seem not to have been of concern to Barcroft or his physiological colleagues, nor are they of current interest. But Barcroft’s discussions of “principles”—Needham’s “regularities”—take careful note of the level of complexity at which any specific control operates.

Lancelot Hogben, when he was a young man teaching at McGill University, wrote a text called Comparative Physiology (10); it was included in a series on animal biology edited by Julian Huxley. This book was organized according to general ideas: response—the manifestation of vital activity; metabolism—the sources of vital energy; coordination—the integration of vital activity; reproduction—the building up of a new animate unit. It is my impression that the uses of the word “vital” here and similar phrases in Haldane’s Respiration do not imply an antimaterialist philosophy but recognize additional factors inherent in the organization of complex, interacting systems. These additional factors constitute some of the physiological principles that Barcroft discussed. The challenge of integrative physiology is taken up by a number of authors in Boyd and Noble (3).

W. M. Bayliss, in 1922, published the first edition of his Principles of General Physiology. This encyclopedic work, originating out of Bayliss’s teaching responsibilities, had a lasting impact on our subject both in Britain and in North America (23). Bayliss reprints what nowadays would be a surprising statement by T. H. Huxley: physiology’s “subject-matter is a large moiety of the universe—its position is midway between the physico-chemical and the social sciences.” Bayliss, like Barcroft, thinks well of Claude Bernard, whose “attitude is far more inspiring than that of those who regard living things as in perpetual conflict with external nature....” He quotes Bernard: It is not by struggling against cosmic conditions that the organism develops and maintains its place; on the contrary, it is by an adaptation to, an agreement with, these conditions. Bayliss then recommends “Kropotkin’s attractive book, Mutual Aid.” [Barcroft revised the chapter on respiration for the 4th edition (1924) of this text, published after Bayliss’s death.]

The terms comparative and general physiology have had different meanings at different times and

² A peak in the White Mountains of California is named Mount Barcroft to honor his work in high-altitude physiology.
different places. Does Barcroft’s Architecture fit into one or both of these categories? He certainly considered a wide variety of organisms, seeking common factors in functional organization and emphasizing evolutionary aspects. Moreover, he wanted to make plain what physiological features had general applicability. There was overlap between Bayliss and Barcroft. However, the emphasis in Bayliss’s text on general physiology was reductionist, looking to explain specific functions in terms of underlying mathematics, physics, and chemistry. Barcroft’s physiological objectives were ultimately integrative, identifying physiological features in the whole organism, using the findings detailed in Bayliss’s and in Barcroft’s own writings as starting points. Bayliss: “It is obvious that general laws cannot be duly described and explained without concrete instances.”

The Architecture is a volume in a series entitled Cambridge Comparative Physiology, coedited for that university press by Barcroft himself. We may, however, guess that comparative physiology, narrowly defined, lacked for Barcroft the idea that a proper study for human beings was our own species. The study of “lower” organisms was certainly important for its own sake, but was especially interesting if it contributed to the understanding of human life. There is no need in this present heroic era of molecular biology to emphasize that there are many common structural/functional similarities between very different organisms—intestinal bacteria, snails, mice, and people. A. F. Huxley (11) has put generalizations concerning the uniformity of nature into perspective: such “generalizations, unless very carefully worded, are not of universal application.... It is usually impossible to tell whether they apply to a particular phenomenon until that phenomenon has been thoroughly investigated and explained. ‘Uniformity’ is in most cases a result of common ancestry, and so is explained by the theory of evolution, but the other side of the coin is that evolution is a process which generates diversity.”

A historian would examine also the structures of personal, academic, institutional, and economic life that would have impinged on the Cambridge school of physiology, the center of Barcroft’s adult life, the cultural environment within which he produced his scientific and synthetic work (see Refs. 7 and 18). For him it was, essentially, a stable milieu, one that allowed for the development of a free-thinking, independent, scientific existence. However, he had a wider life than that circumscribed by Cambridge. He was by ancestry, birth, and upbringing an Ulsterman. He was an establishment figure in British life, honored by a knighthood. For more than half his life he was a practising member of the Society of Friends, a Quaker, and was therefore challenged profoundly by two world wars. Deciding to abandon the Quaker “peace testimony,” he contributed scientifically to the war effort. His knowledge of human respiratory physiology involved him during World War I in research on poison gases, including HCN. Bravely, even foolhardly, he used himself as his own experimental subject. He contributed by research, and in committees, to the overall improvement of nutrition in Britain during the 1939–1945 wars.

**HOW MAY WE READ BARCROFT'S FEATURES IN THE ARCHITECTURE OF PHYSIOLOGICAL FUNCTION 64 YEARS AFTER PUBLICATION?**

How may we identify features that reveal the architecture of current physiology to students? Like Barcroft, we shall not be looking for “laws” but for identifiable features in the physiology of organisms. As a tourist I take return visits to the architectural features of physiology discussed in Barcroft’s book.

On the first return visit I look again at homeostasis, the regulation of our internal environments. Just three renovations are considered here, microenvironments, modulation of function, and variability. Others will certainly be noticed by the reader.

**Microenvironments**

The brain in mammals has a relatively constant internal environment with respect to pH, temperature, and oxygen partial pressure. A question not taken up by Barcroft is, How may we sample, or deduce, the quantities, composition, and properties of various internal microenvironments?

The environment of different groups of brain cells is certainly not everywhere uniform in respect to hu-
moral substances—endocrines, paracrines, autocrines, transmitters, etc. Strangely, for what reason I have not fathomed, Barcroft chose to leave aside any major consideration of hormones when discussing the internal environment. In the chapter on Duplication he referred to “adrenaline or some closely allied substance” and suggested tentatively that the central nervous system might control the supply of this substance both by release from local sympathetic nerves and by release from the adrenal medulla. But hormones receive scant consideration elsewhere in the book (see Ref. 7).

Scans show that localized increased neuronal activity is associated with increased blood flow. Specific brain functions may be tentatively localized by such associations (see Ref. 6). The milieu of these active cells will be regulated in a complex manner but will not remain constant. Barcroft, remembering his early perfusion studies correlating oxygen uptake and activity in various tissues, would have been delighted with this—although he would have probably left the field to others because he disliked working in busy fields. This was connected with his originality: “If any subject got really busy, I think he enjoyed going off into something new” (R. A. Peters in Ref. 23).

Diversity of function is determined in the brain by morphological relationships and their functional correlates, by different humoral substances, and transmitters, by many receptors whose density changes with time. This leads to a somewhat different concept of the brain internal environment at the level of fine structure, the actual environment of the cells and their processes. And the contexts, or environments, of neuronal activity, structurally and functionally, include their past history as well as present situation. Moreover, receptors and second messengers and membrane channels bring the outside of the cell and the cell contents into intimate functional relationships, unimaginable to Barcroft and his contemporaries.

Modulation of Function

Contemporary concepts of modulation of a biologically active system would be new to Barcroft, although he had identified, as we have seen, integrative, antagonistic, and parallel processes.

Inconstancy and Variability

Barcroft recognized that the internal environment of tissue other than brain was less closely controlled. Variability can indeed be considerable. The tissues of the hand and forearm when exposed to cold are certainly not controlled at a relatively stable temperature or pH or oxygen tension as they cool down— as Barcroft knew well. Forearm muscles are essentially in an anoxic state during sustained, maximal contraction; Barcroft noted this when considering myoglobin as a potential oxygen store. The present writer had the privilege of being a subject in such experiments carried out by Joseph Barcroft’s son, Henry Barcroft, Professor of Physiology in the University of London. In these circumstances the venous blood draining through a cannula in a vein deep within my forearm muscles was startlingly blue-black.

Indeed, chapters could be written about the inconstancy of various internal environments and of the different responses of different cell types to such variations. Would it be useful to write an account of physiology based on the concept of variability of the many internal milieux? Possibly in physiological pathology. In physiology itself constancy remains a useful unifying concept from which one can then shift to studying divergence. More attention can, however, be given to divergency: in many tissues, we are able to define more precisely the physiology of the varying microenvironments in which a given cell exists. Barcroft seems not to have been particularly interested in this; even Starling’s forces and regional differences in the permeability of blood and lymphatic capillaries were not discussed in the Architecture.

On the second return visit I look again at concepts of physiological control. Would it have been possible for Barcroft to ask questions related to the architecture of regulatory mechanisms when considering the constancy of the internal environment? Analysis of physiological regulation by a systems approach using cybernetics—mathematical and engineering models of negative feedback control—was, in 1934, largely in the future (see Ref. 25). Should we have expected Barcroft to have discussed related topics such as the location, role, and properties of monitors, the transfer of information from monitors through central processors to structures effecting change in an appropriate
Barcroft could have helped his readers by explaining more clearly, in the cases he considered, which physiological feature is being regulated and which features are changing. If any one system is controlled, then elements of some others must be allowed to vary to let that system be controlled.

I note here, in parenthesis, the brave attempt by Guyton, Coleman, and Granger (8) to construct a diagrammatic schema—a very large foldout—that pictures the interrelations of 354 blocks of different facets of circulatory function, each block represented by one or more mathematical equations. This paper concluded: "... [t]he field of circulatory physiology is on the verge of changing from the realm of a speculative science to that of an engineering science."

Speculation and engineering science both serve physiology well, but physiologists, along with the social and environmental scientists, have to face up to the problem of complexity in every aspect of their subject. With few exceptions, neither textbooks nor more advanced reviews of physiology have done this. Beginning and advanced students alike have had to put together, virtually unaided, their own ideas as to how diverse physiological control systems interact. We will need all the help we can get from mathematicians and computer scientists.

The teaching programs pioneered by McMaster Medical School—McMan, McPuff, and so on—are convenient, simple aids that familiarize students with interacting systems in the contexts of common medical conditions. Different advances beyond these models are required if we wish to comprehend the organism. Mechanical modeling of the circulation had a certain popularity in the early years of this century; these models were constructed to respond to certain changes appropriately, a rise in arterial blood pressure occurring, for instance, with increasing peripheral resistance given the same output. The few responses modeled by such simplified systems were, naturally enough, crude compared with the those seen in a living person.

In the chapter discussing teleology Barcroft wrote about apparent anticipations by the fetus of functions that make little sense before birth. But he did not consider further in the Architecture, as E. F. Adolph (1) was later to do, the ontology of regulatory processes or their evolution in terms of natural selection.

I call attention to the great social importance of certain principles in the physiological sciences, specifically to the importance of Bernard’s concept of a relatively constant internal environment of the tissues, Cannon’s homeostasis. Much of current evidence-based medicine rests on this concept. In diagnosis, blood tests rely on it. It is the rationale behind much therapy—no matter whether the treatment of a dehydrated infant with oral water, salts and an energy source, the routine walk-in dialysis of a person with chronic kidney failure, the treatment given to a traumatized soldier, or that received by a juvenile diabetic.

It may also be noted that advanced methods in medicine have been dependent also on techniques developed by a century of physiologists and physiologically minded researchers: techniques of recording and monitoring of pressure, volume, flow, potential change; of cannulation, perfusion, cell and tissue culture, etc.

THE FEATURES OF CURRENT TRENDS IN PHYSIOLOGY AND A MODEST PROPOSAL

Revisiting Barcroft’s Architecture 64 years later puts us back at that same spot. What physiological structures, what principles, may be identified now to lend coherence to current research, to scholarship, and, it follows, to teaching?

Physiology, as defined by what physiologists do, teach, and write about, changes with time. We have only to look at past expectations as to what physiology may achieve, or at texts identified as physiology, or at examinations given to physiology students, or at physiological problems investigated by graduate students, to realize that what was included within the subject in one generation differs from the content of physiology in the next. There is no consensus across time—nor is there from laboratory to laboratory—as to what constitutes physiology, although there is a discernible continuum. There is a scholarly necessity for each age to make an attempt to see what physiology is about and to examine and try to understand the hidden structures that constitute its current prin-
principles, its foundations. An unexamined subject may not be worth teaching.

Our examination is not to establish territory—there is no conceivable territorial map for science, which remains unified. We examine what we do and know best in order to contribute more effectively to a collective endeavor.

Is there hope that a researcher and thinker of Barcroft’s or L. J. Henderson’s stature, of which there are many in today’s physiological communities, will have the necessary time and inclination to devote to such a synthesis? We could then begin to think physiology.

No one may come forward. What then do we do, those of us who feel we should be able to discuss the principles of physiology with our students and colleagues? Do we have to construct, each of us in isolation, the underlying structures of our subject? This is what, at the present time, we expect of our students. The texts they read seldom reveal, and rarely consider, the principles contained within the physiological information the writers present so effectively.

A collective approach might, however, just be possible. Individual physiologists, teachers, and researchers alike could bring forward for general consideration what they think are the fundamentals of a new architecture of physiological function. Knowledgeable, reflective, and imaginative physiologists are everywhere. Although style and interest may reflect local history and circumstance, each submission would be valuable. At the century’s end it would seem possible that workers from diverse backgrounds, each having the necessary open and generous attitude, could contribute to this endeavor. Teachers and researchers, no matter where in the world they work, would then feel, perhaps for the first time, that they have a place within the community of physiologists. The scholarly discoveries made this way could be incorporated into texts, influence the writing of research papers, and encourage workers, from time to time, to review their work in relation to wider contexts.

How may this be effected? Can the constituent national and regional physiological societies of IUPS contribute through the Teaching Committee of that organization? Should the APS Education Committee, or AJP editors, as a Centennial or Millennial Project, take on such a responsibility? Perhaps other options are possible? It would not be an insignificant project. Its organization would require much thought. Bringing the project to a conclusion would take time and persistence.

Features that we identify will, like Barcroft’s, prove interesting and helpful; they will be a source of pride. Review, argument, and restructuring would keep them currently useful. New features would often be added, and old ones changed or let go, reflecting the dynamic state of the body of physiology. Certainly, students will benefit from discussions designed to bring coherence to our humane discipline. Attempts to reveal, examine, and understand the experimental and scholarly structures of physiological function would again show their features to be remarkable and the labor of reconstruction admirable.

Uwe Ackermann of Toronto University and Penny Hansen of Memorial University of Newfoundland have helped me develop this paper. I remember significant earlier discussions in the UK with Hugh Begbie, Jim Gowans, John Kenny, and the late Tommy Hughes and the late David Whitteridge. I remember with thanks Hugh Begbie, Jim Gowans, John Kenny, and the late Tommy Hughes and the late David Whitteridge. I remember with thanks these persons for their kindness and tolerance.

Address reprint requests to author.

References


22. Richards, S. A. Temperature Regulation. London, 1973. (See Fig. 6.9 in Ref. 5.)


Information about Joseph Barcroft, his life, and his scientific contributions may be found in:

