Benchmark Papers in Human Physiology

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MICROCIRCULATION

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Series Editor's Preface

The Benchmark Books Publishing Program is a new and unique concept, a concept that has rapidly spread to myriad fields and which has already won wide acceptance. In essence, each volume contains reproductions of the original articles vital to the development of a particular field, or to a major concept within a field. When the publisher asked me to be Series Editor for the "Benchmark Papers in Human Physiology," I decided that I should not only encourage leaders in various subdisciplines of human physiology to prepare volumes but that I should undertake two myself. The two, *Homeostasis: Origins of the Concept,* and *Contraception,* were both published in 1973. The present volume, by Dr. Mary Wiedeman, will soon be followed by others, edited for example, by Hebbel Hoff, James Warren, Julius Comroe, T. H. Benzinger, Doris Merritt, and S. M. Husain. In due time, then, this series will contain a collection of the most important original publications in the major areas of human physiology.

Dr. Mary Wiedeman has long been recognized as a leader in the field of microcirculation. She is also a superb writer. Recently she undertook to revise the classic textbook "Physiology and Anatomy," by Esther Greisheimer. In view of the fact that I authored a competing text, I know all too well how successful Dr. Wiedeman's revision is!

Microcirculation, in current jargon, is what it's all about. The rest of the circulatory system, and indeed the respiratory system too, are designed to deliver blood with an adequate oxygen load to the microcirculation, that is, to the capillaries, where blood–tissue fluid exchange occurs. This is where the action is, and therefore, knowledge of microcirculation is essential. In this volume, the classic, early papers are presented, beginning, quite logically, with William Harvey. The giant in the field, August Krogh, is accorded a separate section, and the volume concludes with the landmark papers that followed. Characteristically modest, Dr. Wiedeman includes but one of her own publications, a crisp, meaty article that provides essential data on the dimensions of these microvessels.

Microcirculation is a rapidly expanding field. A second volume will be needed in a few years.

L. L. Langley

Contents by Author

Contents

Introduction

At present, the term "microcirculation" is used to designate blood flow through small vessels at the capillary level. The microcirculatory bed is that portion of the cardiovascular system involved in the transfer of nutrients and the removal of metabolic waste products. Minute precapillary arterioles and postcapillary venules are included with the capillaries as the major components of the microcirculatory system.

Although the term microcirculation is relatively new, the study of the flow of blood through very small blood vessels dates back to Malpighi, who used magnifying lenses to look at blood vessels in frog lung and mesentery 300 years ago. During the 300 years since those observations were first recorded, an untold number of investigators have been exploring vascular beds in practically every tissue of a large variety of amphibians and mammals. The ingenuity that has been shown in the design of techniques for microscopic observations of the circulation of blood through arterial and venous vessels is breathtaking. It is difficult to understand why our knowledge of the structure and functional behavior of capillary networks is not complete, if one considers the talent, the vigor, and the excellence of the investigators who have devoted themselves to the study. The fact remains that there are still areas of disagreement regarding the nomenclature, architecture, and control mechanisms of this special area of the circulatory system.

It is of interest that the structural organization of all of the microcirculatory networks that have been studied reveal more similarities than dissimilarities. Although minor differences in vascular patterns (between, for example, skin and skeletal muscle) seem to be associated with the structure of the tissue in which the vessels lie, the basic pattern remains the same.

A consideration of the entire vascular system leads one to the conclusion that the heart and the macrocirculation are present for the sole purpose of supplying blood to the microcirculation, where the delivery of life-sustaining nutrients to tissue cells and the removal of their metabolic waste takes place. It is therefore appropriate that a great deal of study has been devoted to the design and regulation of these minute vessels.

The results of investigations using *in vivo* microscopy have been, until recently, primarily descriptive. To some extent, the anatomical structure and physiological functions of the terminal vascular bed have been clarified. The concept of a preferential, or thoroughfare, channel has been presented, challenged, and is now partially dispelled.

Vasomotion, the spontaneous contraction and relaxation of both arterial and venous vessels (independent of innervation), has been described and assigned a function in the regulation of blood flow into and out of capillary networks. The concept of the Rouget cell as a major contractile element has been abandoned, and capillary contractility has been disproved.

The phenomenon of vasomotion (the word first appeared in the literature in 1944) may be seen wherever smooth muscle exists—in arteries, arterioles, precapillary sphincters, venules, and veins. Such activity in venous vessels, especially if intravascular pressure serves as the mechanism that controls its frequency and intensity, may serve as an effective aid to venous return of blood from postcapillary vessels. Vasomotion may also serve as the regulator of arterial blood flow through capillary nets and as a mechanism whereby capillary vessels could be protected against sudden or prolonged increases in pressure that might rupture their thin walls.

The concept that intraluminal pressure change activates vascular smooth muscle and that the resultant vasoconstriction controls the flow of blood into capillaries has recently been expanded to explain autoregulation of blood flow in terminal beds. "Autoregulation" is defined as the capability of an organ to regulate its blood supply in accordance with its needs, or, in a more restricted sense, as the tendency of an organ to maintain constant blood flow despite changes in arterial perfusion pressure. Thus far, autoregulation has been noted and described in the kidney, skeletal muscle, brain, intestine, myocardium, and liver of experimental animals, including dogs, cats, rats, bats, and calves. There is evidence that it also occurs in the brain and kidney of humans.

The entrance to a capillary network is guarded by the precapillary sphincter, whose contractile activity is regulated by its local intravascular and extravascular environment. Once whole blood or plasma has entered the capillaries, its flow path is determined by the various resistances occurring within the nets. These resistances result from pressure changes in the venous vessels that may temporarily curtail outflow from the capillaries or from alternation in arterial pressures that vary according to the activity of the precapillary sphincter. Thus blood flow within the capillary network changes from moment to moment, frequently reversing direction and often bypassing one route to follow another. The primary control of the flow lies in the spontaneous contractile activity of the precapillary sphincter, a smooth muscle cell that is independent of control by the central nervous system, but one that is influenced by local changes in intraluminal pressure and by the accumulation or washout of metabolic by-products and humoral agents (metabolic autoregulation).

A brief description of the structural organization of the large vessels that deliver blood to the exchange vessels is in order here. From the large artery to the terminal arteriole, each arterial vessel is accompanied by a vein. A major artery gives rise to numerous smaller arteries that have a diameter about one-half that of their parent vessel and which branch off at right angles. These branches occur at irregular intervals along the length of the artery, which actually terminates by forming an arterial anastomosis or arcade with another artery of the same type that lies parallel some distance away. The branches, called small arteries, are approximately one-fifth the length of their parent vessel, but they give rise to a relatively large number of arterioles with a small diameter (about one-third that of the small artery). The arterioles continue to become terminal arterioles, from which the capillaries originate. Arterial arcades are formed at all levels, and it is therefore almost impossible for a capillary network to be isolated from the main blood supply unless an extensive obstruction occurs.

On the venous side of the system, postcapillary venules are formed as capillary nets begin to converge. In diameter, they are almost twice as large as the arterioles that they accompany. Venules converge to form twice as many small veins as there are small arteries. Venules have a diameter three times as large as the arterioles; small veins are three times larger than small arteries.

The next step after this rather cursory survey of the current state of our knowledge of the structural and functional aspects of the microvasculature is to review some of the outstanding papers that have led to this understanding.

This book is divided into five parts: I. Early Investigators; II. From van Leeuwenhoek to Krogh; III. The Era of Krogh; IV. The Renaissance After Krogh; and V. In the Last Decade.

Part I necessarily begins with the work of William Harvey, who first postulated the existence of small hair-like vessels to connect the arterial and venous systems, a mandatory condition if blood truly did circulate from the heart to tissues and lungs and back again to the heart. Also included in this section are papers that prove the existence of the postulated vessels, which could not be seen or accurately described until the development of magnifying lenses—an event that took place some 50 years after Harvey had made his original speculations. Space restrictions permit the inclusion of only a few of the most innovative papers, but a survey of a number of informative works is presented. There are some seemingly fallow periods that account for extended periods of time between the investigations that are reported in this section (as well as between Parts I and II). The primary reason for this is the repetitive nature of some of the earlier works, presumably due to a lack of communication—the result of the sparcity of circulated journals and of geographical distances. "Early Investigators" covers the period from 1628 to 1688.

Part II provides a survey of the work done between 1733 and 1852 on microcirculation. Because much of the work is available only in book form, it would be difficult to do justice to the ideas and conclusions of the investigators by including only small excerpts from their publications. Instead, a short summary of their work is presented, along with a reference list designed to help interested readers locate the original publication.

Part III is devoted entirely to the work of August Krogh, with excerpts from his book *The Anatomy and Physiology of Capillaries.* The book was compiled from Krogh's lectures at Harvard in 1922 and acts as a survey of prevailing concepts. Krogh draws heavily on workers immediately preceding him and on his contemporaries and thus gives us a clear picture of the progress made from the middle of the 1800s to his time. Only a small portion of Krogh's extensive work is reproduced here.

Part IV contains works dealing with fresh, new ideas and techniques. I apologize for the omission of interesting and relevant papers by proven investigators in the field, but it was necessary to conserve space. Selection was made on the basis of a desire to present work that was the most influential in promoting subsequent research. Pioneers in the establishment of a group that was later to be identified as microcirculatory anatomists and physiologists, such as Bloch, Knisely, Irwin, Zweifach, Fulton, Webb, and Nicoll, are well known, and the works of some of them are presented here. Many current investigators are former students or followers of these men.

This part is called "The Renaissance After Krogh" because it is undeniable that Krogh's book was the stimulus for an explosive effort to confirm, expand, or refute his stated concepts. It became fashionable to study microcirculation, and much emphasis was placed on actually looking at small blood vessels directly rather than attempting to deduce peripheral vascular changes from indirect parameters. The latter approach was referred to as working around the "little black box," which contained hitherto unseen and unknown regulatory responses and adjustments of the microcirculation to variations in the macrocirculation. Part IV includes papers from 1932 through 1955.

Part V consists of papers published between 1961 and 1968 that contain several new approaches to the study of microvascular beds, a reiteration and clarification of some older concepts, and some corrections, refinements, and applications of previously collected data.

More information is available each year, and new applications of *in vivo* microscopy are apparent in the current literature as technical advances permitting more accurate quantitative measurements of variations in blood pressure and blood flow are made. Intravascular phenomena, such as platelet aggregation, red and white blood cell behavior, and vascular responses to toxic materials introduced into the system, are now being observed through the microscope. The potential for advances is limitless.

I

Early Investigators

Editor's Comments on Papers 1, 2, and 3

1 **Harvey:** Excerpts from *Movement of the Heart and Blood in Animals*
K. J. Franklin, trans., Blackwell Scientific Publications Ltd., Oxford, 1957, pp. 70, 87

2 **Harvey:** Excerpts from "An Anatomical Disquisition on the Motion of the Heart and Blood in Animals"
The Works of William Harvey, Robert Willis, ed., The Sydenham Society, London, 1847, pp. 54–55, 68

3 **Harvey:** The First Anatomical Disquisition on the Circulation of the Blood, Addressed to Jo. Riolan.
The Works of William Harvey, Robert Willis, ed., The Sydenham Society, London, 1847, pp. 89–92

The three papers presented first represent the very beginning of the idea of microcirculation. William Harvey's essay on the movement of the heart and blood is well known, but his letter to John Riolan, written in 1649, has had less exposure.

The length of Harvey's initial paper (72 pages) and of his subsequent letter (16 pages) to Riolan, who sought to refute the Harverian theory of blood circulation, precludes inclusion in their entirety, but excerpts from these writings must be included if we are to visualize the entire history of the study of microcirculation. The passages that follow are selected to show that logical reasoning demanded the existence of microvessels to connect the arterial and the venous circulation, as stated in *De motu cordis.* The rebuttal to criticism from a colleague 21 years later shows how vigorously Harvey was forced to defend his revolutionary idea.

Excerpts from the 1957 translation of *De motu cordis* by K. J. Franklin appear first. For comparison, they are followed by a translation of the same passages by Robert Willis, who compiled the works of Harvey in 1847.

1

Reprinted from *Movement of the Heart and Blood in Animals,* by William Harvey, K. J. Franklin, trans., Blackwell Scientific Publications Ltd., Oxford, 1957, pp. 70, 87

Movement of the Heart and Blood in Animals

WILLIAM HARVEY

CHAPTER ELEVEN

The second supposition is confirmed

IN order that the second supposition which I have to confirm may be better appreciated by my readers, I must refer to certain experiments which make it clear that the blood goes into each member through the arteries and flows out of it through the veins; that the arteries are the vessels which carry blood away from the heart, and the veins the vessels and pathways for the return of the blood to the same heart; that in the members and extremities the blood passes from the arteries into the veins either directly by anastomosis, or indirectly through the porosities of the flesh, or in both ways, just as it passes (see earlier) from the veins into the arteries in its cardio-pulmonary course. Hence it is manifest that it moves from one region to a second and back again, that is to say, from the centre to the farthest parts and thence back to the centre. If after that premise you make a calculation as before, it will at that very point be manifest that such an amount of blood cannot be supplied from the food intake or necessarily be required for nutrition.

* * * * * * *

Editor's Note: A row of asterisks indicates material that has been omitted from the original article.

CHAPTER FOURTEEN

Conclusion of my description of the circuit of the blood

MAY I now be permitted to summarize my view about the circuit of the blood, and to make it generally known!

Since calculations and visual demonstrations have confirmed all my suppositions, to wit, that the blood is passed through the lungs and the heart by the pulsation of the ventricles, is forcibly ejected to all parts of the body, therein steals into the veins and the porosities of the flesh, flows back everywhere through those very veins from the circumference to the centre, from small veins into larger ones, and thence comes at last into the vena cava and to the auricle of the heart; all this, too, in such amount and with so large a flux and reflux—from the heart out to the periphery, and back from the periphery to the heart—that it cannot be supplied from the ingesta, and is also in much greater bulk than would suffice for nutrition.

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