Structure and Function of the Circulation

Volume 1

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Edited by

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FOREWORD

In order to produce a superior scholarly treatise in biomedical science, three important conditions need to be met. First, the subject needs to be of recognized importance and preferably one in which a sizeable volume of new knowledge has been added recently. Second, it needs to be quite evident that the field involved requires much more up-to-date coverage than it has received and third, the choice of the editors and in turn the authors needs to be recognized as outstanding.

This major treatise fills these criteria in an admirable way. There are few who would deny the importance of knowledge concerning the circulatory system. This all pervasive system is the route by which virtually all of the cells and tissues of the body receive their nutrition and it is the major route by which metabolic waste products are carried away. Furthermore, the diseases that involve the circulatory system are, by far, the underlying causes of death and morbidity in the largest number of Americans, Western Europeans and several other populations of industrialized nations. Not only is atherosclerosis-induced-ischemic disease of the heart, brain and extremities widespread in these populations but venous occlusive disease also takes a great toll from phlebothrombosis, pulmonary embolism, etc.

These disease processes and their serious consequences would not merit a treatise like this were it not for the rather remarkable advances that have occurred recently in our understanding, especially of the lesions of the most common and serious disorder of the arteries, namely atheroscalerosis. Similarly the general understanding of the intimate morphology and function, i.e. the cell biology and the molecular biology of the normal vascular channels has also advanced rapidly in the past decade. All of this recent progress makes it a very opportune time to develop a treatise of this type.

The major factor in any scholarly work is the quality of the scholarship of the major contributors to these volumes. In this instance the choice of the chief editor could not have been better.

Colin J. Schwartz has been an active investigator of almost all aspects of vascular structure and function in Australia, England, Canada and now in the USA. His contributions have included work almost equally divided between studies of structure and function. Furthermore he has delved deeply into investigations that have, in turn, been concerned with lymph and lymphatics, with veins and for many years with arteries. Furthermore he has carried into all of these inquiries a careful and critical approach and a probing intellect. These qualities as well as the perspective of a modern pathologist enlightened by almost a quarter of a century of study of the vascular system have helped him to shape these volumes. He has developed an outstanding outline of subjects for the series. He has chosen excellent authors for each topic and he has been able to convince each of these capable scientists to develop an authoritative chapter in the field in which he or she works. This is a great accomplishment. The result is a scholarly work that should serve as a standard reference for those interested in the vascular system for many years - although hopefully it will be revised and reprinted when further progress in the field makes that desirable. At present it is the only comprehensive review of modern knowledge of this important system.

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March, 1979

PREFACE

The "Structure and Function of the Circulation" has been divided into three volumes, of which this is the first. The need for a series such as this became apparent during the scientific sessions of both the first Lindau Conference in April of 1970 and the second conference held in Heidelberg in October of 1973. With the urging of my good friends Dr. K. T. Lee and N. T. Werthessen at an exploratory meeting in Boston, plans for this large and ambitious undertaking began to crystallize. Development of the three volumes was further catalyzed by the encouragement and helpful criticism of a number of colleagues at a subsequent meeting hosted by Dr. Stewart Wolf at a Totts Gap, Pennsylvania.

The Lindau Conferences and many subsequent discussions clearly identified a need to collate in a comprehensive and scholarly manner existing knowledge concerning the structure and biology of the circulation in health and the implications of this knowledge in achieving or facilitating a better understanding of basic disease mechanisms. Emphasis has been directed primarily to the many facets of "normal" arterial, venous, and lymphatic structure and function. The three volumes cover a broad spectrum ranging from gross and comparative vascular anatomy to the basic ultrastructure and cellular biology of the components of the circulation. Additionally, three chapters cover the historical evolution of our understanding of the circulation, from Greco-Roman times to the era of Sir Thomas Lewis, father of contemporary cardiovascular physiology, and to the present.

It is my hope that this interwoven collection of essays by scholars from around the world will serve as a useful reference source for all students of cardiovascular disease, be they involved in medical or surgical cardiology, or the basic cardiovascular sciences. Hopefully, the "Structure and Function of the Circulation" will also provide a substative scientific infrastructure upon which cardiovascular research might continue to grow and flourish.

As the matrix outlining the content and scope of these volumes was under development, I became acutely aware of many areas where our information base remains inadequate. Some such areas include the broad field of comparative physiology and biology of the circulation, and the control or regulation of normal vascular endothelial pinocytosis. Other essentially uncharted areas which illustrate further this deficiency include topics such as the nature of the interactions between arterial endothelium and medial smooth muscle, the physiological role of endothelial contractile filaments, arterial phagocytic functions, and the determinants of endothelial anti-thrombotic properties.

In developing the three volumes which comprise the "Structure and Function of the Circulation" I am deeply indebted to Dr. Werthessen who has served as managing editor. Mr. Seymour Weingarten, formerly of Plenum Press, and Dr. Mark Altschule of Boston have also provided much help in the development of these volumes, as have the staff at Plenum Press. Last but not least, I wish to thank the authors, not only for their excellent contributions, but also for their forbearance with the foibles of the editor.

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THE ARTERIES IN GRECO-ROMAN MEDICINE

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It is not coincidence that the original meaning of the Greek word "arteria" was windpipe, long before the discovery of the two different kinds of blood vessels had been made. The use of the same word for two organs belonging to different physiological systems was no accident. It points to one of the great errors in the early history of physiology, the notion that the heart was the focus of the respiratory, as well as the center of the vascular system. Early medicine has always been associated with many crude and fantastic superstitions. The astonishing feature of the medicine of ancient Greece from the 6th century B.C. onward was its complete divorce from this type of thinking, though in the folk medicine of the classical period, there was plenty of it.

Another feature of ancient Greek medicine was that by the end of the third century B.C. a vast volume of anatomical and physiological knowledge had been acquired. Empedocles seems to have been the first of the Greek thinkers to attempt to work out a connection between blood movement and respiration. Aristotle explains that he attempted to account for the in-and-outward movement of the air and the movement of the blood inward and outward from the surface of the body in terms of the strictly physical process of the water-clock.

From simple notions like these, the early Greek doctors had to interpret their observations of the actual behavior of human bodies in sickness and in health. By the end of the fourth century B.C., they apparently had a good description of the location of the main blood vessels. The focus of the system was the heart, as is shown by Aristotle's account, which makes no distinction between arteries

and veins. Aristotle makes an inexplicable error in attributing three ventricles to the heart of the larger mammals and shows no signs of any knowledge of the cardiac valves.

Aristotle's conceptions of the vascular system show an enormous improvement on that of one of the most famous of the earlier treatises of the "Hippocratic" corpus, that on The Sacred Disease (i.e., epilepsy). It regards the head as the starting point of the main blood vessels. The descriptions in the various "Hippocratic" treatises of the blood vessels show so many contradictions and inconsistencies that we need not pursue them here.

Before Alexandrian days, considerable progress had been made in the knowledge of the vascular system, even before any Greek doctor had become acquainted with the interior of the human body at first hand. The main topographical features of the two great systems of vessels connected to the two-ventricled heart had been discovered before the end of the fourth century. The "thick" or "hollow" vein (the vena cava) and the aorta, each with its own branch-network permeating the body and the limbs, as well as the three main "trees" of the bronchial system and the arteries and the veins in the lungs were described, as were the general location of the principal organs inside the human body, the stomach, the intestines, the spleen, the kidneys, and the liver, and their connection with the portal system.

At the beginning of the third century B.C., if not earlier, Praxagoras (the younger?) found that the two separate great trunks of blood vessels--still all called veins--were two quite different kinds of tubes. The distinction between arteries and veins was thus established. Herophilus showed that the coat of the arteries is about six times as thick as that of the veins. Furthermore, in a corpse the veins collapse if emptied of blood, while the arteries, like the bronchial tubes, do not. Praxagoras insisted that the arteries contained no blood but only air. He declared that when removed from a body, they would continue for some time to pulsate. In this error of the bloodless arteries, he was followed by one of the great anatomical discoverers of history, Erasistratus, who first worked out in detail the correct anatomy of the heart and discovered the valves and the way they worked. Unlike Herophilus, he refused to regard the auricles as part of the heart, looking on them as merely the terminal appendages of the great blood vessels, the vena cava, and the pulmonary veins.

This mistaken idea of Praxagoras, more than any other single factor, prevented the ancients from arriving at the discovery of the circulation of the blood. But absurd as it might seem to us, the theory was founded on true, though incorrectly interpreted, observation. Praxagoras, when he cut open the chest of the animal he dissected, may well have found that the main arteries were neither collapsed nor filled with blood, but emptied and full of air.

When death takes place, the vasoconstrictor center governing the arteries is strongly stimulated by the increase of carbon dioxide and lack of oxygen.† Some explanation of the inconsistency of these findings has been given by the Swedish pathologist Dr. Fåhreus, who made a number of autopsies at least twenty-four hours after death. He says that on introducing a cannula connected with a micrometer into the carotid or the femoral artery, he found a negative pressure varying from a few millimeters to one decimeter. If you now begin the autopsy and open the thoracic cage, the pressure immediately rises to zero owing to the absorption of air by the arteries. He believes that the explanation of this negative pressure is the following: pressure in the arteries becomes negative because after death part of the arterial system dilates. This dilation cannot take place in the big arteries; it must therefore be the little arteries that dilate and draw a certain quantity of blood from the big arteries. This phenomenon varies with the age of the person. The height of the negative pressure increases sharply from the ages of 18 to 70 and then remains relatively constant. Nor is it instantaneous at the moment of death. This may perhaps explain why the author of De corde found the ventricle, but not the aorta empty.

It is natural to suppose that the pulse had been observed by doctors before the distinction between the two vascular systems had been discovered. Galen tells us that the ancient physicians applied the term pulse (σφυμος) only to those movements of the blood vessel which were sufficiently pronounced to be perceptible to patients or to cause pain like those in inflamed parts, and never to the movement in the healthy parts. Aristotle, like Plato, was aware of the normal beating of the heart which he distinguished from the type of throbbing which he calls *"leaping,"* due to a pathological state of the blood. He also concluded that the movement or throbbing of the blood vessels is due to the heart. *"All the veins,"* he tells us in the De respiratione, *"beat at the same time, since they are connected with the heart. They beat more strongly in the young than in the old."*

In contrast both to Erasistratus and to Galen, Herophilus regarded the auricles as forming a part of the heart proper, as modern anatomists do. He saw quite clearly that the two great vessels connecting the heart with the lungs were of different kinds, that the pulmonary artery was an artery par excellence, and that the pulmonary

†See Abel, K., Die Lehre vom Blutkreislauf in Corpus Hippocraticum in Hermes LXXXVI, pp. 192-219, also the paper delivered by Dr. Fåhreus, entitled "Empty Arteries" delivered to the Fifteenth International Congress of the History of Medicine held in Madrid in 1957.

vein was a vein.† None of his actual descriptions either of the heart or the vessels leading into and out of it have survived, but from the accounts of his doctrines given by Galen and the Anonymous Londoner, we can be sure that he considered that both systems contained blood: the veins that derived from nourishment, and the arteries, both blood and pneuma. Herophilus seems to have known, too, that arterial blood differed from venous.

Less fortunate was his description of the wonderful arterial network, which it is rather tempting to regard as an over-imaginative reduplication of the circle of Willis.†† This organ which appears to have been transferred by Herophilus to the human brain from a structure most easily recognizable in the ox††† and a number of other domestic animals,* was to play a most important role in Galen's account of the physiology of the brain and the nervous system. It is clear that he thought the arterial system contained both blood and pneuma, and that he accepted the idea already noted in Aristotle, that the function of respiration was to cool the innate heat in the heart.

Erasistratus, who dissected the human cadaver, gave so accurate a description of the heart and its valves that Galen could not improve on it. He accepted Praxagoras' theory of the empty arteries, and like Harvey, he postulated rather than observed the connections between the arterial and venous capillaries.**

He seems to have regarded the heart as a kind of double pump, the right side distributing blood and the left pneuma to all tissues of the body. This simple scheme, as Galen was not slow to point out, simply would not work, as blood from the right ventricle can

†De usu partium, VI 10 (K.III, 445) and Rufus of Ephesus, De nom. part, ed. Dareberg-Rulle 162. Contemporary Greek practice was to name all the vessels connected with the right ventricle veins, and all those connected with the left ventricle, arteries. This led to a good deal of terminological confusion, since from time immemorial, the windpipe and its branches had been called arteries before the identification of any of the blood vessels. Once the three different sets of vessels in the lung had been differentiated, the bronchial tubes were called the "rough" arteries, the pulmonary veins, the vein-like or smooth arteries, and the pulmonary arteries, the artery-like veins.

††C. M. Goss "The precision of Galen's anatomical descriptions compared with Galenism," Anat. Rec. (1965), 152.

†††Cf. Siegel, Galen's System of Physiology, pp. 109ff.

*S. Sisson & J. D. Grossman, The Anatomy of Domestic Animals (Philadelphia 1948), pp. 626 & 732.

**See Galen, De venae sectione, 2 (K.XI, 153).

only be pumped into the lungs through the pulmonary artery. Moreover, how does it explain the fact that if you wound or prick an artery, blood always jets out?

If the arteries contain only air, the work of distributing the blood to all the tissues must fall upon the right ventricle of the heart. But this can only pump it via the pulmonary artery into the lungs. How then can it get into the vena cava which is obviously the main stem of the venous system? Moreover, wounded arteries bleed, a fact which Erasistratus himself does not attempt to deny.

There is no reason to doubt that Erasistratus was acquainted with the fact that all muscles contain veins, arteries, and nerves; veins to provide them with food, arteries to provide them with pneuma, the breath of life, and nerves to endow them with the power of contraction.

The purpose of respiration, Erasistratus maintained, is to fill the arteries, which in this case must surely be not the bronchial tubes but the blood vessels of the same name.†

Erasistratus did realize that the expansion of the arteries or pulse wave caused by the systole and diastole of the left ventricle was a purely mechanical phenomenon. It was not due to any peculiar vital force or power of pulsation, or possessed by the arteries as such, quite independently of the heart's movements. The air drawn into the heart via the lungs became by some unexplained principle, the vital spirit. It was distributed by the heart and the arterial system throughout the body. It was this that made the body alive.

His doctrine of the triple skein of vein, nerve, and artery also enabled him to provide a plausible theory of muscular action.

Celsus has nothing new to tell us about the arteries except that, unlike Erasistratus, he accepted the fact that they contain blood, that they do not collapse when empty, and that they do not heal, indeed they cause the most violent hemorrhage. He is also acquainted with the anastomosis of the arteries and the veins. He does not appear to be at all precise about the distinction between arteries and veins, and in many places talks about throbbing veins.

As late as the 2nd century A.D. there were still doctors who believed that the arteries contained not blood but air. Galen thought it worth while demonstrating experimentally the falsity of this assumption, though this had been recognized by most medical practitioners and schools. Even after the anatomy of the heart and the working of its valves had been accurately described, there was little or no

†Galen, 1 (K.IV, 471).

agreement about what actually went on in the heart and the great vessels.

It is to Galen that we must look for the gathering together of all the currents of ancient medicine still existing in his day, and the combination of what he believed to be valid in them into a carefully articulated system.

So far as the arteries are concerned, Galen distinguishes them from the veins by the fact that they have two (or three?) coats, whereas the veins have only one. *"The arteries,"* he tells us, *"have two intrinsic coats, the outer* [tunica aventitia] *like that of the vein, the inner* [tunica media] *about five times as thick and harder. It consists of transverse fibres. The outer coat, like that of the veins, has longitudinal fibres, some slightly oblique, but none transverse. The inner thick hard tunic of the arteries has a woven sort of membrane on its inner surface, which can be seen in the large vessels. Some regard it as a third coat* [tunica intima].†

He follows Erasistratus in regarding the heart as consisting only of the two ventricles. He, therefore, also adopts his rather awkward terminology for the great vessels connecting the heart with the lung.

It was inevitable that in his descriptions of the human vascular system he should make mistakes by attributing to the human body features he had noticed in the animals he dissected, chiefly ungulates and simians. His description of the arterial system contains mis-attributions from both these sources, but it is not always easy to be certain which. On certain occasions Galen does tell us from which animal his description has been taken. In Book XIII of the Manual of Dissection entitled "On the veins and arteries," having described the opening of the peritoneal cavity and the greater and lesser omenta, he proceeds to describe the portal system, pointing out that the detailed vascular arrangement is not the same in all animals.

"But all animals have one point in common--the veins which attach themselves and grow into the omentum, the spleen, the stomach, and the whole of the intestines come off from the vein which originates

†De Anat. Admin. VII Cap 5. Mrs. May commenting on a similar passage to that quoted, taken from the De usu partium VI 11 seems to have overlooked the description given in the Anat. Admin. when she remarks in her note 46 to p. 304 of her translation, Galen, On the usefulness of the parts of the body (Cornell University Press, 1968), that Galen overlooked the tunica intima.

at the porta hepatis. Accordingly we shall first begin with a summary of what there is to see of that in the apes. For this animal is more like mankind than are the remaining animals."

In the XIIIth book of the Manual of Dissection, Galen gives the following description of the aorta and its ascending and descending branches:

"I will start from the heart which...is the starting point for all the arteries in the body. I say that from the heart springs out an artery in the same manner as does the trunk of a tree from the earth. And this artery is the largest of all the arteries in the body... And from it these latter have their origin. First of all it divides itself into two tremendous portions which resemble the large limbs of a tree. Then each of these two divides itself into others, and it keeps on dividing frequently in this way, until all its subdivisions come to an end...just as the division of the branches of a tree finds its end in small twigs...Now on the great artery, before it breaks up into divisions, you can see two offshoots like that which emerges from the seed of a plant when it germinates. And of these two, you see that one is wider and longer than the other, and you find that it encircles the whole heart in a ring [left coronary artery], *and surrounds it at those positions at which its two cavities* [ventricles] *unite with one another and adjoin each other* [descending branch]. *But the other offshoot* [right coronary artery], *which is narrower and shorter, distributes itself, especially to those portions of the heart of which Aristotle holds the view that they are a third ventricle..."* (trs. Duckworth, pp. 172f.)

"*After the two offshoots* [the coronary arteries], he tells us: "*you see the two mighty arteries into which the aorta divides itself. Of the two, the broader is the descending branch, the narrower the ascending.*" His description of the former runs as follows:

The artery which goes to the lower parts of the body "*mounts on the fifth thoracic vertebra in the place upon which there lies also the vein* [azygos] *which nourishes the lower thoracic region. And this artery travels with this vein and distributes itself together with it, and branches* [posterior intercostals] *sprout off from it which go to the inter-costal spaces just like the twigs of that vein. And from these arteries branches go outward, which travel with the veins to the outer thoracic regions. For their origin is beside that of the veins, and they distribute themselves similarly to those muscles to which the veins are distributed...Now when this main artery* [aorta] *pierces the diaphragm, to this, on its course, it often gives off branches of considerable size, and sometimes small branches. In the same way a branch to the left side...springs off from it, after it has passed beyond the diaphragm, at its first entry into the regions found below the thorax and within the abdomen in front*

of the kidneys. After this branch come two arteries and these are those...of which I said that they extend to and distribute themselves in the liver, spleen and stomach and in the whole mesentery with the exception of a small portion. These arteries are not coupled in pairs, but one comes off after the other. They have their origin upon the anterior part of the main artery. But all arteries coming after them have a paired origin. Of these, two very large ones go to the kidneys. And after them come two others whose origin is paired, like the origin of the veins on every single vertebra.

"With regard to the unpaired artery which has no fellow and which arises below the kidneys [inferior mesenteric]*...it breaks up in the lower mesentery. Accordingly there is no need for a long account...because of the two following considerations. In the first place although there go to the peritoneum numerous veins of arachnoid or capillary tenuity, springing from many veins but mainly from those which go to the testes, with no single one of these veins do we find an accompanying artery; although we have investigated and sought it out in all animals especially in those of large size* [oxen, horses, asses, mules and even elephants]." (trs. Duckworth.)

Galen now tells us he has mentioned this because some anatomists have erred in assuming that the arteries which encircle the urinary bladder connect with the aorta.

"For they do not reach to that artery but only to the obliquely directed ones [iliac arteries] *which branch off from the great artery and to the lower limbs passing across the broad bone, the sacrum. From these branches break off which subsequently hang freely without entering any one of the structures lying in this place. And you will find that there are always two of these branches. On rare occasions I have found a third delicate twig barely visible* [middle sacral artery]. *These branches split, divide, and break up upon all the structures which overlie the broad bone. But the two arteries which result from the division of the artery lying upon the vertebrae extend as far as the upper ends of the thighs, after passing beyond the lower ends of the muscles around the joint* [deep circumflex iliac arteries]. *But after they have mounted the upper ends of the thighs they distribute themselves completely in all the subdivisions of the lower limbs."* (trs. Duckworth.)

Another description of the descending aorta is given in the tenth chapter of the 16th Book of the De usu partium. Here Galen describes nature's wisdom in devising the location of the vessels which pass through the diaphragm, the vena cava [ir rior] the esophagus and the great artery [aorta] as follows:

"Passing through the lower parts of the thorax, the largest artery ...sends off outgrowths [aa intercostales] *on each side to the*