Handbook of Physiology

SECTION 2:

Circulation

VOLUME I

HANDBOOK OF PHYSIOLOGY

A critical, comprehensive presentation

of physiological knowledge and concepts.

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Circulation

VOLUME I

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Preface

The section on the circulation of the *Handbook of Physiology* is offered in three volumes. The first of these was planned to cover the physiology of the heart and its controls, along with certain material about the volume of the blood and the biophysical background of the organs of the circulation. The second volume was planned to include the functional morphology of the vessels and their coordination in regulating the distribution of blood flow to the several organs. The third volume was planned to deal with the circulation as the functions of an organ system whose normally coordinated or abnormal action plays upon the organism as a whole.

This original plan has been modified somewhat in the interests of prompt authors and at the expense of tardy ones. Some have advanced into Volume I; we hope that some chapters originally scheduled for Volume I may be fitted into the later ones.

The circulation is a subject whose ramifications are protean. Not only does it have an intrinsic regulation feeding back from the circulatory organs themselves, but changes in the circulation alter the functions of other organs which in turn work new changes in the circulation. Another complication in dealing with the physiology and biophysics of the circulation is the fact that certain fields are in vigorous controversy.

It is to be expected, therefore, that some topics will be covered more than once by different authors. We have tried to provide that the two coverages are not mere repetitions and a great deal of material has been discarded for this reason. On the other hand if the overlap is not really an overlap, but shows the material or argument in different context, from different viewpoints, and with different interpretation, the outcome seems to us to be good.

Each chapter is written in the hope that it will be an authoritative systematic account of the present status of the field and a contribution to Physiology as a science in its own right. The chapters are as detailed as over-all space will permit. Coverage of all the literature is not attempted. Citations are restricted, for the most part, to the factual evidence and theoretical interpretations that bear upon concepts that are seriously advocated at the present time. Recent contributions are not allotted space because of their recency, but only as they are constructive of current ideas.

Each chapter is written to fit the needs of three groups of readers: *1*) the graduate student who wants to go more deeply and broadly into the meanings of current physiological concepts and their background than he can in standard text books; *2*) the teacher who is dissatisfied with the comprehensiveness of his understanding outside his own specialty; and *3*) the investigator who will use it as a springboard for references and current concepts in a field which he is beginning to explore. The contributions are written by qualified experts, modern in viewpoint, and emphatically are not esoteric polemics between specialists.

In selecting these specialists, advice was sought on an international basis. One of us met in Ghent with a committee of representative European physiologists selected and chaired by Prof. C. Heymans. This group gave valuable advice concerning our tentative chapter list and nominated authors for each of the chapters. This editor also met with a similar group in London, selected by O. G. Edholm and Prof. J. McMichael. In the hands of these men the plan was further revised and additional authors were nominated. The final selection of authors and alternates and the final revision of the plan were made by an *ad hoc* committee accepted by the Board of Publication Trustees and composed of knowledgeable members of our own Society. The

list of chapters and authors will, in the minds of these advisors, give the *Handbook* a comprehensive definitive coverage with an international viewpoint.

The editors want to express their gratitude to these advisors, to the authors who have so conscientiously and constructively done their arduous tasks at great personal sacrifice, to our colleagues here in Georgia, R. P. Ahlquist and Carleton Baker, who have helped willingly and well. Especially valuable has been the knowledgeable and cooperative assistance of John W. Remington who has turned to, well beyond the call of duty. We are most indebted to the energy and accuracy of the departmental secretary, Mrs. Juanita Coufal. Our greatest debt of all is to Mrs. Walter J. Brown Jr., whose clairvoyant insight into the meaning of strange sentences from abroad, whose feeling for the right word in their "translation," and whose understanding of physiological principles have borne worthy fruit.

W. F. HAMILTON, *Section Editor*

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CHAPTER 1

The circulation and circulation research in perspective

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CHAPTER CONTENTS

THIS CHAPTER is divided into two sections: the first represents a perspective of the general features of the circulatory system and considers some of the vascular mechanisms concerned with the redistribution of blood flow in accordance with regional metabolic requirements. The second deals with changes of opinion that have taken place within the memory of the present author with regard to the mechanisms by which cardiac output is nicely adjusted to the vicissitudes of everyday life. The role that improvements in methodologies have played are briefly discussed. Since the perspective presented is essentially a review of reviews, references are largely restricted to surveys made at various periods of the present century that the reader may care to consult as extensions to this brief discussion.

In perusing this exposition, the reader is warned that it represents the considered interpretations of an oldster who has not been privileged to participate actively in circulation research for a number of years. There are both advantages and disadvantages in watching the research game from the sidelines; one is not so close to trivial incidents that perspective is lost, yet one is unaware of how important they may be in determining the final result. Consequently, the present author's considered judgment as to the status of current opinion on many problems may not accord with that expressed in subsequent chapters by those still active in circulation research.

THE TECHNIQUE OF EVALUATING SCIENTIFIC DATA

It has been a part of the present author's philosophy that assessment of current opinion of course requires recognition of new data procured through constant improvement in methodologies. However, it is likewise important to acknowledge valid discoveries and deductions of the past and to integrate new ones with them. In assessing older data, and doctrines derived from them, an author must constantly remain aware that results once considered crucial have, in many instances, become less certain when viewed in the light of new advances. Further, the interpretation of experimental results, both old and new, depends on the sagacity of the investigator and on the scientific atmosphere at the time. That is to say, investigators acquire diverse senses of values as a result of their scientific training; few are completely free from bias, and many are afflicted with a natural disposition

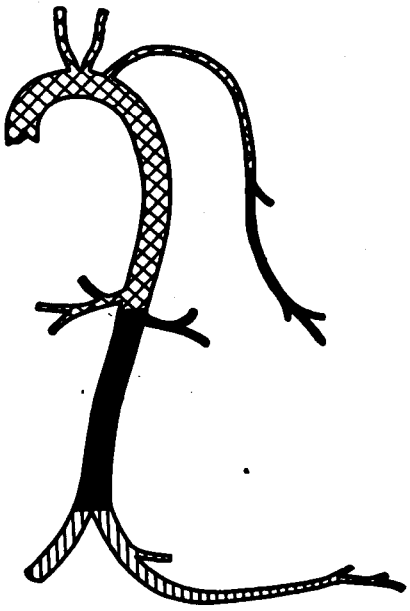

FIG. 1. Diagram illustrating the translocation of successive stroke volumes through the aorta and its branches. [After Lequime (43).]

either to maintain allegiance to or to revolt against traditional viewpoints.

THE ARCHITECTURE AND FUNCTION OF THE CIRCULATORY SYSTEM

From a functional standpoint, the systemic circuit may be divided into *a*) a distributing system (left ventricle, aorta and its branches, and their final subdivisions into arterioles); *b*) a division for the interchange of substances (capillaries and venules); and *c*) a collecting system (small and large veins, venae cavae, and right atrium). The pulmonary circuit similarly begins with the right ventricle and drains into the left atrium.

The entire cardiovascular system is lined with a continuous smooth layer of endothelium which minimizes friction between the flowing blood and vascular walls, and thus limits resistance to flow to shearing forces in layers of blood near the vascular walls.

The Distributing System

The architecture of the arterial tree is adapted in many ways to the proper distribution of blood but also introduces a number of complexities in its propulsion. The main branches of the aorta divide dichotomously, each time widening the stream bed and broadening the areas of distribution. The longitudinal divisions of the abdominal aorta into iliac and femoral arteries and the extension of axillary arteries into the brachial and radial arteries (fig. 1) create physical resonating systems of low natural frequencies that modify the fluctuating aortic pressures and flow in their transmission to the periphery.

The greatest proportion of blood injected into the aorta by the left ventricle leaves it by numerous lateral branches which form parallel circuits (fig. 2). This physical arrangement serves two important dynamic purposes: *1*) it permits redistribution of blood from one territory to another through regional changes in resistance without necessarily altering mean aortic pressure, and *2*) it reduces the total resistance to efflux from the arterial system. The latter is occasioned by the fact that, as in parallel electric circuits, total peripheral resistance (TPR) depends on reciprocal relations, for example,

$$1/TPR = 1/r_1 + 1/r_2 + 1/r_3 \cdots 1/r_n,$$

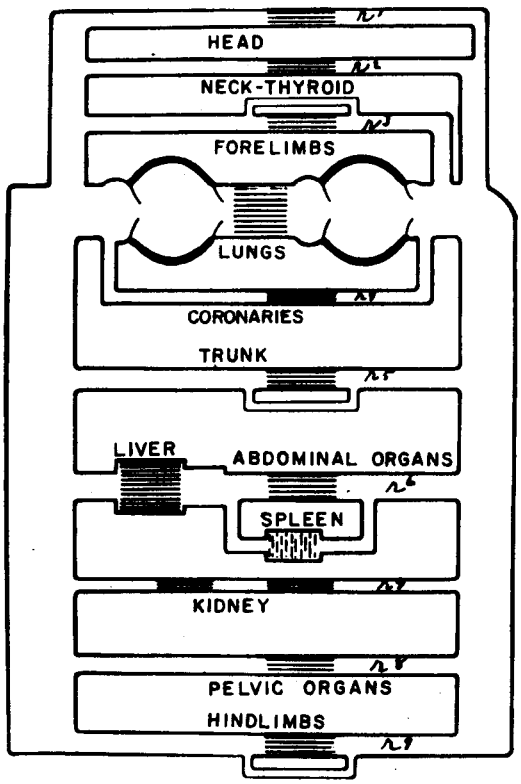

FIG. 2. Diagram illustrating the principle of parallel circuits and resistances. [Modified from Wezler & Böger (67).]

in which r_1, r_2, r_3, etc. represent regional or territorial resistance in the different parallel circuits shown in figure 2 (Wezler & Böger, 67). As an example of the relation of parallel circuits to TPR, it has been estimated that whereas the regional resistance of the cerebral or coronary circuits of dogs have magnitudes of 18,000 dyne-sec per cm^5, the TPR is very much less in proportion, as the regional flow is less than the total cardiac output.

Dynamics of the Arterial System

Since the distributing system accomplishes its biological functions in a mechanical way, numerous attempts have been made to express its dynamics by mathematical formulations. A detailed exposition and an evaluation of their present status is of course excluded in an introductory chapter. The historical fact may however be noted that mathematical treatment of pressure waves in elastic tubes dates from the early work of Euler (1775), Young (1808), W. E. Weber (1866), Resal (1876), Moens (1878), and v. Kries (1892). The interested reader may consult the reviews by A. Müller (45), H. Straub (58), A. Aperia (1, 2), Wezler & Böger (67), Gómez (23), Wezler & Sinn (69), Womersley (74), and W. Sinn (54). A survey of such reviews reveals that, whereas there is at present no consensus as to particulars, there is agreement on general mathematical formulations which, for our purpose, can be translated into simple language [see also (27, 59, 66)].

Pressure and flow in the arterial tree are maintained by the rhythmic action of the cardiac pump. During each systole, the left ventricle ejects a definite volume of blood into the aorta—about 60 to 100 ml in man—variously called the stroke volume, systolic discharge, and pulse volume. The period of ejection is very short; about 0.25 sec at normal heart rate and less during cardiac acceleration. Moreover, fully two-thirds of the stroke volume is displaced into the aorta within about 0.1 sec, and very little during the final 0.05 sec of systole. Since the aorta, at the onset of ejection, is already distended under a pressure of about 75 mm Hg, aortic uptake is accomplished partly by accelerating the stationary blood column and moving it ahead—kinetic energy—and partly by distending the elastic walls. The potential energy thus stored in the elastic walls presses back on the blood in accordance with Newton's third law of motion and causes the rise of systolic pressure. In short, the elasticity coefficient, which can be expressed in dynes per cm^5, is the basic determinant of pulse pressure (67).

The systolic elevation of pressure thus created in the aorta is transmitted as a pressure wave through the arterial tree at rates varying from 3 to 14 meters per sec. However, as already intimated, the form of the pulse pressure is altered in transmission by damping and by summation with reflected or standing waves, and possibly by the unequal rates at which harmonics of the pressure pulse are transmitted [Peterson (48)].

In contrast to the high speed with which pressure waves are propagated, the velocity with which blood flows through the arterial tree ranges from 14 to 18 cm per sec. The reason for these differences may be visualized by reference to figure 1. As indicated by the cross-hatched area, blood ejected during any given systole is accommodated in the aorta and its immediate branches. Blood already within this space is displaced under pressure to a more distal segment of the arterial tree as indicated by the black area. This translocates blood to a third segment under pressure, as indicated by the lined area. Thus whereas the pressure wave may reach vessels in the feet within 0.2 to 0.3 sec, corpuscles ejected during any heart beat do not arrive there until several more heart beats have occurred.

At the onset of diastole, the blood column reverses momentarily during closure of the semilunar valves; then it moves forward again as the elastic aortic walls recoil slowly and reconvert the stored potential energy into energy of flow. This buffering function that maintains a constant flow through capillaries was recognized by Borelli (1680) and by Hales (1733), and was baptized as the *Windkessel* by E. H. Weber (1834). Although, in a sense, the entire distributing system aids in smoothing blood flow through the capillaries, the aorta and its immediate branches probably constitute the effective compression chamber; the volume uptake of more peripheral branches per mm Hg per unit length decreases rapidly, owing to increasing stiffness of their walls [Remington (50)].

The elastic properties of the aortic walls are largely due to the elastic fibers dispersed throughout the intima, media, and adventitia. Their conformance to Hooke's law probably explains the almost proportional relationship between pulse pressure and aortic uptake at ranges of end-diastolic pressure between 40 and 100 mm Hg. Within these pressure ranges the corrugated collagenous fibers merely unfold and only act to stiffen the walls at end-diastolic pressures above 100 mm Hg. The aortic walls also

contain some obliquely oriented smooth muscle cells which are apparently inserted on elastic fibers (4). Their action and function are difficult to assess. It is the current opinion that they exert tension on the elastic fibers and thus affect both the caliber and distensibility of the aorta *in situ* (4, 6, 68).

In the so-called muscular arteries, such as the carotids, brachials, radials, iliacs, femorals, mesenterics, etc., elastic and collagenous fibers are found chiefly in the intima and adventitia; the media, which comprises two-thirds of the wall's thickness, is composed almost entirely of smooth muscle fibers arranged concentrically or, as some histologists say, spirally (68). The muscle fibers are under a plastic as well as contractile tonus. The former determines the viscous characteristics of the wall; the latter resists the tendency of internal pressures to distend the arteries. Physically, the muscle elements are arranged in parallel with the elastic and collagenous fibers; they participate in resisting distention by internal pressures and replace the action of collagenous elements in stiffening the walls under high internal pressures (4, 68). The autonomous state of contractile tonus is increased by mechanical and chemical agents, as well as through excitation by vasoconstrictor nerves. Hilton (34) has recently presented evidence that muscular arteries, such as the femoral, may dilate secondarily to a primary dilatation of arterioles, as a result of the centripetal spread of a wave of inhibition within the arterial walls.

It was formerly believed that the contractile tonus of the smooth muscle fibers alters the distensibility of the muscular arteries and perhaps also adapts their capacity to the volume of circulating blood, but exerts no significant effect on resistance to flow. During the past two decades evidence has accrued that changes in the diameter of long arteries may affect regional resistance materially. The claim that vascular contraction acts as an accessory mechanism in the propulsion of blood is based on tenuous evidence only; smooth muscles contract much too slowly to follow the pace set by the heart.

Arterioles

The arterioles constitute the terminal branches of the distributing system and are the primary stopcocks that regulate capillary flow. Their walls are relatively thick compared to their lumens. The abundant circularly arranged muscular elements are under an autonomous state of contraction (tonus) which can be augmented or inhibited by chemical agents or by the action of vasomotor nerves. Vasoconstrictor fibers are generally routed over sympathetic pathways. It is in fact probable that so-called sympathetic dilators to the coronary arteries are misnamed; they seem to cause dilatation through release of metabolites [Gregg (24)]. Vasoconstrictor nerves have been demonstrated for vessels of all organs, but the intensity of vasomotion induced is less marked in vessels of the lungs, brain, and heart. Because of these differences in vasomotor reactivity, increased discharges from the medullary vasomotor center can induce large changes in splanchnic and renal resistances, thereby mechanically diverting more blood to vital organs, such as the brain and heart. This hemodynamic concept is not new. For example, L. Hill (33) stated in 1900, "It is by means of the great splanchnic area that the blood supply of the brain is controlled. . . .We have in the vasomotor center a protective mechanism by which blood can be drawn at need from the abdomen and supplied to the brain." [See also Folkow (16–18).]

Neurogenic vasodilatation is generally induced through inhibition of vasoconstrictor activity which, however, still leaves arterioles under a state of autonomous contraction. In the heart, abdominal organs, and skeletal muscles, this residual tonus can also be inhibited by action of sympathetic vasodilator nerves, thus causing additional dilatation. In vessels of the head, pelvic organs, and genitals, excitation of parasympathetic nerves induces extreme dilatation. The interpretation of Gesell (21) that such vasodilatation is not due to direct nervous action but through release of vasodilator metabolites has recently received considerable support (18, 65). In the skin, vasodilatation may occur through operation of axon reflexes, and in mucous membranes by action of posterior root dilators (18, 65).

Through reflex control of vasomotion, shifts of blood from viscera to the skin and vice versa may take place, as for example during exercise and digestion as well as in hemorrhage and shock (32, 49, 72).

Control of Capillary Blood Flow

The capillary walls consist of a single layer of endothelial cells mounted on a basement membrane. The thin walls adapt the capillaries admirably for interchange of substances between the blood and tissue spaces. According to older views (8), a "cement substance" between cells is produced by them and can be modified by such agents as the Ca:K ratio and hormones. Advances in methodologies, including

electron microscopy, reveal no evidence of any substances between the endothelial cells [Kisch (38)]. At present opinions are divided as to whether the exchange of substances occurs through submicroscopic intercellular fenestrations or through ultramicroscopic perforations in the endothelial cells [Bennett *et al.* (3), Kisch (38), Pappenheimer (47)].

The passage of solutes and solvents through the endothelial walls is largely regulated by capillary pressure and flow [Landis (40)]. During the early part of the present century, capillaries were believed to be straight subdivisions of arterioles. Capillary pressure and flow were considered to be regulated solely by the intensity of arteriolar and venular constriction. The concept that capillaries could change their caliber actively began with observations of Dale & Richards (13) that histamine apparently constricts arterioles and dilates capillaries. It received major support from the microcirculatory studies of Krogh and his colleagues (39) and from the human studies of Lewis (42). Krogh's observations, made chiefly on amphibia, were not generally confirmed by microcirculatory studies of mammalian blood vessels [Clark & Clark (10)], and his inference that active changes in capillaries are caused by a squeezing action of pericytes (Rouget cells) attached to their walls, is currently out of favor [Burton (6)]. A new concept of the finer regulation of capillary flow than is provided by arteriolar vasomotion was introduced by Chambers & Zweifach (7). Their microcirculatory studies of the tongue and mesentery revealed that arterioles give rise first to thin-walled, contractile metarterioles or precapillaries which lead into arteriovenous channels 12 to 16 μ in diameter. As schematically shown in figure 3, these thoroughfare channels give off side branches that form an anastomotic network of true capillaries. The metarterioles and precapillary sphincters undergo periodic contractions at intervals of 15 sec to 3 min. It is therefore the present consensus that whereas the arterioles dominate resistance to flow from arteries to capillaries and hence the pressure gradient, the metarterioles and their sphincters control capillary filling and patency to a finer degree.

The smallest postcapillary venules (prevenules) should probably be included in the category of "minute vessels" as defined by Lewis (42) and are likewise concerned in the interchange of solvents and solutes. According to Hooker (35), small venules are distinguishable by their somewhat larger size

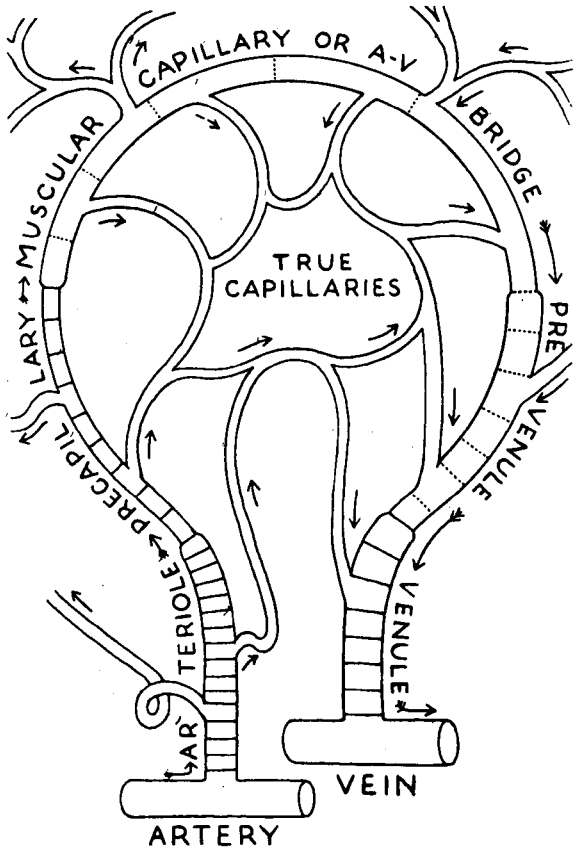

FIG. 3. Diagram of true capillary network and A-V capillary bridges. [After Chambers & Zweifach (7).]

than capillaries and by the presence of a slight investment of connective tissue. In some regions smooth muscle cells are seen in venules 20 to 30 μ in diameter; in other regions they are absent in small veins visible to the eye [Franklin (20)].

Collecting Veins and Venous Return

Blood from the venules is collected by merging veins of increasing size. Their thin walls are composed of many collagenous and scanty elastic fibers in which muscle cells are dispersed in circular, spiral, or longitudinal directions [Franklin (20)]. Veins collapse when incompletely filled and, when distended to a cylindrical shape, display only limited distensibility [Clark (11)]. Up to internal pressures of 5 to 10 cm of water, the increment of pressure per increment of volume is quite small, but above such pressures dP/dV rapidly increases until the veins become relatively indistensible.

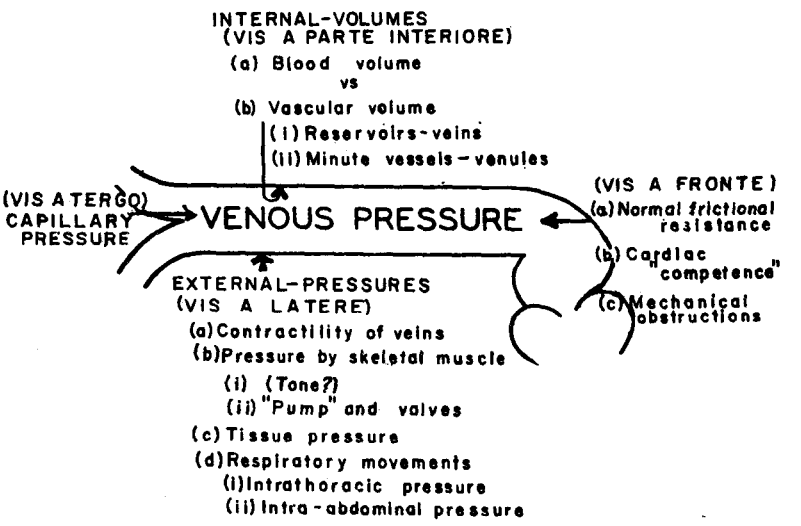

FIG. 4. Factors affecting venous pressure. [After Landis & Hortenstine (41).]

Normally, blood is propelled through the collecting system by a pressure gradient of about 6 to 8 cm of water between the peripheral veins and the right atrium [Brecher (5)]. The various coefficients that determine the gradient are nicely summed up in the diagram of Landis (41), reproduced as figure 4.

Only a few points deserve editorial comment: the author has been impressed with the major extent to which the venous pressure gradient is controlled by cardiac activity. For instance, when the cardiac output increases, more blood is drained from the atrium per unit time, central venous pressure decreases, and the pressure gradient augments through reduction of the *vis a fronte*. Evidence clearly indicates that the small and large veins contract as a result of venomotor activity [Franklin (20), Gollwitzer-Meier (22), McDowall (44)]. Further, veins participate in vascular contractions reflexly induced from the carotid sinus [Heymans & Neil (32)]. Despite contrary opinions, the present author believes that the extent to which such reduction in venous capacity augments venous return has not been established experimentally.

ADJUSTMENT OF CARDIAC OUTPUT TO METABOLIC REQUIREMENTS

It has long been recognized that enhanced metabolism is associated with increase in heart rate and presumably with a greater cardiac output. The question whether stroke volume also increases has been debated for the past 60 years. At the beginning of the present century, technical procedures were essentially limited *a*) to metering aortic flow in rabbits, calculating volume flow per unit body weight, then extrapolating results to man; and *b*) to estimation of cardiac output in dogs and horses by use of the Fick principle (1870, 1886). Nevertheless, Tigerstedt (62) in his *Lehrbuch* (1897) ventured the guess that the stroke volume in man ranged from 50 to 100 ml, values that have subsequently proven correct (14). But data acquired by such imperfect methods showed such inconstant ratios between heart rate and cardiac output that the two were considered independent variables. This interpretation fitted in with Englemann's concept that cardiac rhythmicity, excitability, conductivity, and contractility could be altered independently by humoral and nervous agencies. On the other hand, experiments of Howell and Donaldson (1884) on N. Martin's limited circulation preparation had indicated that cardiac output varies consistently with venous supply and right atrial pressures [for details, see Tigerstedt (63, 64)].

During the first decade of the present century physiologists began to question the accuracy of data obtained by available methods and the applicability to intact animals and man of values obtained from use of partially or totally isolated hearts. Progress during the next 30 years was beset with many frustrations in attempting to develop better procedures (46). The efforts made to understand the laws of cardiac performance and to estimate changes in cardiac output in man under different conditions illustrate admirably that a goal in research is reached only through development of a great number of methodologies which, though inadequate, do offer

clues for their betterment. Hence a brief historical recall does not seem out of place in an introductory chapter.

Methods for Studying the Determinants of Cardiac Performance

The reactions of isolated ventricles of frogs, contracting isotonically and isometrically under various degrees of filling, had been studied by Frank (19) in 1895. He found that within limits stepwise increases in end-diastolic filling and pressure determine the magnitude of the all-or-none response. He concluded that the magnitude of end-diastolic pressure was the basic determinant.

In 1905, it was my privilege to witness Y. Henderson's demonstration of a method for recording the volume curves of the ventricles in dogs. This technique appeared to be a definite advance, because it permitted registration of the details of ventricular filling and ejection as well as the magnitude of successive stroke volumes. It therefore constituted a better way for determining the principles underlying ventricular performance. As reviewed by Henderson (29), he and various associates concluded *a*) that atrial contraction contributes so little to ventricular filling that it could be ignored and *b*) that the ventricles contract in so uniform a manner that curves taken at different heart rates can be superimposed like triangles in geometry. Further analysis indicated *c*) that stroke volume is not affected by increases in venous pressures above the normal, and *d*) that stroke volumes change very little at ranges of heart rate from 20 to 100 per min, but, *e*) that at higher heart rates they decrease progressively, because contractions encroach more and more on the rapid inflow during early diastole. The corollary followed that the only way that cardiac output can be altered is through changes in heart rate. Henderson's conclusions were contested partly on the grounds of unreliability of the procedure and failure to recognize the importance of atrial systole, but chiefly because all his reports were linked with the hypothesis that acapnia is the cause of shock (30). In short, Henderson violated a well-known principle in advertising, namely, that favorable features of a product must not be associated with unpopular notions. Physiologists have been slow to learn that new viewpoints are more often accepted on the basis of their psychological appeal than on the validity of data and the conservatism with which conclusions are drawn.

During my visit to Starling's laboratory in 1923, he told me that his decision to develop a heart-lung preparation was motivated by his impression that opening of the chest of an anesthetized dog did something that weakened cardiac contractions. The preparation developed with Jerusalem and Patterson allowed heart rate, venous inflow, and arterial resistance to be altered one at a time. It immediately came into general favor for studying the principles of ventricular behavior. On the basis of observations made with various associates (56, 57), Starling concluded, contrary to Henderson, that cardiac output is not altered by changes in heart rate between 60 and 160 per min, and can be changed only by alteration of filling and stroke volume. Starling (56) held that changes in end-diastolic volume or stretch, rather than pressure, were the basic determinants (Starling's law of the heart).

It is not uncommon in research that adversaries are right in general but wrong in particulars. This was the conclusion to which Katz and I came in 1922; we found elements of truth in both Henderson's and Starling's interpretations. Since knowledge is slow afoot, but wisdom limps far behind, it was not until later that the present author (70, 71, 73) realized that the concepts could be harmonized with each other and also with the postulates of Englemann [see also Katz (36, 37)]. It remained a question, however, whether changes in end-diastolic pressure and volume or alterations in contractility, produced by humoral or nervous influences, constituted the prepotent factor in stresses to which the body is submitted under normal conditions. For instance, when it seemed demonstrated that venous pressure rises during moderate exercise [Eyster (15)], it seemed a reasonable assumption that stroke volume increases during exertion in accordance with Starling's law despite cardiac acceleration. Katz, Opdyke, and Bulkley and their respective co-workers have studied the importance of varying impedance to ventricular filling in heart preparations in which one ventricle only performs work.

It is not surprising that all the dynamic factors capable of affecting ventricular performance were not thought of by experimenters of past generations and remained fertile fields for study in the present era. Better apparatus was designed and new types of special circulatory preparations were developed. While the results of numerous studies still seem contradictory in many respects, they will undoubtedly be integrated in subsequent chapters. Here, it is only possible to refer very briefly to a few of the many notable contributions of recent years: Katz and his

co-workers (36, 37) have related ventricular pressure/volume curves to work diagrams, and focused attention on factors affecting stroke work. Sarnoff and collaborators (53) have related stroke work of the right and left ventricles to pressures in corresponding atria as ventricular function curves. More recently, they restressed the importance of ventricular tension-time in cardiodynamics, and revived the old idea that the force of atrial contractions is of controlling importance. Nylin, Bing, Holt, and their respective collaborators have measured the residual ventricular volumes more accurately, and others have emphasized the emergency value of the "cardiopulmonary reserve" in increasing cardiac output. Holt and Duomarco, independently, have shown the importance of end-systolic pressure as an additional regulatory coefficient of cardiac output and work. Guyton and his group (26) have studied the intrinsic response of the ventricles to changes in venous return in dogs whose reflexes were all abolished. Rushmer and his school (51) developed many ingenious appliances that permitted continuous quantitative recordings of multiple cardiac activities in unanesthetized dogs. They concluded that changes in cardiac output during exercise are caused entirely by chronotropic and inotropic effects mediated by the diencephalon and modulated by reflexes of vascular origin. Thus the wheel of circulation research has revolved back to concepts prevalent at the beginning of the present century.

Methods for Determining Cardiac Output in Man

Pari passu with the growth of laboratory techniques for elucidating mechanisms of cardiac adaptation, continued efforts were made during the present century to establish more reliable methods for measuring cardiac output in man. While many technologies, such as roentgenkymography, cineroentgenography, electrokymography, ballistocardiography and the integration of pressure pulses achieved some measure of usefulness, the greatest advances have come from improvements in the application of the Fick principle and the blood-dilution technique of Stewart-Hamilton [Hamilton (28)]. Early attempts to obtain probable values for blood gases indirectly or to use foreign gases led to many confusing results (9, 25, 28, 63). Two technical developments—Stadie's method of obtaining arterial blood samples by arterial puncture (55) and Cournand & Ranges' method for obtaining mixed venous blood by cardiac catheterization (12)—were largely responsible for the great impetus to recent studies of cardiac output in man under normal and pathological conditions. For instance, it was definitely established (14, 28, 43) that cardiac output may increase from about 4 liters per minute at rest to 20 or more liters per minute during strenuous exercise. Simple calculations indicate that the heart cannot deliver such large quantities of blood by an increase in heart rate, say from 70 to 180 per min, without considerable increase in stroke volume. Nevertheless, the net information gained by other avenues of approach led to the conclusion of a conference in 1955 (59) that the Frank-Starling postulate is operative only to a minor degree (52): For example, the views were well documented that demonstrable changes in end-diastolic tension and ventricular size were not necessarily associated with more forceful ventricular beats and that both systolic and diastolic sizes decreased as the heart accelerated during exercise. It was not generally recognized that these conclusions corresponded in great detail with those of Henderson (29) in his 1923 review. However, it must be noted that at that time Henderson slyly amended his concept of the uniformity of cardiac behavior by adding an intrinsic ability of the ventricles to alter their process of filling and ejection.

There is no doubt that the current emphasis on the central nervous system control of cardiac output (60, 61) was strongly influenced by advances in the field of neurophysiology, chiefly in unraveling the structure and functions of the reticular formation and diencephalon. This is a good illustration of how advances in one field of physiology accrue through those made in cognate ones. In our zeal to accept such a concept we must not lose sight of the fact that physical and chemical changes in the environment of cardiac tissue also affect its reactivity. Indeed, with the rapid development of endocrinology and knowledge that hormones, such as epinephrine, pitressin, thyroxin, and aldosterone, cause changes in cardiac reactivity, one senses already an inclination in some laboratories to postulate a dominant endocrinological control of cardiac output.

Venous Return, the Fulcrum of the Circulation

Regardless of the direction that future thinking with regard to the mechanisms of cardiac adaptation to stresses may take, it must conform to the obvious fact that the heart cannot pump more blood than is returned. As phrased by Henderson, "venous return is the fulcrum of the circulation." The present author finds it difficult to understand why so much current

emphasis is given to mechanisms of blood supply that can be only temporary emergency mechanisms. Accepting current estimates that the ventricles contain residual volumes that may exceed those ejected, and that the pulmonary venous system also constitutes a reservoir of blood, my calculations indicate that the total cardiopulmonary reserve can be pumped out within 5 or 6 sec after the onset of strenuous exercise. Thereafter, augmented cardiac output can be maintained only by a corresponding increase in venous return.

Despite many earnest efforts to elucidate the sources of additional venous blood and the mechanisms by which venous return is augmented (5, 22, 26, 31, 41), most of the conclusions are based on inferences and extrapolations rather than on direct experimental evidence. Hence the study of venopressor mechanisms remains a promising field for future investigations.

A few words in conclusion: the reader may infer that the author of this chapter has reached an age when the tendency to recall significant advances of the past exceeds his capacity to appreciate the full value of contemporaneous ones. They may be reassured however that he had no intention of downgrading the highly significant contributions of the present generation of active workers. Since these new advances will be stressed predominantly in subsequent chapters, it seemed appropriate to recall that the scholarly assessment of current work also requires recognition of accomplishments of the past and some knowledge of the underlying reasons for frequently changing points of view. Research, as the word implies, consists in searching again and again to make quite certain that propositions regarded as established are indeed true. A historical perspective teaches us not to repeat investigations made by simpler means too often, just because more complicated methods have become available.

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CHAPTER 2

The historical development of cardiovascular physiology

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CHAPTER CONTENTS

FROM THE TIME that humans started to think and to observe themselves and their surroundings, they have been interested in the way in which living things work. Of course we are mostly interested in ourselves: what makes us tick has been the subject of long centuries of search and research. Cross analogies between muscles and bones on the one hand, and levers and tackle on the other, must have early developed. Certainly analogies from levers and tackle were early applied to ideas on muscular motion, and it may very well have been that notions about muscle action suggested the development of various kinds of levers and pulleys. Certainly people must have thought hard how to devise ways whereby muscular work could be made easier. Analogies from human feelings were applied to the way in which forces in nature may work. Animistic ideas still color our language about the movement of the winds and waters. It took many long centuries before functional or physiological generalities could be tentatively expressed.

Cardiovascular function is central to an understanding of mammalian and human physiology. The history of this phase of intellectual advance is long and full of intense human interest. It also has had great practical significance in stimulating ways by which knowledge of the operation of the heart and blood vessels could be applied to practical medical affairs in the diagnosis, prognosis, prevention, and treatment of disease. It is also stimulating in a practical way to consider how our knowledge of the operation of the heart and blood vessels was obtained.

The first consistent comprehensive scheme to explain the manner in which animals work was developed by Galen, the great Greek physician to the Roman emperor Marcus Aurelius. His explanation, applicable to those living things we call "mammals," persisted for 1500 years. While it may have been the practical success of cinchona bark in "curing" fevers, which really overthrew Galenical scholasticism in the seventeenth century, it was the theoretical consequences of the demonstration of the circulation of the blood in animals, by William Harvey, that eventually removed the arbitrary Galenical system, and established modern experimental methods to make possible the science of physiology.

HARVEY'S PREDECESSORS

Through injury and warfare, with resulting wounds and bleeding, people even in primitive societies universally developed ideas at a very early time about the heart beat, and how warm blood is necessary for life. The relation of the pulse to the heart beat was vaguely appreciated in antiquity, and became formalized in such great static ancient cultures as the Chinese, the Hindu, and the Egyptian. These early notions on the