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Some Axioms, Popular Notions, and Misconceptions Regarding Cardiovascular Control

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CURRENT rapid progress in science and technology is providing an ever-expanding array of new research tools for the acquisition, storage, analysis, and interpretation of physiologic data. Such new technics offer unprecedented opportunity for reappraisal of traditional concepts and for evolution of new concepts of function and control. This report is designed to evaluate critically some widely accepted fundamental concepts of cardiovascular physiology and to suggest future trends in this area as they appear to be affected by the current technologic revolution in research methods.

At times scientific progress depends less upon the acquisition of new knowledge than upon the removal of conceptual obstacles. According to Sir Francis Bacon,1 "It is idle to expect any great advancement in science from the superinducing and engrafting of new things upon old. We must begin anew from the very foundations, unless we would revolve forever in a circle with mean and contemptible progress." This aphorism (no. 31) suggests a need for evaluating the validity of past and present cardiovascular research in terms of specific criteria. At the risk of exciting more controversy than agreement, the following axioms are proposed for this purpose.

Axiom I. An important objective of cardiovascular physiology is elucidation of the mechanisms of function and control in animals and man under normal conditions.

Axiom II. The use of ambiguous and poorly defined terms tends to obscure ignorance and impede progress.

Axiom III. Ideally, investigation of physiologic mechanisms should be conducted with minimal disturbance of either the organ system or its controls.

Axiom IV. Experimental data are applicable without reservation only to the specific conditions under which they were collected.

Axiom V. Extrapolation in the application of experimental data to species or to conditions of function different from those in which the information was collected should be based on knowledge of the kind and extent of deviation of the experimental from the normal.

Axiom VI. The circulations of anesthetized animals must be regarded as experimental models of normal cardiovascular function.

Axiom VII. Experimental models are frequently desirable and useful, but their validation requires quantitative comparison of the specific model with the physiologic mechanism or condition it is designed to represent.

These axioms were designed to be suffi-
entially apparent that they can at least be employed as yardsticks in evaluating traditional cardiovascular concepts and current trends in research.

**Popular Notions in Cardiovascular Physiology**

In addition to the seven axioms listed above, certain concepts have become so widely accepted that they are rarely questioned or critically evaluated.

1. The cardiovascular system of an anesthetized or thoracotomized animal constitutes a suitable experimental model for studying the normal circulation in the same species.

2. The circulations of conscious, healthy dogs serve as suitable models for studies applicable to man.

3. Ventricular function can be adequately described in terms of heart rate, the Frank-Starling mechanism, and changes in myocardial contractility.

4. Cardiac output is determined by venous return.

5. Simple explanations are more likely to be correct than are complex mechanisms for elucidating physiologic function and control.

6. Most of the problems of cardiovascular function and control are currently under study.

Each of these six statements contains undeniable elements of truth and yet each also embodies sources of error and misconception. Critical evaluation of these widely held views constitutes the principal objective of this paper. At the end of each appraisal, some questions are posed to point up the issues and to stimulate reactions. These queries are intentionally provocative rather than informative. In some instances specific axioms, identified by Roman numerals, appear to be relevant. Additional axioms are suggested by the review of certain of the popular notions.

**Evaluation of These Popular Notions about Cardiovascular Physiology**

In the past, severe limitations in measuring technics frequently forced physiologists to extrapolate from studies conducted under obviously abnormal conditions. "The unassisted hand and the understanding left to itself possess but little power. Effects are produced by means of instruments and helps which the understanding requires no less than the hand"; (Bacon, Aphorism no. 2). In recent years, whole batteries or systems of new research tools have become available to provide more direct and quantitative information than was ever available in the past. Some of these new technics have been adapted for use in healthy, active animals and aid in evaluation of the selected popular notions in terms of the stated axioms. The experimental methods employed have been described elsewhere in detail, and in most instances experimental records are presented as examples to illustrate specific points rather than as definitive reports of research. In aseptic surgical operations ultrasonic flowmeters were installed on the root of the aorta or on the main pulmonary artery, and indwelling cannulas for registration of ventricular pressure were installed. Left ventricular diameter was frequently recorded by a sonocardiometer. Various analogue computers were employed to derive additional variables, including stroke volume, ventricular outflow per unit time (cardiac output), acceleration of the blood, rate of change of ventricular pressure, duration of systole, heart rate, instantaneous power, stroke work, and work per unit time (fig. 1). These technics for continuous analysis of ventricular function in standard engineering terms have been described in detail. With ultrasonic flowmeters installed on the superior mesenteric artery, renal artery, and terminal abdominal aorta, the distribution of blood flow to the splanchnic bed, kidney, and hindquarters could be monitored continuously.

Although the dogs were alert, spontaneously active, and healthy in appearance at the time of the experiments, they cannot be regarded as normal in a strict sense. The previous major surgery and other unknown factors could have led to unrecognized respiratory or circulatory dysfunction (axiom III). The data presented in the illustrations are applicable with these reservations to such dogs (axiom IV), but not to other species without
specific confirmation by definitive measurements (axiom V). Preliminary results of similar experiments on primates have tended to confirm those obtained on dogs.8 Hopefully, observations from such experiments on healthy dogs and monkeys will stimulate corresponding measurements of appropriate variables in human subjects to evaluate the applicability of these generalizations to man (axiom VII).

**Popular Notion no. 1. The Cardiovascular System of Anesthetized or Thoracotomized Animals Constitutes a Suitable Experimental Model for Studying the Normal Circulation in the Same Species**

General anesthetics are employed to suppress pain and induce unconsciousness. None would seriously question that other changes in the central nervous system are produced as well. A large proportion of modern cardiovascular research is being conducted on anesthetized animals. For example, in *Circulation Research* during the year 1961, 63 studies on the heart and 39 studies on the peripheral vascular system in animals (excluding humans and fowl) were reviewed. Only six of these studies (6 per cent of the total) involved special efforts to conduct the experiments on alert, active animals without anesthesia.7,9-13 One report14 dealt with some circulatory effects of thoracotomy and intermittent positive-pressure respiration, but this experiment was conducted under light thiopental anesthesia.

Clearly, the degree to which abnormal experimental conditions invalidate extrapolations can be decided only after careful analysis of individual studies. An essential step in this evaluation is knowledge regarding the nature and extent of the changes occurring during preparation and before the control levels are established, as well as those occurring during the subsequent experimental procedures. To evaluate this sort of experimental distortion, measurements must be made before, during, and after preparatory manipulations.

Changes in left ventricular performance which may occur during intravenous administration of sodium pentobarbital (20 mg./Kg.) are illustrated in figure 1. During the control period, continuous fluctuation of the many recorded variables is characteristic of any alert healthy dog. For example, the heart rate was relatively slow (60 to 110) and highly irregular, partly as a consequence of sinus arrhythmia. Over the years, these characteristics of the heart rate have become established as favorable signs that operated dogs are in good condition with minimal intrathoracic abnormality. Acetylcholine in doses of 100 and 200 γ, rapidly injected intravenously, produced dramatic effects including transient reduction in stroke volume, ventricular pressure, duration of systole, power stroke work, and diameter. These changes were associated with increased cardiac output, heart rate, accumulated work, change in pressure with change in time (dP/dt), and acceleration of aortic flow.

After administration of the pentobarbital, the left ventricular performance promptly shifted to new baseline conditions. The spontaneous fluctuations disappeared in the different variables. The heart rate ascended to a higher level and became very stable. The dog was only lightly anesthetized, moving spontaneously or in response to tactile stimuli. The responses to acetylcholine in the same doses were greatly altered. The altered baseline conditions affected not only the magnitude of the changes in variables but actually reversed the direction of the deflection in certain instances (stroke volume, dP/dt, work/2.5 sec.). Although the heart rate approached the same peak levels, the amount of change was slight because of the tachycardia induced by the barbiturate. The changes in the baselines of performance in figure 1 are somewhat greater than are observed with slower administration of the barbiturate.

The cardiovascular system becomes very stable under barbiturate anesthesia. The artificially stabilized circulation imposes a need for the investigator to induce changes for the study of cardiovascular responses to various loads. For example, changes in heart rate must be induced, cardiac output must be increased by artificial means such as intrave-
Left ventricular function continuously described in an alert, healthy animal in terms of 12 standard physical terms derived from direct recordings of aortic flow, left ventricular pressure, and left ventricular diameter. Changes in left ventricular function produced by inducing light anesthesia with intravenous sodium pentobarbital are illustrated on the right. Some effects of acetylcholine (ACH) are reduced or reversed after anesthesia.
Changes in right and left ventricular function and in blood flow through intestine and hind quarters accompanying general anesthesia, tracheal intubation, artificial respiration, thoracic incision, and exposure of the heart. A volume load was imposed before and after anesthesia by transiently opening a femoral arteriovenous shunt.

ccephalon (H₂ fields of Forel). However, when a volume of nerve tissue is indiscriminately excited by electrical stimulation, even the most discrete stimulus is not likely to evoke exactly the pattern of neural activity that occurs spontaneously during normal function. These considerations suggest that no experimental procedure can serve as an unquestioned substitute for spontaneous exercise, or any other normal response, even when these procedures were employed on healthy conscious dogs.¹⁵ Response to the same procedures displays even greater discrepancies from normal when the dog is anesthetized or throracotomized.

General anesthesia is clearly required in any experiment that involves inflicting pain on animals. Selection of anesthetic agents should be undertaken to have minimal effects on the baselines of function and on control mechanisms of the system under study. The barbiturates are very widely used in cardiovascular physiology, even though they are known to affect profoundly the baselines of cardiovascular performance and the control mechanisms (figs. 1 and 2). Short-acting barbiturates produce only transient unconsciousness and might be regarded as a good choice for minor surgical procedures in preparation for collecting data after consciousness returns. This is misleading because sustained cardiovascular effects of sodium pentothal have been observed for as long as 2 and 3 hours after the return of consciousness in a few exploratory experiments.

In experiments requiring general anesthesia for placing stimulating electrodes in the brain, we routinely use chloralose, having demonstrated to our satisfaction that this agent produces less alteration in cardiovascular...
lar function than the other agents tested. Barbiturate anesthetics are still used in this laboratory for the surgical procedures involved in implanting the various gages, but we wait days or weeks for recovery before collecting data from such preparations. Muscle-blocking agents, such as suxamethonium, have significant effects on the circulation in intact animals. The effects of common anesthetic agents on the cardiovascular system have been described in greater detail by Van Citters et al.16

Many of the experiments in current literature employ general anesthesia for simple experimental procedures, such as electrocardiography, venipuncture, and arterial sampling, which are routinely accomplished on human subjects with no anesthetic of any kind. Catheterization or cannulation is accomplished with only topical anesthetics, even in children. In many experiments on the heart and peripheral vascular system, the data can be obtained from conscious animals without pain or discomfort by exercising care and kindness. Even untrained dogs can be induced to lie down with some petting and gentle handling. If his front legs are taped together, the animal will lie quietly so long as no pain is inflicted. Taping the hind legs together will give somewhat greater control, but is not necessary if access to the femoral vessels is desired. Under these conditions, a very large proportion of the current cardiovascular research could be conducted on healthy conscious animals to produce more meaningful data without inflicting pain on the animals.

**Effects of Thoracotomy**

Thoracotomy was also employed in a large proportion of the studies (vide supra) on the heart (71 per cent). Profound changes occur in the function of the cardiovascular system during the process of anesthetizing an animal, intubating the trachea, incising the thoracic wall and finally exposing the heart (fig. 2). To illustrate how extreme these changes can be, sample records were selected from a series of animals in which the performance of the right ventricle and left ventricle were simultaneously monitored in terms of the variables indicated in figure 1 and, in addition, flowmeters in the superior mesenteric artery, renal artery and terminal aorta indicated variations in the distribution of blood flow to the splanchic bed, kidney, and hindquarters. Changes in the responsiveness of the cardiovascular system were also tested by opening a wide bore arteriovenous shunt between the left femoral artery and left femoral vein. Opening the shunt promptly increased the blood flow in the terminal abdominal aorta (fig. 2, bottom record in the right column). The changes in right ventricular function accompanying the opening of the arteriovenous shunt could be observed more readily after anesthesia, being somewhat obscured by spontaneous fluctuations in these variables while the animal was alert.

During the administration of anesthesia, with tracheotomy and thoracotomy, the performance of the right and left ventricles progressively deteriorated with a reduction in ventricular pressure, instantaneous flow velocity, stroke volume, and stroke work. The heart rate remained elevated and the cardiac output tended to fluctuate under several conditions: during the tracheal intubation, at the beginning of artificial respiration, on the incision of the skin on the thorax, and finally during a wide intercostal incision into the thorax. The flow through both the superior mesenteric artery and the terminal aorta diminished after the thoracotomy. In the example given, the first view of the heart and the control baseline for a standard physiologic experiment on this animal would have occurred under conditions illustrated at the extreme right of figure 2. The investigator would ordinarily be unaware of all the changes indicated in the sequence of preparation in this particular animal.

At the completion of the experiment illustrated in figure 2, a heart-lung preparation was established. During the additional arterial and venous cannulations and installation of the Starling resistance, the performance of the ventricles deteriorated even further. On the basis of such observations,
we are inclined to agree with Hamilton that isolated hearts or heart-lung preparations pump much less blood than would a normal heart at corresponding heart rates. The shrinkage of a heart that occurs with thoracotomy may become even more extreme in a cardiometer.

Studies on unanesthetized dogs are of particular importance in studying the nature of the integrated cardiovascular responses that occur during spontaneous activity. These observations provide information regarding the kinds of response ultimately to be explained by more rigidly controlled experimental conditions. Experiments designed to provide detailed analysis of the components of the control systems are very difficult to carry out on alert, active animals. Nevertheless, we must have specific and quantitative information concerning the characteristics of the responses we wish to explain. In addition great care must be taken to ascertain that the experimental model and the changes induced by the investigator do in fact represent the phenomenon under study. Also, the experimental results from rigidly controlled experiments on dogs must be interpreted in terms of the changes in baselines and in performance produced by the experimental preparation (figs. 1 and 2). Clearly, the experimental conditions for a particular study must be chosen only after careful consideration of these and similar factors. Before deciding to employ anesthesia, thoracotomy, or a heart-lung preparation in an experimental protocol, one should consider several pertinent questions.

Queries Regarding Popular Notion no. 1

1. If an experiment on cardiovascular function and control is carried out on the circulation of a dog under anesthesia (figs. 1 and 2), can the experimentally induced responses be appropriately attributed to a normal animal of the same species? (I, III, IV, VII)

2. Do the baseline conditions of cardiovascular function in an anesthetized or thoracotomized dog correspond to a normal resting dog? If not, to what normal functioning state do the conditions illustrated on the right of figures 1 and 2 correspond? (V)

3. To what normal cardiovascular adaptations do the experimentally induced changes correspond? For example, are intravenous infusions or the opening of arteriovenous shunts equivalent to any normal physiologic adjustment? (VII)

4. What types of physiologic experiments require the use of anesthesia, of thoracotomy, or of perfused hearts or tissues?

5. What factors should influence the choice of anesthetic agents when they are required?

These considerations suggest the following additional Axioms.

Axiom VIII. With the development of techniques for comprehensive analysis of cardiovascular function in alert active animals, general anesthesia, thoracotomy, and heart-lung preparations are not essential for studies of cardiovascular responses.

Axiom IX. The use of general anesthesia to perform on animals the same procedures that are routinely accomplished on human subjects with nothing more than topical anesthesia (venipunctures, catheterization, etc.) may complicate interpretation of experimental observations without contributing significantly to the humane treatment of animals.

Popular Notion no. 2. The Circulation of a Conscious Healthy Dog Can Serve as a Suitable Model for Studies Applicable to Man

As judged by the physiologic literature, dogs and rats are the best substitutes for human subjects in cardiovascular research. Newton enunciated the following rule: "Therefore, to the same natural effects we must, as far as possible, assign the same causes. As to respiration in man and in a beast; the descent of stones in Europe and in America ..."

The frequency with which experimental data collected on animals are unreservedly applied to human subjects suggests that a large segment of the physiologic community agrees wholeheartedly with Newton on this point. There are cogent reasons, however, why extreme caution is needed in applying both data and concepts from animal studies to
A. In the heart-lung preparation, increased diastolic distention of the ventricles is generally accompanied by increased stroke volume. B. In intact dogs, increased diastolic distention and greater stroke volume characteristically occur during changes in posture from standing to reclining, and C, commonly during changes in heart rate associated with respiratory activity. D. Changes in ventricular output not correlated with corresponding changes in ventricular dimensions are usually ascribed to changes in "contractility," which is not clearly defined but is commonly described in terms of diverse recorded variables. E. During exercise, the changes in left ventricular function included very large increases in heart rate, cardiac output, accumulated work, with relatively small increases in stroke volume, stroke work, and little change in diastolic diameter.

Many obvious differences between dogs and normal persons or patients with cardiovascular disease.

Men can be enumerated: body size, posture, habitus, diet, cerebral structure and function, skin, etc. Anatomically, the hearts
Changes in left ventricular function with exercise (see fig. 4E) or sympathetic discharge to the heart schematically represented in terms of 10 variables of which five are amounts or quantities and five are the rates at which these variables change. In general, the rates of change are greatly increased while the quantities are slightly increased or reduced, primarily by shortened duration of systole.

of dogs and men appear similar, but the configurations of the chambers differ somewhat. For example, the right ventricle does not extend to the apex in the dog. Also, the heart is vertically oriented in a narrow thorax in dogs and obliquely positioned in a broad thorax in man. In the vascular system, the dog possesses a well-developed hepatic sphincter, which can impede outflow from the splanchnic bed. These are but a few examples of the many differences that might be listed.

The pumping action of the heart is similar in dog and in man, judging from the correspondences in changes in pressure, flow, and dimensions. The wave forms of ventricular pressure, ejection velocity through the aorta, the arterial pressure, and the change in dimensions are very similar in direct records from either man or dog. In addition, Braunwald et al. have demonstrated that the ventricular pressure, the rate of change of pressure, and the duration of systole during exercise in man change in much the same way as they do in dogs (figs. 3 and 4). Wave forms of changing ventricular dimensions in man and dog are quite similar when recorded by means of variable resistance gages consisting of rubber tubes filled with mercury.22, 23 Extending the comparison of human and canine ventricular function even further, Braunwald et al. recently reported the results of experiments in which radiopaque silver clips were sutured to the surface of right or left ventricles of 25 patients undergoing cardiac surgery. Cinefluorographic films permitted measurements of changing ventricular dimensions after recovery. The measured changes in ventricular dimensions very closely resembled corresponding measurements performed on dog hearts several years ago. On the basis of such studies the conclusion is justified that many correspondences in function between the hearts of man and dogs can be demonstrated by direct measurements. This observation does not imply necessarily that the control mechanisms are comparable.

The central nervous systems of man and dog have many gross features in common, but differ in certain details. The structure and function of the autonomic nervous systems and their transmitter substances appear to be fundamentally similar, but also display some differences. For example, the cervical sympathetic nerve fibers and the vagus are joined as a single trunk in the dog. The cardiac responses to l-epinephrine apparently differ, although the effects of norepinephrine are similar in the two species. Carotid and aortic pressoreceptors and chemoreceptors are apparently present, suggesting that at least some sensing and feed-back mechanisms are common to both species. Although the search for correspondences is still in an early phase of development, evidence has been presented suggesting that the following statements may apply to both normal men and healthy dogs:

The size of the heart and of the ventricular chambers is generally maximal during rest in recumbent position. Virtually any change from this condition is promptly ac-
COMPANIED BY A REDUCTION IN THE SYSTOLIC AND DIASTOLIC DIMENSIONS OF THE CARDIAC CHAMBERS. Thus, lifting the head, slight degrees of passive tilting, or merely becoming alert may produce such a reduction in heart size. The changes in diastolic dimensions that occur during changes in posture or during the respiratory cycle are accompanied by a change in stroke volume and stroke work in the direction postulated on the basis of the Frank-Starling mechanism (see Popular Notion no. 3). Stroke volume diminishes rather markedly when either man or dog changes from recumbent to standing positions, even though the trunk of the latter remains in a horizontal attitude. In dogs, the increase in cardiac output in the transition from standing rest to exercise, ranging from mild to moderate, results primarily from increased heart rate with little contribution (0 to 30 per cent) by increased stroke volume. To be fair, this conclusion is contrary to the views of some other investigators. In man, the stroke volume increases considerably more than in the dog during the transition from rest (ereet) to very mild exercise. Progressively increasing levels of exercise produce increasing cardiac output primarily from increased heart rate, with little increase in stroke volume. At extremely high levels of exercise, human subjects display a pronounced increase in stroke volume, with the heart rate remaining relatively constant at levels near 180. Correspondingly high levels of exercise have not been induced in dogs in this laboratory; the dogs sit down on the moving treadmill, if it runs too fast. Wang et al. found little or no change in stroke volume over a wide range of exercise in dogs. Thus, there are some discrepancies in the details of the stroke volume response in man and dog, although the general patterns appear to be similar. The ejection velocity, rate of change of ventricular pressure, and other characteristics of ventricular ejection apparently increase in much the same way during exercise by man and dog. This superficial account merely indicates that correspondences between cardiovascular function of man and dog can be demonstrated by direct measurement of certain critical variables. This does not mean, however, that other correspondences can be assumed without being directly demonstrated. For example, the ventricular response to eating resembles that to exercise in dogs, but it would be most unwise to assume the resemblance occurs in man without definitive measurements. Many more opportunities exist for quantitative descriptions of phenomena in health and disease in dogs to form the basis for a search for similar responses in man.

Queries Regarding Popular Notion no. 2

1. What steps are necessary to ascertain that a cardiovascular reaction in a dog is comparable to that in man? (VI)

2. What other cardiovascular responses in dogs have correspondence demonstrated with reactions in human subjects? (VII)

Axiom X. Before extrapolating from one species to another, an investigator has a responsibility to determine to the best of his ability the extent to which appropriate correspondences have been established for the functions or control mechanisms under study.

Popular Notion no. 3. Ventricular Performance Can Be Adequately Described in Terms of Heart Rate, the Frank-Starling Mechanism, and Myocardial Contractility

Heart rate is readily defined as the number of cardiac cycles per minute. Although problems may arise concerning the definition of a cardiac cycle in the presence of conduction disturbances or ectopic pacemaker activity, a generally accepted measure of heart rate can be obtained by counting or recording pressure pulses or electrical activity generated once during each ventricular contraction. In general, a physiologic variable that is well defined offers no problem in deciding what should be measured. In fact this might be regarded as a criterion of a clearly defined entity.

In his Linacre Lecture on the Law of the Heart, Starling stated, "This adaptation of the heart to variations in the demand made upon it occurs equally well after total destruction of the nerves connecting the heart.
with the central nervous system. So we must conclude that the governor mechanism in virtue of which the heart is able to do more or less work, according to the amount of blood which has to be sent on and the resistance to the flow presented by the arterial pressure, must be situated in the walls of the heart itself and presumably in the muscle fibres of which these are composed. The law of the heart is thus the same as the law of muscular tissue generally, that the energy of contraction, however measured, is a function of the length of the muscle fibre."

Although there is now general agreement that the sympathetic nervous system can have powerful influences on cardiac function through neural reflexes, the Frank-Starling mechanism is commonly assigned a dominant role in general cardiac control by many investigators. There is no question that the Frank-Starling mechanism describes the changes induced experimentally in the heart-lung preparation (fig. 3A). Under certain conditions, increased stroke volume and stroke work associated with greater diastolic size can be consistently demonstrated in both healthy dogs and man. For example, in dogs a progressive increase in both left ventricular diameter and aortic flow consistently occurs concomitantly during the transition from sitting or standing to the recumbent position (fig. 3B). Spontaneous changes in heart rate are frequently, but not always, accompanied by changes in ventricular diameter and flow in a manner that would have been predicted from the Starling experiment (fig. 3C). These data are consistent with corresponding studies on man by Braunwald et al.

Although Starling indicated that the energy of contraction "however measured" is a function of the length of the myocardial fibers, considerable controversy can arise regarding the most appropriate method of determining the energy release by ventricular contraction. With the emergence of technics for recording arterial pressure and cardiac output in man, stroke work was computed generally by multiplying mean aortic pressure by stroke volume. Such computations were based on an assumption that diastolic ventricular pressure was zero, and failed to take into account the wave forms of ventricular ejection velocity and aortic pressure. These computations were based on mean values and neglected kinetic energy, which may reach significant values during the peak flow velocity in early systole. A more accurate indication of stroke work can be obtained by integrating instantaneous ventricular power, derived by continuous multiplication of instantaneous ventricular pressure and outflow, as indicated in figure 1. Honig et al. reported that during nitroglycerin administration, kinetic work may increase 350 per cent and total stroke work by 24 per cent, but the total stroke work computed from mean values increased 4 per cent or decreased 4 per cent, depending upon the time-mean pressure selected.

Contractility is a good example of a term that has been used in so many contexts that it is a barrier to understanding rather than a useful tool for communication (fig. 3D). Biological scientists frequently set up semantic obstacles to scientific progress by coining terms that are poorly defined and misleading. "When the weakness of men has been unable to find true causes, their subtlety has substituted imaginary causes to which they give specious names filling the ears but not the mind." Looking through the literature one finds contractility employed to indicate the "vigor of contraction," the "inotropic" effects of catecholamines, the degree of ventricular emptying, the "force" of contraction, the rate of systolic ejection, and many others. To determine if a change in contractility had taken place, one might select one of a wide variety of variables for measurement, depending upon the inclination of the individual investigator. For example, the ejection velocity and systolic volume, "contractile force" recorded with a strain-gage arch, and "ventricular function curves" have all been employed to study changes in "contractility." Indecision concerning which variable should be measured to detect changes.
in contractility is a sign that the term has not been defined clearly.

This problem does not arise if the pumping action of ventricles can be adequately described in standard physical terms of the sort illustrated in figures 1 and 2. The variables illustrated in these figures constitute a continuous analysis of the left ventricle as a pump and the related standard engineering terms have well-defined units. The precise definitions of these physical terms suggest immediately the measured variables and the mathematical operations required for their detection or derivation. Since precise mathematical models are specified for each of the derived variables, such an application of analogue computers is most appropriate. Furthermore, the validity of the computed results can be verified by longhand or graphical methods, and by totally different technics in other laboratories. Such an analysis is preferred to the use of obscure terms like contractility or inotropic effect (fig. 3D) to indicate changes in the performance of the heart.

In the past, "contractility" has been employed to represent changes in ventricular performance that do not conform to predictions based on the Frank-Starling mechanism. For example, stimulation of sympathetic nerves or spontaneous exercise may affect myocardial function to the point that greater energy release occurs with smaller diastolic and systolic size. The left ventricular response to exercise presented in figure 3E is an unusual example in which the stroke volume and stroke work increased somewhat with a rather marked reduction in left ventricular diameter. This is not a typical response to exertion in this regard, but is included as an example of a phenomenon that might be attributed to increased "contractility." Increased sympathetic discharge to the myocardium is a widely accepted means of changing function in this way.

Based on our experience with spontaneous ventricular responses and the effects of stimulating cardiac sympathetic nerves and sites in the diencephalon, a schematic diagram summarizing changes in ventricular performance associated with these procedures is presented in figure 4. These alterations in specific characteristics are arranged in two columns. On the left the absolute quantities that characterize the ventricular cycle are represented (pressure, volume, work, dimensions, time). On the right side are arrayed the changes that are primarily rate dependent (rate of change of ventricular pressure, ejection velocity, power, rate of change of dimensions, and heart rate).

The systolic pressure in the ventricle is usually increased by increased sympathetic discharge to the ventricles. An increased ejection velocity by the ventricle is associated with an increase in systolic pressure in both the ventricle and corresponding artery. Early diastolic pressure in the ventricle is generally lowered, while end-diastolic pressure tends to be increased by more powerful atrial contraction, producing a much higher atrial pressure pulse. Stroke volume and stroke work are generally increased slightly. Ventricular dimensions tend to be diminished. Both end-diastolic and end-systolic diameters tend to be diminished, but the systolic ejection is frequently so much more complete that the stroke volume is slightly increased with smaller diastolic dimensions. The duration of systole is markedly reduced; in fact, the duration of systole appears to change reciprocally with the changes in heart rate. Thus, the absolute quantities describing ventricular function may be slightly increased, unchanged, or diminished with the exception of ventricular systolic pressure.

In contrast, all the rate-dependent variables are greatly increased during ventricular systole (fig. 4). The ventricular pressure rises much more abruptly, indicating that the myocardial fibers are either more synchronously excited or their contractile mechanisms develop higher tension more rapidly during isovolumetric contraction. The rate of ventricular pressure fall is also faster, indicating either a more rapid relaxation process or a shortened and more uniform duration of the action potentials of the various layers of myocardium. The peak ejection velocity is greatly
elevated, indicating that the contracting myocardium can shorten more rapidly. The instantaneous power record reaches much higher peak levels, indicating that the rate of performing work is greatly enhanced. The increased rate of change of diameter is a direct expression of more rapid ejection. The heart rate accelerates to a higher level due to a changing rate of firing of the pacemaker. It is important to recognize that these changes in rate-dependent variables are by far the most important changes induced under conditions commonly labeled "increased contractility." They can be demonstrated by continuous recording of appropriate variables, when they cannot be detected by mean values or by intermittent measurements.

To produce the events illustrated in figure 4, changes must occur in more than one component of the heart. The heart rate is a manifestation of pacemaker activity. The increased rate of ejection and greater power development clearly result from an altered contractile mechanism. The more rapid rate of pressure rise and pressure fall in the ventricle may result from such things as more synchronous activation (faster conduction velocity), or an alteration in isometric contractile properties. The shortened duration of systole could involve a change in the duration of the action potentials in the individual myocardial fibers. The more rapid rate of relaxation could be related either to shortened action potentials with more synchronous relaxation or to a more rapid drop of contractile tension. These considerations indicate first that we are ignorant regarding the basic mechanism producing the changes illustrated in figure 4. Of even greater pertinence here is the fact that lumping all these phenomena into a single category of increased "contractility" will only retard elucidation of these problems. Now that it is possible to define and continuously to inscribe more definitive characteristics of the ventricles (as in figure 1); the time is ripe to toss aside undefined and confusing terms that block progress by obscuring our ignorance.

Queries Regarding Popular Notion no. 3

1. Although the Frank-Starling mechanism is a basic property of myocardium, are signs of this mechanism consistently apparent during all spontaneous cardiovascular responses? (V)

2. Is the term "energy release" as employed by Starling equivalent to stroke work computed from mean values of stroke volume, or that computed to include kinetic energy by continuous multiplication of pressure and flow, or that computed to include wasted energy in addition to energy appearing as external work? (II)

3. What is a unique definition of contractility? (II) What must one measure to determine if contractility has changed during an experiment?

4. What characteristics of myocardium are expressed more appropriately by "contractility" than by standard physical or engineering terms?

5. What properties of ventricles are not represented by standard engineering terms?

Axiom XI. A scientific term is most useful when it has a unique definition that immediately indicates what characteristics or properties must be quantitatively measured to determine its existence or change in its status.

Popular Notion no. 4. Venous Return Determines Cardiac Output

According to Wiggers,40 "'It is axiomatic that the heart can pump only as much blood as it receives! Indeed, the volume of blood returned to the heart is the basic determinant of cardiac output.'" A precise definition of the "'venous return'" is rarely encountered. The concept would be applicable to an open-ended system in which a pump is filled from a reservoir and expels fluid into another system of tubes under conditions in which the inflow limits the outflow. In a complete circulation the common concept of venous return really implies that "'what goes in must come out.'" So long as blood is neither manufactured nor lost in the heart, the principle of conservation of mass requires that this be true except for small changes in flow rate.
accounting for changes in the volumes stored in the heart. The fact that very high correlation coefficients are obtained from the relationship between "venous return" and cardiac output does not necessarily mean that venous return determines ventricular output. Such a relationship is merely an expression of the fact that venous return is fundamentally identical with ventricular output.

The concept of venous return is clearly applicable in experiments with the heart-lung preparation, in which a venous reservoir can play an important regulatory role. The heart-lung preparation is extremely stable over extended periods. To study cardiac responses, the investigator must assume control and induce changes in the system. One convenient method of increasing the circulating flow rates is to increase the filling pressure in the right ventricle by adjusting the outflow from the venous reservoir. During the first few beats after elevation of ventricular filling pressure, the inflow into the ventricle slightly exceeds outflow as the diastolic distention of the ventricle progressively attains high levels (fig. 3A). Perhaps an increase in "venous return" could be visualized as occurring during the transition from one steady state flow condition to another, but the quantity involved is a small proportion of the total flow per unit time. A transitional change in ventricular volume should not be confused with the total venous inflow or total cardiac output. By common usage, changes in "venous return" frequently are proposed as the initiating mechanism to explain alterations in cardiac output by appropriate variations in diastolic distention in accordance with the Frank-Starling mechanism (fig. 3A, 3B, 3C).

Gregg and his associates found that in open-chest dogs, the end-diastolic pressure, stroke volume, and stroke work showed almost perfect correlation. In closed-chest dogs, under anesthesia, the agreement was also excellent during rapid intravenous infusions. The more closely the experimental preparation approached the normal state, the greater was the deviation of the responses from the predictions derived from the heart-lung preparation until, in the essentially normal dog, "there is no directional correlation between left ventricular end-diastolic pressure and stroke volume, stroke work, or any of the other parameters measured or calculated." Similar observations have been made in both unanesthetized dogs and man, although caution must be exercised in assuming that diastolic ventricular volume is directly related to diastolic pressure. Since both ventricles respond to the same pacemaker and receive sympathetic discharges at the same time, they can increase their output at the same time. If increased blood flow occurs simultaneously through the pulmonary and systemic circuits, a change in "venous return" need not be postulated as a causal mechanism. Evidence has been presented indicating that neither central venous pressure nor thoracic blood volume is invariably increased during exertion in man.

The term "venous return" has been rather loosely applied to the changes in pressures, flows, volumes, and other factors illustrated in figure 5. On one occasion or another, each has been assigned a dominant role in determining the "venous return." Most of the factors illustrated in figure 5 could be individually identified, and precisely defined in reasonable functional terms. These definitions should be so carefully evolved that the critical variables involved in each should be immediately apparent in terms of transient and sustained changes in velocity of flow, volume flow, pressures in particular regions, pressure gradients between specified sites, blood content, or blood volume distribution in different parts of the venous system. Guyton et al. defined mean circulatory filling pressure (MCFP) in terms of the relation between the total blood content of the systemic circulation and the capacity of the arteries, capillaries, and veins lumped together. An expression for the combined capacity of such widely different vascular channels appears to defy unique definition. The need for the term "venous return" disappears when the various individual factors are recognized and defined.
Changes in "venous return" are described not only in terms of the volume flow of blood from the venous system into the heart but also in terms of many different variables represented in this schematic diagram. Properly defined, these variables could effectively replace the term "venous return."

Queries Regarding Popular Notion no. 4

1. Since a donkey can move forward only as rapidly as his cart follows him, is his forward velocity determined by the force applied to him by the cart? (V)

2. Does the term venous return have a unique operational definition? What variable must be measured to determine whether or not venous return has changed? (II, XI)

3. Would it not be preferable to refer to well-defined individual factors (e.g., those in figure 5) rather than lumping them under a single heading such as "venous return"?

4. What portion of the venous system corresponds to the reservoir in the heart-lung preparation?

Axiom XII. Changes in function induced by an investigator during physiologic experiments indicate potential rather than actual mechanisms. The responses to artificially induced loads indicate what can happen rather than what does happen during normal spontaneous reactions.

Popular Notion no. 5. The Simplest Explanation of Natural Phenomena Is Most Likely To Be Correct

The search for simplifying concepts to explain natural phenomena has been carried on for a very long time. "We are to admit no more causes of natural things than such as are both true and sufficient to explain their appearances. To this purpose the philosophers say that Nature does nothing in vain, and more is in vain when less will serve; for Nature is pleased with simplicity, and effects not the pomp of superfluous causes." (Newton, Rules of Reasoning in Philosophy, Rule 119) Similarly, Galileo indicated that Nature brings about her effects in "the most common, simple and easy way."150 These two great minds brought simplicity and clarity to concepts of uniform and accelerated motion. The natural laws they described are obvious in a vacuum, a condition that can be approximated on this earth only in laboratories. Fairly complicated interactions must be considered to explain the motion of real bodies in the atmosphere. Similarly, simplified concepts of cardiac function and control can be derived from rigidly controlled laboratory conditions, but more complicated relationships must be taken into account to understand the spontaneous cardiovascular responses of everyday life.

Control of various portions of the cardiovascular system is vested in at least four categories of mechanisms: local mechanical properties, local chemical factors, circulating hormones, and neural controls. One local or intrinsic mechanism in the heart is the length-tension relation (Frank-Starling mechanism). In peripheral vessels, the local accumulation of vasodilator substances and the factors leading to autoregulation directly affect sites of controlled resistance. Circulating hormones can influence both the heart and blood vessels, but their role in normal control is not fully elucidated. These substances become particularly potent when the autonomic controls have been interrupted (denervation sensitivity). The fact that human subjects function well after thoracolumbar sympathectomy does not mean that these neural controls played no important functional role while they were intact. The four categories of controls actually may be regarded as supplementary or partly redundant. Elimination of one set
of controls may be countered by the remaining control mechanisms. The potential complexity of the neural mechanisms affecting the cardiovascular system is suggested by the fact that individuals may faint from the sight of blood, blush from a spoken work, or develop tachycardia in advance of exertion. The prospects of finding simple control mechanisms for systems under the influence of the central nervous system seem extremely remote.

The central nervous system is more complex than our most advanced electronic computers. Is it rational to assume that simple explanations are more apt to be correct even here? The nervous system is theoretically capable of such extremely intricate patterns of outflow to the somatic motor system as must be involved in playing the piano, aerobatics, or even threading a needle. Electrical stimulation of selected sites in the diencephalon can produce a bewildering array of responses \(^5\) (see figure 18, chapter 3). Stimulation of certain sites may produce rather discrete responses in terms of heart rate of ventricular pressure or dimensions. Such observations suggest that neural pathways exist that could evoke a wide variety of different cardiovascular patterns.

A search for simplicity in the neural control of visceral function can be successful if the organization of the nervous system provides only a finite number of stereotyped responses. For many years, the autonomic nervous system has been visualized as discharging en masse to elicit only a few full-blown patterns of response. The possibility that the sympathetic nervous system can exhibit functional and spatial discrimination was neglected or denied for the most part until the emergence of the vasodilator system in skeletal muscles was brought forth by Uvnäs,\(^5\) Folkow,\(^5\) and their associates. Recently Löfving\(^5\) and Folkow et al.\(^5\) reported evidence for functional differentiation of the peripheral vascular adjustments into various patterns of flow distribution, dependent upon the nature of the afferent discharges arriving at the autonomic cardiovascular centers. Löfving\(^5\) stimulated cortical depressor areas in the rostral cingulate gyrus and demonstrated fairly selective adjustments in the blood flow distribution to muscle, kidney, or intestine.

In a discretely localized area of the diencephalon (at or near the \(H_2\) fields of Forel), electrical stimulation produces changes in left ventricular performance that have many features in common with response to exercise on a treadmill.\(^5\) In figure 6, the left ventricular response to running on a treadmill and to a number of spontaneous responses was recorded. After administration of chloralose, stimulation in the region of the \(H_2\) fields of Forel produced the responses illustrated on the right of figure 6. This illustration is merely an extension of observations reported previously\(^7\), \(^15\), \(^5\), \(^5\) to indicate that a pattern of response grossly resembling exercise can be elicited in either anesthetized or unanesthetized dogs from specific locations within the brain. In some instances, the magnitude of the changes in heart rate, ventricular pressure, and ejection velocity was much greater than was ever observed during spontaneous responses, including heavy exercise or startle reactions (see ref. 26, fig. 17, chap. 3). Stimulation in or around this site will also produce changes in the distribution of blood flow to the splanchnic bed, kidney, and hind quarters in the same general directions as occur during exercise\(^7\) (see also ref. 26, fig. 9, chap. 8).

The reductions in splanchnic or renal flow produced by the diencephalic stimulation were exaggerated as compared to changes during responses to spontaneous exercise.\(^7\) In many instances, but not all, extreme degrees of hyperpnea could be produced by stimulation in the same general locations. Occasionally, alternate movements of the extremities were induced, as though the animal were running while lying on its side. One interpretation of these observations is that neural pathways in the base of the brain can elicit a comprehensive pattern of response affecting the heart, peripheral blood vessels, respiratory activity, and skeletal muscles to produce a response like exercise. Neural pathways converge on the region of the \(H_2\) fields of Forel from many regions of the brain, suggesting that even if the outflow pattern is stereotyped, impulses from many different cerebral structures could
Changes in left ventricular function during spontaneous cardiovascular adjustments to exercise, eating, changes in posture, and tilting. In the center panel, chloralose anesthesia produces significant changes in the baselines of function but much less than barbiturates (see fig. 1). Stimulation of selected sites in the diencephalon produces changes in ventricular function in the same general directions as did exercise, except for the ventricular diameter.

Unfortunately, eliciting such a response by electrical stimulation gives no assurance that such a pathway is actually involved in spontaneous activity. (IV)

If the autonomic control over visceral function consists of a finite number of patterns that are elicited under predetermined conditions, the prospects for understanding these mechanisms by analytical methods are much improved. The left ventricular responses during several different spontaneous actions do have many features in common. As a matter of fact, the ventricular responses can be divided into two main categories: those associ-
ated with recumbency and those associated with all other kinds of sudden change. For example, the responses to eating, startle, and exercise have many features in common (fig. 6). In fact, one could make a case for the notion that sudden ventricular adaptations are likely to resemble preparation for exertion (the old fight or flight concept). The consistency with which the pattern of blood flow distribution like that of exercise can be induced by electrical stimulation indicates that stereotyped patterns of peripheral control are a distinct possibility as well.

The consistent appearance of similar patterns of cardiovascular response during spontaneous acts might be attributed to a form of conditioning rather than to structure of neural pathways. For example, the first time a dog exercises on a treadmill at a constant speed and grade, the initial effect is a grossly exaggerated response in all the recorded variables, which then return to the lower levels sustained during the period of steady exercise. With each successive exercise period, the amplitude of the initial overshoot is smaller. After five or six exercises under the same conditions, overshooting is often absent and the ventricular responses promptly attain the levels that are sustained during the entire exercise. This sequence of events indicates that the magnitude of the cardiovascular response may be influenced by autonomic conditioning. A similar phenomenon in the heart rate of human subjects has been described by Faulkner. For example, during five conditioning trials of a standardized work intensity, the degree of tachycardia diminished progressively, particularly with respect to the anticipation and the initial adjustment to work. When the subjects were exposed to an unknown exercise demand, the heart rate response was equivalent to preparation for a maximal workload in anticipation and during the initial adjustment.

If a man climbs the same set of stairs at about the same rate every day for many years, the repetitive experience in this endeavor might aid in the presetting of reasonable levels of cardiovascular flow and distribution, perhaps with adjustments from feed-back controls. Although this concept appears superficially reasonable, we are not accustomed to thinking in terms of autonomic conditioning, particularly after only a few conditioning exposures. Newton et al. repeatedly sounded a tone in tests on trained dogs and observed no average heart rate increase. On one single occasion, the same tone was accompanied by an electric shock to the foreleg. Heart rate increased by 10 to 20 beats per minute after 10 to 30 repetitions of the tone alone. In contrast, no specific motor-conditioned reflexes developed in as many as 30 trials with electric shock and the same tone. This experiment suggested that some degree of autonomic conditioning is possible with one trial. The potential role of conditioned reflexes in physiologic control has not attained general acceptance among physiologists in the West although it has been a cornerstone of Russian physiologic thought for many years. Cerebral control of the circulation accompanying voluntary acts and by autonomic conditioning should not be neglected or ignored even though these are by no means simple mechanisms.

Queries Regarding Popular Notion no. 5

1. If simplicity is a sign of validity, how can neural controls involving complex central nervous system connections conform to this criterion?

2. Do stereotyped cardiovascular responses represent built-in pathways to produce patterns of autonomic outflow or are these evidences of autonomic conditioning, or both, or neither?

3. Does the common practice of averaging or lumping data to provide a description of a single response for a group of subjects obscure elements of physiologic variability, which represent real control mechanisms? Is this practice a kind of search for "common, simple and easy" explanations?

Axion XIII. Although newly discovered natural laws may frequently bring order and clarity out of chaos, simplicity is not a reliable criterion for the validity of postulates regarding physiologic function or control mecha-
nisms. Indeed, the physical scientists are also finding that simple theories do not suffice in many fields (i.e., nuclear physics, non-linear mechanics, etc.).

Popular Notion no. 6. Most of the Problems of Cardiovascular Function and Control Have Been Explored or Are Currently Under Investigation

According to Bacon, "The creations of the mind and hand appear very numerous, if we judge by books and manufactures; but all that variety consists of an excessive refinement and of deductions from a few well-known matters - - -." (Aphorism no. 9) Thus biologists appear to be so preoccupied with what is known that they tend to ignore that which is unknown. Research areas that are not under investigation rarely come up for discussion, and tend to elude attention. At any particular stage in history, a field of scientific interest gives the impression of stability and completeness, which is quite artificial. In this respect, a discipline like cardiovascular physiology may be compared to a stage setting composed of papier-mâché buildings, which appear to be solid from a distance. The unwary could easily conclude that the important problems are solved, that the structure is substantial and complete, and that only the details or cracks need be filled in. A probing finger or a pointed question can easily penetrate this façade and expose large areas of emptiness or ignorance behind. A view of the activity in cardiovascular research laboratories suggests that work is progressing on a broad front, so that the distribution of effort is fairly well dispersed throughout the field of interest.

From another point of vantage, we are still working on the same old problems. In 1733, Stephen Hales published an account of some experiments made on the blood and blood vessels of animals. By cannulating the arteries and veins of horses, sheep, a doe, and several dogs, he studied changes in pressure induced during movement, bleeding, and other procedures. By making casts of the ventricular chambers he estimated the total ventricular volume, the area of the aortic orifice, the ejection velocity, cardiac output, the surface area of the left ventricle, and the weight of blood sustained by the left ventricular contraction. These are only a few of his experimental measurements, but through them Hales
expressed concepts that have a modern ring. He observed how hemorrhage produces reduction in arterial pressure. During straining of the muscles, especially the abdominal, blood from all parts was impelled to the vena cava; consequently there was a greater supply for the heart, which must therefore throw out more at each pulsation and increase the force of the blood in the arteries. He also mentioned that "the blood moves fastest and most freely through the lungs when they are in a dilated state." He enunciated the principle of the "windkessel." Of greatest significance, Hales recognized that "The force of the blood in the veins and arteries is very different, not only in animals of different species, but also in animals of the same kind and that not only in those of different sizes and weights, but also in dogs of the same size and weight, and even in the same animal, the force of the blood in its vessels is continuously varying... Now since this force of the blood is so variable, it is the more requisite to be furnished with a good quantity of observations, thereby to find out, the more nearly, a medium of those forces, not only in the same animal, but also in those of different ages, sizes and kinds, whence haply some curious observations may arise."

We are still wrestling with precisely the same problems that confronted Stephen Hales nearly 230 years ago. Howell's American Textbook of Physiology, published in 1896, contains lucid descriptions of many current issues (i.e., neural controls of the circulation, diastolic suction, etc.).

During the past 10 or 15 years, progress in cardiovascular research has been accelerating by virtue of new quantitative research technics (i.e., cardiac catheterization, indicator-dilution technics, angiocardiography, and electronic apparatus for continuous recordings of pressures, dimensions, and flows). To ascertain the extent to which the recent research effort is evenly distributed, a series of four charts was prepared. In the first, representation of the entire field of cardiovascular research was attempted under the following categories: molecular, cellular, organ and tissue, applied physiology, and clinical physiology (fig. 7A). Attention was then directed to the anatomy, function, and control of the components of the cardiovascular system, the portion outlined with heavy lines in figure 7A. By a list of some properties common to each major component of the system, a set of 20 squares was drawn (fig. 7B). A survey of the American cardiovascular literature for 1960 disclosed a very heavy concentration of effort in three squares dealing with excitation of the heart and the analysis of pressure pulses and vibrations in the heart and arteries. Thus, certain of the cardiovascular problems that have been of particular interest for 230 years, still occupy a very large proportion of the total research effort. In general, the areas of interest that have not been explored are awaiting the attention of someone with sufficient interest to develop the required research technics. For example, the compliance and contraction of the microcirculation should be studied by direct and continuous recording of pressure, dimensions and flow. Technics for such studies are currently emerging.64

Pressure-flow relations for whole organs are being studied in many laboratories. Although these studies tend to be interpreted in terms of changes in arteries and capillaries, the entire vascular bed is lumped by the experimental technics. The studies of specific vascular beds (fig. 7C) are not uniformly distributed, being concentrated on the changes in resistance and in capillary exchanges in muscle, skin, and kidneys. The tissue fluids, lymph, and extravascular conditions are of real importance, but have received little attention over the years.

Research on the problems of cardiovascular control has been confined largely to the effector organs with some attention directed toward the sensing mechanism for blood pressure (arterial distortion receptors) and a lesser effort on other intrathoracic distortion receptors, the functions of which remain quite obscure. Complete description of a neural control system must include not only the sensing elements but the sensory pathways, relay mechanisms, integration centers, association areas, motor centers, efferent pathways, and finally the effectors. The feed-back loop that adjusts systemic arterial blood pressure...
has been described quite well in anesthetized animals. The relationships between baroreceptor reflexes under these conditions and responses in normal animals and man have not yet been established. The control of cardiac output is commonly ascribed to local controls in the tissues (i.e., concentration of vasodilator chemicals in individual tissues). If this be the case, what explanation could be offered for the observation that during successive treadmill exercises, dogs display progressively smaller initial overshoot in the various parameters of ventricular function? Although it is possible that cardiac output is neither monitored directly nor controlled by neural reflexes, the relationship between cardiac output and oxygen consumption requires more definitive explanations than are currently available. We must also search for sensing and control of the peripheral distribution of blood flow of total blood volume and its distribution. If the total blood volume is relatively constant over a period of months and the concentration of its various constituents remains within narrow ranges, the total quantity of various blood elements (cells, small organic molecules, electrolytes, etc.) must remain within narrow ranges over extended periods in spite of variations in intake and output. Under these conditions, what monitoring and controlling mechanisms are involved in maintenance of the normal composition of body fluids and blood?

Although the extent of our ignorance may be somewhat exaggerated in figure 7, the unequal distribution of effort is real. The opportunities for exploring unexplored and untrammelled areas to produce new and exciting discoveries are very great. Most of the unexplored areas await only appropriate questions that could lead to experimental designs using existing technics, or the development of new research tools.

Discussion

A number of quotations from great minds of the past (Newton, Galileo, Pascal) were included in this survey because they seem so very pertinent in the current stage of biological research. These pointed remarks were gleaned from men who were engaged in the conversion of physics from a descriptive, almost mystical, field of interest into a quantitative science based on measurement and mathematical analysis. The concept that water follows a piston because “nature abhors a vacuum” did not satisfy Pascal.65 Can we afford to be satisfied with the idea that the circulation is regulated to meet the “needs” of the tissues, that the ventricles respond by an increase in contractility or that the heart pumps the quantity of blood that comes to it?

Hopefully, we are now on the threshold of a major revolution in biology by which it will be converted into a quantitative science by means of new technics of measurement stemming from the current technologic advances. This critical evaluation of cardiovascular physiology is designed to promote more rigorous definitions and more direct measurements under conditions in which the data are to be applied in the hope that these measures may accelerate progress in understanding of cardiovascular function and control in normal animals and man.

Summary

The present status and future prospects of cardiovascular research have been evaluated in terms of a series of axioms that may serve to summarize this report and to guide our efforts in the future.

Axiom I. An important objective of cardiovascular physiology is elucidation of the mechanisms of function and control in animals and human subjects under normal conditions.

Axiom II. The use of ambiguous and poorly defined terms tends to obscure ignorance and impede progress.

Axiom III. Ideally, investigation of physiologic mechanisms should be conducted with minimal disturbances of either the organ system or its controls.

Axiom IV. Experimental data are applicable without reservation only to the specific conditions under which they were collected.

Axiom V. Extrapolation in the application
of experimental data to species or to conditions of function different from those in which the information was collected should be based on knowledge of the kind and extent of deviation of the experimental from the normal.

Axiom VI. The circulation of anesthetized animals must be regarded as experimental models of normal cardiovascular function.

Axiom VII. Experimental models are frequently desirable and useful, but their validation requires quantitative comparison of the specific model with the physiologic mechanism or condition it is designed to represent.

Axiom VIII. With the development of techniques for comprehensive analysis of cardiovascular function in alert, active animals, general anesthesia, thoracotomy, and heart-lung preparations should be less frequently employed for studies of cardiovascular responses.

Axiom IX. The use of general anesthesia to perform on animals the same procedures that are routinely accomplished on human subjects with nothing more than topical anesthesia (venipuncture, catheterization, etc.) may complicate interpretation of experimental observations without contributing significantly to the humane treatment of animals.

Axiom X. Before extrapolating from one species to another, an investigator has a responsibility to determine to the best of his ability the extent to which appropriate correspondences have been established for the functions or control mechanisms under study.

Axiom XI. A scientific term is most useful when it has a unique definition that immediately indicates what characteristics or properties must be quantitatively measured to determine its existence or change in its status.

Axiom XII. Changes in function induced by an investigator during physiologic experiments indicate potential rather than actual mechanisms. The responses to artificially induced loads indicate what can happen rather than what does happen during normal spontaneous reactions.

Axiom XIII. Although newly discovered natural laws may frequently bring order and clarity out of chaos, simplicity is not a reliable criterion for the validity of postulates regarding physiologic function or control mechanisms.

References


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Study the Normal

Neglect of a proper study of healthy signs is the secret of the failure of many who undertake to master auscultation and percussion.—Austin Flint, 1881. The Quiet Art: A Doctor’s Anthology. Compiled by Dr. Robert Coope. Edinburgh & London, E. & S. Livingstone Ltd., 1952, p. 119.
Some Axioms, Popular Notions, and Misconceptions Regarding Cardiovascular Control

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