

INTRODUCTION.

In mammals the life process requires production, accumulation and utilisation of energy applied in a purposeful way, to manipulate the immediate environment, and adapt it to the continuing needs of the organism. For the most part, energy is produced by oxidation of carbon compounds by atmospheric oxygen, with production of carbon dioxide which is then eliminated by excretion back into the atmosphere, and oxidation of hydrogen from lactate to produce water and pyrophosphate bonds to produce stored energy in effector cells.

Control of energy production involves the cellular concentrations of the respiratory gases, and their relationship with vital activities to regulate energy accumulation, transfer, and utilisation as required. The process of living becomes entirely dependent on the oxygen supply and removal of carbon dioxide, and their concentrations, which balance the metabolic activity, and the residual energy content the balance between energy accumulation and kinetic energy represents. Continuation of the living state requires continual regulation of the respiratory gas concentrations in active cells commensurate with their level of activity, to which the gas levels are linked to become indicators of the life process. The level of metabolic activity in the cells needs to be matched in the associated activity of the cardiovascular and respiratory systems to maintain it. The product of the two concentrations becomes related to the total energy produced or acquired (stored energy), while the ratio indicates the rate at which energy is made available to move fluid and energy from one area to another (i.e., kinetic energy). Stored energy times kinetic energy together indicate overall movement of energy, or momentum. Movement of energy in the body only occurs in association with fluid movement as 'kinetic energy of flow'. This implies that the whole process of living is dependent upon the continuing concentrations of respiratory gases, which alone regulate each of the individual parameters controlling circulatory activity, and each one becomes proportional to different multiples of the gas concentrations which are present.

Being 'alive' and continuation of the life process requires close regulation of the respiratory gas concentrations to produce the required amount of energy and metabolism consistent with the needs for modifying the environment, both external and internal (e.g. temperature control), and energy for movement and other activity including gland secretion, neural function, renal function, digestion and assimilation of food, together with circulation of the blood with sufficient energy to perform all these functions. Maintenance of the living state requires storage/ accumulation of energy in fluid compartments as well as kinetic energy to maintain shape and size of the cells and volume of the systemic circulation, momentum in tissue fluid, and muscular activity to perform external work as may be necessary to preserve a functional state.

Stored energy becomes related to oxygen concentration and 'effector cell survivor mode', while kinetic energy depends on carbon dioxide concentration cubed, and 'functional or kinetic mode'. Each of the parameters which define these functions depends on fixed multiples of oxygen and carbon dioxide concentrations for each, and their individual values only change as the gas concentrations are altered, but they maintain the same relationship with each other, and variations only occurs as the relative gas concentrations are altered.

Physical activity of any region is initiated by depolarisation of effector cells leading to altered cell volume and so respiratory gas concentrations in that cell. As a result there is altered metabolism and metabolic rate with changed cell and organ dimensions, vascular size and shape, the volume and energy content of fluid compartments, with altered momentum of associated fluid movement. Changed external work capacity follows with readjustment of gas concentrations from kinetic energy in the cardio-vascular system, and gas concentrations from the lungs leading to repolarisation of effector cells as the fluid volumes readjust in each affected area.

The mechanical sophistication of the circulation is reflected in the intricate way fluid and energy is distributed to fill the needs of individual cells, and the main fluid compartments of the body. The many directions of application of cardiac activity, depending on the areas it supplies, and the functions it performs, compels the ventricle to continually adjust its activity to meet these requirements. The degree of difficulty encountered in moving fluid between body compartments, is reflected in the prevailing level of arterial blood pressure.

The feature of the circulation which is most apparent is that of motion, which in the vascular system, reveals itself by the movement of a quantity of blood, the stroke volume, at a given linear velocity of flow, through tubes of a particular size, and the frequency with which this activity is repeated.

The relative size of the vessels depends on the ratio of speed and resistance prevailing in each, so that ideally blood moves at a linear velocity which is equivalent to the pressure distending the vessel, allowing the strain on its wall to be reduced approximately to zero. The basic volume of each individual vessel is physically determined by the volume of fluid moved, the speed at which it moves, and the resistance encountered. Resistance can be expressed as equivalent to a further amount of momentum needed to overcome the inertia existing in the system because of the size of the vessels, and the internal resistance to flow of the contained blood. The greater the linear velocity compared with resistance, the smaller the diameter and volume the vessel will assume.

These are the features which regulate the circulation of blood, and they depend upon the volume of fluid exchanged between fluid compartments (essentially that exchanged between cells and the extra-vascular fluid) and the speed with which it is moved, to produce the venous return. The latter depends on the momentum given to fluid expelled from the cells, and the resistance to flow it has to overcome. The size and arrangement of blood vessels is determined by the prevailing flow conditions, to keep vessel wall strain to a minimum.

The purpose of this book is to consider the efficiency of energy generation in the circulatory system, in the light of the initiating function of the venous return to the heart. The application to fluid distribution, of the energy generated by the ventricle in response to this manifestation of cell activity, is the immediate objective.

It might be supposed that this subject had already been fairly completely explored in the first half of the twentieth century by investigators such as Frank, Starling and his colleagues, and later Wiggers and Katz. The spectacular success of Starling's use of the 'Heart-Lung' preparation culminating in the 'Law of the Heart', related the physical activity of the heart to its metabolic

activity and physical dimensions in such a decisive and satisfying way, that it seemed to close the door to many cardiac physiologists who turned instead to what appeared to be the more rewarding fields of electro-physiology, coupled with exciting discoveries in molecular biology. The investigation of the circulation as a unit was held in such low regard that on one occasion the late Howard Florey, who was at that time president-elect of the Royal Society, remarked to the author that the days of "blood and guts" physiology, by which he presumably meant whole animal experimentation, were over. The future he felt belonged to molecular biology.

Indeed this molecular field has provided most spectacular discoveries which will continue to occur. Nevertheless since the time when this remark was made, Sarnoff has contributed much illuminating material on the factors which determine ventricular oxygen consumption and efficiency, and interest has now returned to the factors which influence circulation in the smaller blood vessels.

My own involvement in this field dates from 1946 and was mostly concentrated in the following years to 1954, when changes in circumstances persuaded me to abandon it temporarily in anticipation that others would soon expand upon the ideas which I hold to be inherent in Starling's work.

For some reason this has not happened in the way I expected it would, and I now feel compelled to record my interpretation of the manner in which momentum is maintained in the circulation, and its significance for the other variables which are encountered. I do this in the hope that these ideas or even some variation of them, may lead to further profitable investigation in this field.

Understanding the genetic code, and the manner in which its instructions influence the structure and function of the whole organism, does not necessarily allow the investigator to fully comprehend the integration of tissues and organs into a functioning whole. Moreover, the interaction of the organism with its environment, while dependent on the genetic make-up, is also dependent upon the impact of that environment directly on individual tissues and organs. Together they bring about adaptations in physical and functional behaviour that enable each individual to maintain its internal environment and ensure its continued function and ultimately its survival. This direct interaction with environment is therefore equally important with molecular biology and the genetic code in determining physiological function, and its continued investigation, even at the most rudimentary level, is essential.

Since the second world war and the emergence of cardiac surgery as a major discipline, investigation of circulatory function has largely passed to clinicians. From a physiological viewpoint, the disadvantage of this transfer is that the choice of investigational material is inclined to be limited and largely confined to subjects with significant pathology. Furthermore in the absence of basic information regarding ventricular efficiency and blood pressure maintenance, there must be a considerable handicap in the interpretation of results. It is in the hope that a change in perspective may assist here, that I offer this alternative view.

While Harvey believed that movement of the blood was the prime function of the heart, the idea of

movement seems to have retreated somewhat into the background over recent years, and the concept of 'stability', to have largely replaced it as a major circulatory consideration. Although it might be disputed by some, the tendency now seems to be to regard the maintenance of 'normal levels' of blood constituents as the basic function of the circulation, and the actual movement of fluid of somewhat secondary importance.

The view one adopts of the relative importance of each of these two approaches, will greatly influence the final appreciation of circulatory function accepted by the observer. Bernard's concept of a stable internal environment, might seem to indicate that minimal disturbance of this environment was the desirable norm, with a resultant diffusion of nutrients and metabolites between the tissue cells and associated capillaries occurring in a relatively gentle fashion. Harvey's approach on the other hand, with its emphasis on movement of blood, might lead one to expect more rapid and frequent changes in the fluid environment of the tissue cells.

There is, of course, no conflict of ideas in the real sense, but simply confusion in the way one sees the function of the circulation, and particularly the importance one gives to the idea of stability, and the manner in which it might be maintained. Is stability obtained by minimal disturbance of the fluid surrounding the cells, with diffusion of nutrients and metabolites maintaining 'normal' levels of these substances, or is there instead rapid and frequent replacement of fluid in close contact with each cell, with a consequently rapid supply and removal of nutrients and metabolites, so that the stability of the internal environment is maintained as a result? If the mechanics of the circulation is approached from this latter point of view, what differences in one's conception of the circulatory system might appear? It is from this aspect that the function of the circulation is considered throughout this book.

Such a view makes it necessary to closely examine the movement of fluid which, while it is outside the limits of the vascular system, remains an essential part of the 'circulation', and it is the mechanics of this movement of fluid which is meant by the term 'extra-vascular circulation'.

The metabolic processes involving energy production take place in individual cells. For this to occur, supplies of nutrients and oxygen are necessary, and the circulation accomplishes this task. At the same time metabolites and waste products must be removed for detoxification or excretion.

But the circulation has another function. Increase in energy levels within the cells, while available to remove end products of metabolism, and maintain the cellular membrane with its polarising potential involving irregular distribution of ions and so on, must also be balanced by a sufficient level of energy outside the cell to present nutrients and ions for transfer back into the cell again as may be necessary.

The regulation of cellular activity therefore depends upon an adequate balance being maintained between these two sources of energy, the intra-cellular energy production, and the extra-cellular energy which must 'balance' it, if transfer across the cell membrane is to function in a sustainable manner. This extra-cellular energy can only be supplied with the circulating fluid which supplies the cell with oxygen and nutrients. It is the present contention that maintenance of the required

level of energy in the extra-vascular compartment is a basic function of the circulation. This account examines the mechanical forces that regulate the energy level in the cell environment, and the quantitative relationships between it and the energy produced by ventricular contraction.

Ventricular contraction in turn, also has to provide the transport mechanisms to and from the cell environment, i.e., from lungs, liver, and gut, and back again to lungs, skin, kidneys, and so on.

The implication is that for 'normal' function, a certain level of energy must be maintained in the extra-vascular compartment, and the purpose of the present account is to outline and quantify this energy in terms of the energy provided by cardiac function, and used for its other basic functions.

A diagrammatic representation of the energy distribution involving the extra-vascular circulation is set out in figure 1.

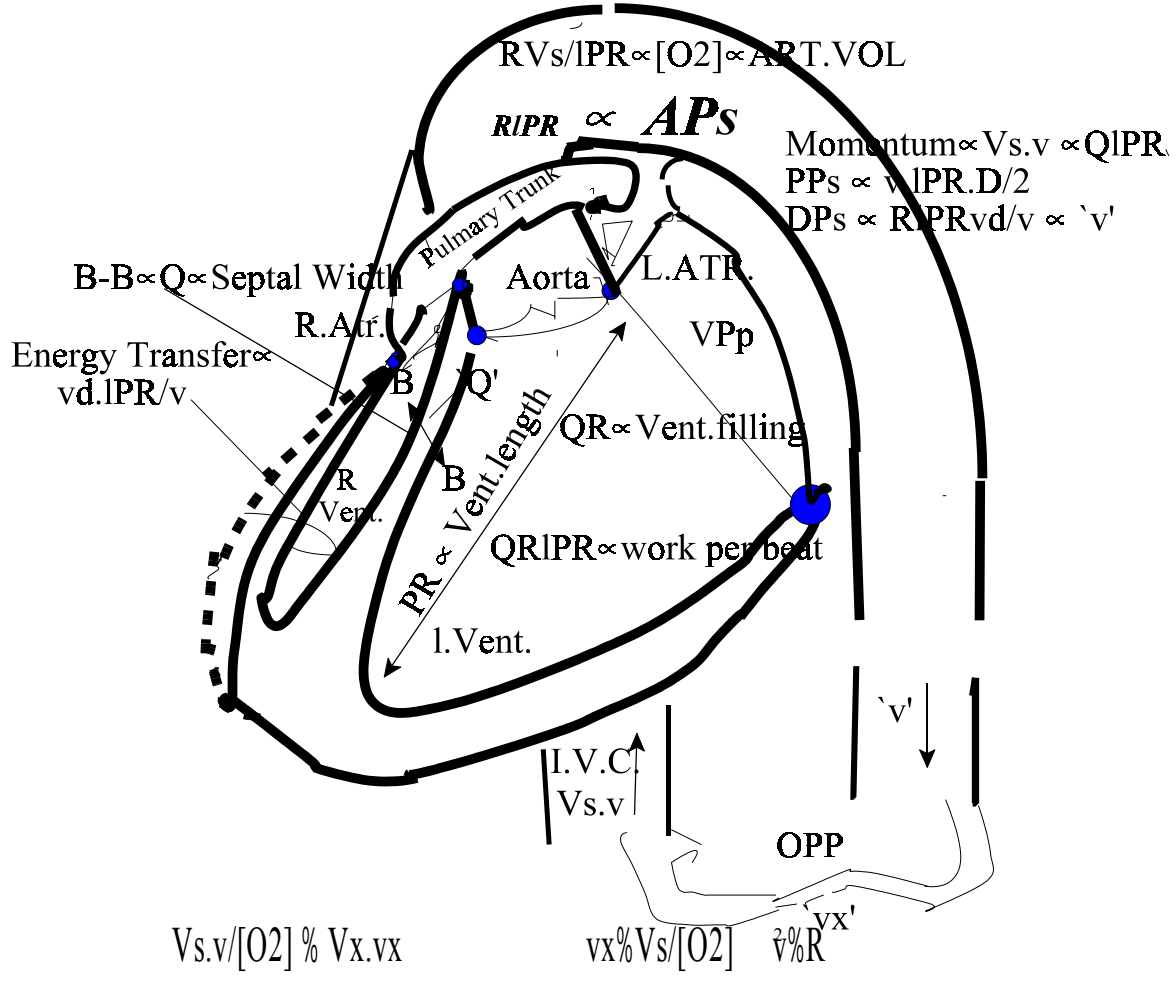
This type of diagram must be a familiar one to readers, except that in this case emphasis has been placed on exchange of energy between the fluid compartments, indicating the areas where energy passes from one to the other. Using this as a circulatory model, the endeavour has been to quantify the energy exchange in terms of the common parameters which may be used to describe circulatory function.

Employment of a model of the circulation in order to comprehend its total function, may appear to be an attempt to avoid the labourious involvement of much direct observation and experimentation.

This is a misunderstanding of the purpose of such a model, which is rather to help decide the direction which further investigation should take. It should be pointed out that present perceptions of the circulation, all result from 'circulatory models' proposed by different observers in the light of their previous experience. Harvey was an anatomist, and so his model involved applied anatomy, and the manner in which an anatomical model would function in the light of the anatomical observations and tests he was able to apply. The fact that no connections between the arteries and veins were observable at that time, did not prevent him from presuming such connections existed, though it was to be some time before direct microscopic observations allowed their presence to be confirmed.

Claude Bernard's model was an applied chemical one, probably based on his chemical estimations of the constituents of body fluids, and observed in the light of Harvey's anatomical model. The relationship between anatomy and the constant composition of the internal environment, was largely a presumption based on his chemical observations together with considerable perspicacity.

The circulatory model constructed and used by Starling (Heart-Lung preparation) was a physico-mechanical one, applying physical principles to the models proposed by Bernard and Harvey. It was nevertheless an incomplete one, insofar as he excluded the extra-vascular circulation completely from his system, though he was fully aware of the interchange which occurs between it and the intra-vascular fluid, as his observations on the function of the plasma protein in the production of urine and extra-vascular fluid both demonstrate.



composition of
E.V.F. controlled
by
 $Vx/vx \% v[O_2]/Vs$
Vent.Work % Q.R.Vx

E.V.F.

$v/R \% PPs/APs$
capillary filling % momentum i.e
 $RlPR/[O_2]$ or $QRvx$ or $Q.OPP$

In effector and
myocardial cells
relationships with
[lactate] are
 $[Lactate].[O_2] \cdot vx$
% R (i.e.;
with linear velocity
of extra-vascular
fluid)
 $[Lactate].[O_2] \cdot$
 $vx^2 \% l.PR$
(i.e.; with
contractility)

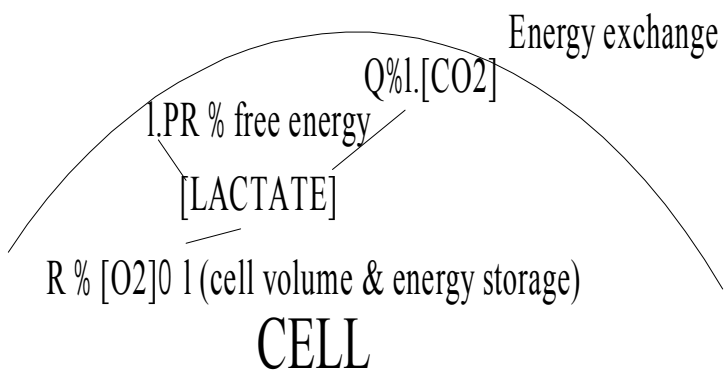


Figure 1

FIGURE 1. The substance of living organisms, as with all other bodies both animate and inanimate, is composed of matter, but the former possess other properties which give rise to and maintain the living process. These properties have to do with the assimilation and excretion to the gaseous atmosphere of oxygen and carbon dioxide which represent the respiratory gases, and which are essential ingredients of the life process. Life consists of the association of the concentrations of molecules of oxygen and

carbon dioxide in fixed multiples to produce each parameter which regulates the life process, through energy accumulation and distribution between cells and tissue fluid on a continuous basis, for the duration of the life of each individual. These parameters influence each other to produce circulatory activity, while they are at the same time each produced and regulated by fixed relationships between the concentrations of oxygen and carbon dioxide, which become the only variables involved in maintaining circulatory activity and the metabolic processes liberating circulatory energy from ingested nutrients.

This is a diagrammatic representation of the circulatory model to illustrate the variations in momentum and linear velocity of flow which result from ventricular contraction, and the significance they have for the maintenance of the major fluid compartments of the body.

a. For the heart and intra-vascular circulation of blood.

The momentum given to the blood is proportional to blood density (D), and the product of vascular volume and the average mean linear velocity of flow sustained in the vascular system throughout the cardiac cycle ($Vs.v$). This is maintained by the peripheral resistance, ($R.v$), expressed as momentum equivalent which must be overcome to produce ventricular filling ($Q.R$), and the internal resistance to flow ($l.O$). Peripheral resistance ($R.v$), stroke volume, and force of ventricular contraction ($l.PR$), together account for the overt energy per beat produced by the ventricle ($Q.Rv.l.PR$). The momentum for ventricular filling is provided by the residual momentum which must be present in the circulation at all times to maintain vascular filling ($R.Vs$), and overcome resistance %to a similar factor ($R.Vs$); and the ratio of ventricular/vascular filling is the circulatory ratio (Q/Vs), which largely determines the mechanical efficiency of ventricular contraction. The ventricular efficiency depends on the modification of ' Q/Vs ' by the ratio of diastolic blood pressure / pulmonary venous pressure (or 'ventricular filling pressure'), so that ventricular efficiency is proportional to $(Q.DPs)/(Vs.VPp)$. The diastolic blood pressure represents the load against which isometric ventricular contraction takes place, and is represented by the product of 'ventricular end-diastolic pressure' and the 'contractility' of ventricular muscle. 'Contractility' represents the ratio of systemic vascular length, and the diastolic length of ventricular muscle fibres (l/L), and equivalent to $(PR.vx/L$ or vx^2). The 'energy transfer factor' ($vd.lPR/v$) indicates the relative amount of energy produced by contraction of the cardiac muscle fibres and transferred to the contents of the ventricle during the contraction. The average mean linear velocity of flow of circulating blood is related to the force of ventricular contraction in the same ratio as stroke volume to vascular volume (Q/Vs), and pulse rate is regulated partly by the linear velocity of blood filling the ventricle from the circulation during diastole. The 'energy transfer factor' ($vd.lPR/v$) is proportional to pulse rate, while the pulse pressure (PPs) is proportional to the energy of motion dissipated per beat in overcoming frictional resistance, the resistance offered by the capillary and cellular membranes to passage of fluid to and from the blood and the tissue cells, together with linear velocity of tissue fluid. Pulse pressure comes to represent the energy level present in each of the main fluid compartments of the body at diastole. The

diastolic blood pressure is a measure of the potential energy which has to be present in order to overcome that resistance, while systolic blood pressure is the overall potential energy required to maintain both pulse pressure and diastolic pressure. Variations in 'Q', 'R', and 'l.PR' are associated with parallel alterations in the size and shape of the ventricle at diastole, which produce changes not only of the total energy released by the succeeding contraction, but also the manner in which the energy is directed between 'Q', 'R', and 'l.PR', so that elongation of the common interventricular septum is associated with increased pulse rate; increased width in the plane of the septum is associated with increased stroke volume; and altered curvature of the lateral ventricular wall occurs when the residual momentum maintained in the circulating blood is altered; e.g., by increased 'vascular filling'. These changes in dimensions represent alterations in the volume of fluid moved (Q), the speed with which it is moved ($v^2.PR$) and the increase in linear velocity of flow given to systemic blood at systole, 'l', (or $Q.l^3.PR$ overall) and as ' γ^2 ' is the resistance to flow expressed as a momentum equivalent which has to be overcome by each ml. of blood (R) before any movement can occur, this becomes 'Q.R.lPR'.

Once the blood enters the aorta, with particular levels of potential energy (blood pressure) and kinetic energy (momentum, or quantity times linear velocity of flow), it becomes isolated from further events occurring within the ventricle during diastole by closure of the aortic valve, and further movement is regulated by alteration of the ratio of potential/kinetic energy, as aortic elasticity and systolic blood pressure is translated into linear velocity of flow, by the relative constriction of the arterioles. Beyond the arterioles the energy is mainly in the form of kinetic energy of flow (momentum), and it is this momentum which then directs volume and energy distribution between intra-vascular, extra-vascular, and intra-cellular compartments of body fluids. In the capillaries, fluid and energy is transferred to the extra-vascular compartment as momentum, boosting the volume and energy in that compartment (as 'Vx' is proportional to 'v.R.vx /OPP') though fluid returns subsequently as 'v' falls to 'vd' in the latter part of the cardiac cycle, when the extra-vascular volume, which is proportional to linear velocity of the blood, is accordingly reduced once more. In this exchange, fluid transfer is restricted by the osmotic pressure exerted by the plasma proteins, and membrane permeability (proportional to $[O_2]$) while the energy transfer depends on 'vd.R' (or 'VPp' if the ventricular efficiency is maintained, i.e., 'vd.R/VPp' remains constant). Intra-vascular volume (Vs) is consequently maintained, while vascular filling depends on the value of 'R', which in the venous system is largely maintained by variation of the internal resistance (viscosity) of the blood and increases as the oxygen saturation of the blood is reduced, and carbon dioxide concentration increased.

This change in viscosity has a considerable influence on the linear velocity of blood returning to the heart, and the various elements of venous return and 'cardiac filling' (see Fig 8.6).

b. Exchange between intra-vascular and extra-vascular compartments.
Equilibrium and fluid exchange depends on the balance of momentum across the

capillary membrane, maintained by the osmotic pressure of the plasma proteins (and the relative permeability of the capillaries which depends on an adequate oxygen partial pressure to sustain it). The volume of extra-vascular fluid depends on $\dot{v} \cdot R \cdot V_s / [O_2] \cdot OPP'$, and while $\dot{R} \cdot V_s / [O_2]$ remains proportional to \dot{OPP}' , it is dependent on the linear velocity of blood, \dot{v} , which is varying throughout the cardiac cycle (\dot{v} is the average mean value for the whole of the cycle, while \dot{v}_d is the figure at diastole). Because $\dot{V}_s \cdot \dot{v}$ is proportional to $\dot{V}_x \cdot \dot{v}_x' \cdot [O_2]$, while the densities of the two fluids have a constant relationship, \dot{V}_x / V_s' is proportional to $\dot{v} / (\dot{v}_x' \cdot [O_2])$. As long as \dot{V}_x' is proportional to \dot{v} , $\dot{V}_s / [O_2]$ is proportional to \dot{v}_x' , so that while \dot{V}_s' and $[O_2]$ are constant, \dot{v}_x' will also remain constant. Changes in momentum in the intra-vascular compartment mostly depend on changes in linear velocity of flow, but the appropriate changes in the extra-vascular compartment require that \dot{V}_x' should alter, rather than \dot{v}_x' , which remains relatively constant, and this has consequences for the exchange of fluid and energy with the cells. The ratio of \dot{v} / \dot{v}_x' is proportional to \dot{R}^3 , while \dot{AP}_s / OPP' is proportional to \dot{R} , and that of \dot{v} / \dot{R} is proportional to \dot{PR}' , and to \dot{PP}_s / \dot{AP}_s' , while \dot{v}_d / \dot{v}_x' is proportional to $\dot{V}_x(\text{diastolic}) / \dot{v}_x'$ and \dot{AP}_s / OPP' , or \dot{R} . While \dot{OPP}' is proportional to $\dot{R} \cdot \dot{v}_x'$, \dot{v} needs to vary as \dot{R}^2 , in order to maintain fluid exchange with the cells. The latter then becomes proportional to $\dot{Q} \cdot \dot{v} / \dot{R}'$ or equivalent to $\dot{Q} \cdot \dot{R}'$, the momentum equivalent of ventricular filling, and also the momentum equivalent for the fluid exchange with the cells, which needs to be provided by the momentum given to the extra-vascular fluid by each ventricular contraction. It must be greatly increased as \dot{R} is increased, to maintain adequate fluid exchange with the cells. To maintain sufficient momentum in the extra-vascular fluid to provide this exchange, requires an increase in \dot{PP}_s' approaching the value of \dot{AP}_s squared, or $\dot{PP}_s \cdot \dot{l} \cdot \dot{PR}$ (i.e., pulse pressure times the free energy in the cells) $\% \dot{AP}_s^2$ (if $\dot{v} \propto \dot{R}^2$)

c. Energy and fluid interchange between the cells and the extra-vascular fluid. The volume of fluid entering the cells from the extra-vascular fluid is determined by the level of momentum in that compartment, and the relative (passive) permeability of the cell membrane. Change in momentum within the extra-vascular space, is related for the most part with \dot{V}_x' , the extra-vascular fluid volume, and is proportional to \dot{v} / \dot{R}' , and \dot{AP}_s / \dot{R}' (ie. \dot{PR}' and $\dot{l} \cdot \dot{PR}'$), and equivalent to $\dot{V}_x \cdot \dot{v}_x' \cdot (\dot{l} \cdot \dot{PR}^2)$ at systole, or \dot{PR}^2 at diastole. The 'passive permeability' of the cell membrane varies with the oxygen concentration, $[O_2]$, maintained within the cell, and related to the cell volume (which is proportional to \dot{R} , or $\dot{l} \cdot [O_2] \cdot \dot{O}$ at systole). The momentum which remains available to move with associated fluid volume into the cell is $\dot{V}_x / \dot{R} \cdot \dot{R}'$, or \dot{V}_x / \dot{R}^2 . To maintain this movement into the cell requires \dot{v} to vary as \dot{R}^2 , and requires this large increase in the linear velocity of blood (and consequently of extra-vascular fluid volume) when the local oxygen concentration is increased.

Within the cell, the level of energy maintained, must be sufficient to 'balance' the

energy provided within the extra-vascular fluid, if the volumes of the two areas are to be in equilibrium overall. The energy on each side of the membrane is proportional to the energy provided by ventricular contraction/apparent viscosity, or $Q \cdot l \cdot PR / O$ (i.e., momentum \cdot [lactate]). Within the cell, this energy is represented by 'transient energy storage' or $l \cdot [O_2] O$ at systole, energy available for exchange with the extra-vascular fluid, or v' (equivalent to the square of stroke volume), and the 'free energy' which has to be maintained within the cell to maintain the two above, together with a steady level of energy needed for the myriad of chemical reactions which the cell must maintain for its continued survival. For proper energy balance between the two compartments, this 'free energy' must be kept at a level consistent with the energy required for these chemical reactions, and with the energy provided by the force of ventricular contraction, proportional to $l \cdot PR'$. To prevent cellular disorganisation, 'free' energy within the cell, either greater or smaller than this required level, must be diverted to or from the energy 'store', or the 'energy exchange' with the extra-cellular fluid. The energy level maintained within the cell is equivalent to $[CO_2][O_2]l^3 PR'$, (where [lactate] \cdot $[O_2]$ is closely related to the 'circulatory length cubed / PR' , and the rate at which energy accumulates in 'transient storage' within the cell, while PR' is equivalent to the rate at which this energy in 'transient storage' is made available again as 'free' energy for cell activity). The potential for energy development represented by [lactate] is equally available to each of the three areas, so the energy provided in each area, i.e., 'storage', 'energy exchange' with the extra-vascular fluid, and 'free energy' for cell activities, depend respectively on $[O_2]'$, $[CO_2]'$, and PR' , with the overall level of energy development depending on the level of [lactate] present within the cell. With each ventricular beat, the energy level within the extra-vascular fluid increases by $Q \cdot OPP'$ overall, which is transferred again to the venous blood later in the cardiac cycle, as the energy in the extra-vascular fluid returns to its diastolic value. The transient increase in energy at systole is $Q \cdot R \cdot v'$ (or volume increase equivalent to stroke volume, stored energy equivalent to R' , and 'energy exchange' equivalent to v' , where v' is proportional to $l^2 PR'$, and also to R squared', i.e., the resistance offered by the limitation of cell permeability, and the flow energy needed to expand the cell volume. The extra momentum equivalent contributed to the cell during systole is then $Q \cdot R'$). The energy leaving the cell during diastole is $Q \cdot R \cdot vx'$, or the momentum equivalent times the linear velocity of flow in the extra-vascular fluid, (provided by the appropriate decrease in cell volume). Because $R \cdot vx'$ is proportional to OPP' , this energy is equivalent to the overall energy contributed to the extra-vascular fluid with each beat, and returned to the venous system at diastole, so that the energy balance at diastole is the same as before the ventricular contraction, despite the variations which have occurred during the cardiac cycle. Ventricular efficiency will only be maintained if '[lactate] times oxygen concentration' remains proportional to l cubed / PR' , so that efficiency depends on $([lactate] \cdot [O_2] \cdot v') / (l \text{ cubed} / PR' \cdot OPP')$. The mechanism which maintains 'free energy' at an appropriate level within the cell at any time is provided by 'transient storage' of energy as 'high energy level phosphate bonds'. This source of energy can be drawn upon to increase 'free energy' as required for cell activities, or for performance of 'external work', e.g. contraction by 'effector cells', while extra

energy for 'energy exchange' with tissue fluid is provided from glycolysis. (%L. O).

Alternatively energy can be withdrawn from the cells on a more permanent basis, by transfer to 'temporary', 'semi-permanent', or 'permanent' energy storage. For 'effector' cells this requires withdrawal of 'lactate' to the 'core' cells, of either liver or kidney, where gluconeogenesis constitutes 'temporary storage', glyconeogenesis becomes 'semi-permanent storage', and fat production leads to 'permanent energy storage'. These processes allow removal of excess energy which might otherwise build up in the cells and disrupt vital processes, but still enable these 'stores' to be drawn upon under the right circumstances requiring further energy production.

Each of these three approaches has been fully exploited since they were first proposed. The anatomical approach extends to the ultra-microscopic, and to the use of other electro-magnetic radiations of even more abstract kinds, which reveal the presumed ultra-structure of the circulatory organs, and throw some light on their function. But these are only indirect observations, based on the use of methods obtained by the application of abstract reasoning to produce the instruments, and ultimately the images, which can only be accepted by the observer, if he has confidence in the abstract ideas on which they are based, that is, through confidence in the functional instruments which these ideas have produced.

Similar conditions apply to the growth of physiological chemistry using modern instruments to expand the 'model' proposed by Bernard, or to the sophisticated mechanical and electronic equipment used to expand the physico-mechanical models arising out of the work of Frank, Starling, and A.V.Hill. Again, confidence in the results can only be accepted if the observer is convinced by the abstract reasoning on which the instruments are based.

Ultimately this resolves itself into the abstract reasoning of the mathematical approach. Physical models and instruments involving electronic principles, all depend on the original observations of Faraday on electro-magnetic fields, and the mathematical basis provided for them by Clerk-Maxwell.

Exploration of these models have all been pushed to a degree of extreme sophistication by succeeding investigators, but despite their efforts, a comprehensive account of the circulation and its functions is still elusive. A further model, based on the more abstract reasoning of the mathematical method, may then give rise to further advances not readily obtainable by other means, and such an approach is that which has been adopted in this account.

Building on the views of Harvey, Bernard, and Starling, it offers a more abstract analysis of the function of the circulation, and allows further comprehension of the principles on which it is constructed. No apology need be made for proposing such a model. It is the classical approach on which all knowledge of the circulation has been originally constructed, to be later tested by extensive experimentation, in order to confirm or deny the proposals and questions which arise from it, as the model becomes increasingly abstract in conception, and sophisticated in design.

The present model is rudimentary and elementary (as were the previous models when first proposed) but it appears to offer the possibility of further advances which can only become

apparent as it is developed further in the future. The purpose of such a model is to determine which questions are likely to produce more illuminating answers, and therefore which ones should be asked, and in what order.

Used in the more usual context, the term 'circulatory model' might be regarded as applying solely to the intra-vascular circulation, but because the energy produced by ventricular contraction has effects which are distributed in some degree to all of the fluid contained within the body, the idea of a circulatory model must be widened to include the whole of the body fluid, and each of its 'compartments' in turn.

In general, body fluid can be regarded as constituting three main compartments, depending on whether it is contained within the body cells, within the blood vascular system, or within the extra-vascular extra-cellular space. Accordingly, a model which applies to one fluid compartment, is of considerably greater value if its constituent parameters also have significance for each of the other two. The aim is to produce models for each of the three compartments, which while meaningful in themselves, can by integration and mutual self-reliance, together produce a functioning whole involving the same or similar parameters for each.

The complete model then, involves not only the intra-vascular section, but also the intra-cellular compartment and its associated energy exchanges, and the interchanges which occur between these two, and the energy retained within the extra-vascular extra-cellular fluid. The extra-vascular fluid occupies a central position, deriving its energy from ventricular contraction by way of the intra-vascular circulation, and in turn providing the energy to balance that produced by cell metabolism, and used in the cellular /extracellular exchange. As the provider of energy to ensure cellular nutrition and metabolism, it is the extra-vascular circulation and its energy exchange which is of immediate importance. The focus of attention must then be directed towards the extra-vascular circulation, while the intra-vascular circulation acts primarily as a source of energy to maintain that in the extra-vascular region, and in the transport of materials to and from that area.

Commencing from this outline, assessment of the extra-vascular circulation both with regard to the volume and the energy it requires, must be related to that supplied to it by the intra-vascular circulation, and ultimately by ventricular contraction. In the main, energy is supplied as energy of motion, i.e., the momentum (mass times velocity) of the fluid passing from the intra-vascular to the extra-vascular compartment. The result of this movement of fluid with its associated energy, is to maintain the volume of extra-vascular fluid at a particular level, and also to transmit movement (velocity) to the fluid in contact with, and passing into the tissue cells, and ultimately to the fluid re-entering the venous ends of the capillaries, and, according to the volume and energy levels, contributing momentum in turn to the blood in the venules, and so to the 'venous return' of blood to the heart.

Because the linear velocity of flow and so the momentum of the intra-vascular circulation, varies continuously throughout the cardiac cycle, both also fluctuate in the extra-vascular compartment, and affect the movement of fluid with its solutes across the membrane of individual cells. Each of these cells has its own individual metabolism and energy production,

depending in part on the external work the cell might perform, but also in part on its internal economy, and in particular, on the energy required to maintain a concentration gradient for certain radicles and ions across the cell membrane. Fluctuating energy levels in the extra-vascular compartment influence the passage of fluid and contained substances across the cell membrane and into and out of the cell, but this flow is regulated and controlled by the energy produced by cellular metabolism.

In this way a balanced regulation of energy controls the volume and energy production of the individual cell. The amount of energy produced by the cell to maintain its volume and constitution, having regard to the external work it performs, requires an equally regulated supply of energy in the extra-vascular fluid compartment, if cellular function is to be maintained at an acceptable steady level.

The immediate question that arises concerns the initiation of energy changes. Is it alteration of the energy produced by the cells which leads to corresponding change in the level of energy in the extra-cellular fluid, or does change in the amount of energy supplied to the extra-vascular fluid, require the cell to produce more energy itself, and alter its metabolism accordingly?

The answer to this question seems to be, that on some occasions cellular activity precedes and initiates the increase in energy provided by the circulation, while in others it is the increased energy present in the cell environment which leads to increased cellular activity.

The body cells can be classified roughly into two groups depending on the manner in which the amount of energy they produce is regulated. Although there is by no means a sharp distinction between the two, in general it can be said that increased energy production commencing within the cells and leading to a compensatory increase in extra-vascular energy, is characteristic of the 'effector' organs and tissues such as muscle, nerve, and glands. Increased energy levels in the circulating fluid initiates increased cellular metabolism in the 'core' organs such as liver and kidney (and to some extent in the heart, although the latter has characteristics found in both groups). These differences are characterised by the preferential use of different metabolic substrates in the two groups, and this has considerable significance for the circulation, which needs to be pursued.

While in the former group, activity is usually initiated and controlled by the nervous system, the general level of metabolic activity in the 'core organs' is determined by the physical energy provided by the circulation, and modified by the activity of metabolic hormones, and by the ambient temperature maintained within the organs of the latter group. To be of maximal value, the circulatory model must take account of these considerations.

Additional factors which have a bearing on the metabolic activity of the liver and kidney, have to do with the special features of the circulation supplying these organs. In both cases much of the blood passes through two sets of capillaries between the arteries and the hepatic and renal veins, and this affects the production and reabsorption of extra-vascular fluid in each case. In the kidney, extra-vascular fluid is for the most part confined within the renal tubules, and this allows a study of the relationship between extra-vascular fluid production and reabsorption by the tubular cells, and the energy relationships between the two. There is no other area in the body where these parameters can be studied so conveniently.

Though the comparison of the relationship between cell metabolism and energy provided to the extra-vascular fluid elsewhere in the body may not be strictly analogous, it can still provide some insight into this energy relationship with which the circulatory model needs to have consistent features.

Both the volume of the extra-vascular fluid and the energy with which it is provided, are functions of the linear velocity imparted to the blood by ventricular contraction. This linear velocity depends on systolic blood pressure and the resistance provided by the arterioles.

With the liver circulation, most of the blood supplying the organ has already passed through the capillaries of the gut and/or associated viscera, which modifies its constitution and gas content before it reaches the vicinity of the liver cells. These cells line the blood sinusoids, and are therefore in close direct contact with the blood. Energy from the circulation is provided directly to these cells, rather than through the extra-vascular circulation as it is elsewhere, while the amount of blood supplied must largely depend on the metabolic activity of the digestive tract and associated glands. Blood supplied to the liver has a lower oxygen concentration than that supplied to other areas on most occasions. Should the extraction of oxygen from the blood be increased by increased metabolic activity in the digestive tract without a comparable increase in blood flow, the oxygen content of liver blood will be even more reduced. At the same time, the metabolism of the liver increases with digestion, further stimulated by the specific dynamic action of certain foods.

This provides the anomaly of increased oxygen requirement for metabolic purposes at a time when the partial pressure of oxygen might well be reduced by increased oxygen usage in the gut. At the same time increased metabolism both in the gut and the liver increases the production of heat with an associated rise in liver temperature, further increasing the demands for oxygen. The problem which this poses of continually increasing liver metabolism as temperature rises, is again one for which the circulatory model must offer a suitable solution. Increasing oxygen consumption when the oxygen partial pressure is reduced, is however common to the cells elsewhere in the body, provided oxygen tension is not reduced to the level where oxidative processes can no longer continue. Conversely, rising oxygen tension leading to inhibition of oxidative enzymes also occurs, and if excessive is termed 'oxygen poisoning'. The regulation of oxygen tension presented to body cells between acceptable limits, and the regulation of the other respiratory gas, carbon dioxide, must also be addressed by the circulatory model.

The relationship between oxygen tension and carbon dioxide tension in the tissues and extra-vascular fluid, is indeed of critical importance for the regulation of oxidative metabolism, because it indicates the capacity of the relevant enzyme systems to achieve oxidation at a satisfactory rate under the conditions prevailing at the particular time being considered. Looked at in this way, not only are the relative levels of oxygen tension and carbon dioxide tension of importance, but the level of intermediate metabolites such as lactate in the case of carbohydrate metabolism, or ketone bodies in the case of fatty acids, must also be affected by the oxidative capacity of the enzyme system.

In those areas where increased external work performance leads to increased cell metabolism, followed by increased energy requirement in the extra-vascular extra-cellular fluid surrounding

it, the initial energy increase is the result of anaerobic processes involving carbohydrate, notably the glycolytic reaction and the production of pyruvate and lactate. In these areas, which may be loosely grouped as 'effector organs', the relative level of lactate is equally important with oxygen and carbon dioxide in indicating the adequacy of oxidative metabolism to supplement and largely replace the initial anaerobic reactions, for sustained energy production in the individual cells. It will come as no surprise to the reader then, that an attempt should be made to relate the relative levels of these substances with various parameters of importance in defining the energy level which must be maintained in the extra-vascular compartment, in order to 'balance' the increased energy produced within the cells, and the exchange of nutrients, metabolites, and ions etc. between the two compartments.

Put as simply as possible, a function of the oxygen concentration maintained in any area, is to regulate the amount of blood supplied to it, by a direct effect on constriction of the arterioles and small blood vessels, which are relaxed when the oxygen concentration diminishes, and constricted again when oxygen concentration rises once more. In a similar way, carbon dioxide concentration, by direct effect upon the venules which are relaxed when this concentration increases, and constricted again as the concentration falls, controls the flow leaving the capillary region, and the venous return to the heart. Oxygen concentration can then be related to the resistance offered per unit linear velocity to each ml. of blood flowing into the area, while carbon dioxide concentration directly influences the amount of blood leaving the area, and consequently the venous return and cardiac output, and more particularly, the stroke volume.

The area between the arterioles and venules is that composing the capillary circulation, and it has the greatest capacity for variation of its dimensions (i.e., length, cross sectional area, and volume) of any section of the intra-vascular circulation. It is also the region from which energy is transferred to the extra-vascular compartment, and this transfer depends directly upon the amount of blood and its 'contained' energy supplied to the capillary bed, and that leaving it during the same period. The implied relationship with the concentration of oxygen and carbon dioxide, will be readily appreciated.

Although it depends very considerably upon the gas concentrations, and upon the energy provided by ventricular contraction, the capillary circulation is not however, entirely passive, but is subject to relative increase or decrease depending on metabolic or other activity of the region. The number of patent capillaries at any time can be altered by local changes in temperature for example, and any change in overall circulatory length, will be determined by the proportion of the cardiac output which traverses the more peripheral capillaries, compared with the 'core' areas. Some active response of the capillary circulation to local metabolism and associated activity is likely to be a major influence in the production and maintenance of the extra-vascular circulation, and many potent vaso-active substances affecting capillary circulation are being recognised, particularly those derived from the endothelial cells of the vessels themselves. The adequate stimulus for release of these agents include such potent factors as bradykinin, hypoxia, acetyl-choline, histamine, serotonin and other factors which by releasing endothelium -NO, may lead ultimately to altered phosphorylation of myosin light chains and muscle relaxation in the walls of blood vessels. The mechanisms are clearly complex, but the ultimate result is associated with changes in the physiological length of the circulation and pulse rate, which between them determine the size of the capillary circulation, together with that of the extra-vascular circulation, as well as the amount of energy supplied by ventricular

contraction.

Attention is therefore clearly focussed on the physiological length of the circulation as an important parameter both for the energy liberated by ventricular contraction, and for the regulation of the extra-vascular circulation and its energy content. In the circulatory model, the effective length of the systemic circulation is ultimately determined by variations occurring in three separate locations linked in a general way with the three separate fluid compartments.

Physical distention of the cavities of hollow organs leads in turn to physical elongation of the blood vessels in the walls of those organs commensurate with the metabolic activity induced by this distention. In a similar way, variations in physical conditions at the integument such as changes in external temperature, may lead to changes in the capillary circulation in the region, and so to the overall length of the circulation. Changes in circulatory length from these circumstances are largely imposed on the circulation from outside, such as ingestion of food or fluid, or by changes in the external environment. Alterations in bodily activity or in the performance of external work also lead to changes in the capillary circulation in the active areas, and are able to influence the overall circulatory length accordingly. To avoid the alarming alterations of circulatory length which might ensue from simultaneous changes in all three areas, some coordinating mechanism to limit overall circulatory length would seem to be desirable. In the effector organs lactate concentration and circulatory length are closely associated, and are considered to be interdependent. Regulation of the blood lactate level could then provide a mechanism which would allow modification of overall circulatory length, in the presence of large variations in any one area.

Between them, the resistance per unit velocity for each ml. of volume in the circulation, the stroke volume, and the physiological length of the circulation together with the pulse rate, define the energy contributed to the intra-vascular circulation per beat, and therefore that available for all circulatory activity. This concept of circulatory regulation is the foundation for all that follows, in which the concentrations of oxygen, carbon dioxide, and lactate, together with the pulse rate, each has a prominent role.

A different situation is presented in the case of the 'core' organs, liver and kidney, where it is the level of energy presented to them by the circulation, that largely regulates the rate of metabolic activity within the cells. This is achieved in the liver by regulation of its temperature by the temperature of the blood presented to the organ, and the mechanisms involved are themselves of great interest. In the kidney, it is the mechanical energy within the circulation that influences cell metabolism, the process being initiated by the filtration of fluid in the glomerulus, and the effect that the energy intimately bound up with fluid flow, then has upon the metabolism of the renal tubular cells. Because energy production is regulated in an entirely different fashion in these core organs, glycolysis is not an essential feature in the initial stages, and in fact these organs are more concerned with the reverse process of gluconeogenesis for which lactate produced by glycolysis in the effector organs is the basic substrate. Gluconeogenesis requires energy, and this energy must be supplied by oxidation within the 'core' organs of other substrates, of which fatty acids would appear to be of most importance, although the intermediate metabolites which constitute the 'ketone bodies', and which are produced by initial oxidation of fatty acids within the liver, are the preferred substrates for metabolism in many areas, and may even replace the oxidation of lactate in some organs where glycolysis is usually

the initial producer of energy.

This in turn may affect the prevailing lactate concentration that becomes established in the blood and extra-vascular fluid as a result of a balance between glycolysis occurring peripherally, and gluconeogenesis occurring within the liver and kidney. As a result, the glycogen stores are continually replenished in the core organs, allowing blood glucose levels, and glycogen stores in the effector organs to be maintained, while the basic production of energy for both the cells, and the extra-vascular fluid derives essentially from fat metabolism.

Fat metabolism can only proceed satisfactorily, if glycogen, glucose, and probably lactate levels are maintained at adequate levels. The reasons why this should be so are explored to some extent in later text, but it can be seen that some degree of glycolysis must always be present, initially to maintain the energy balance between cells and extra-vascular fluid in the effector organs, and so 'underpin' continued metabolic activity in these areas.

The metabolism of the core organs in turn is regulated by the level of metabolism prevailing in the effector organs, and if this level should fall below some critical value, that of the core organs might also fall alarmingly. Hypothermia might then become established, and unless corrected, become progressive to the stage where vital functions are suspended. The relationship between fat metabolism and carbohydrate metabolism which has been briefly outlined could have implications for the control of blood lipid levels of some significance, and requires further mention at an appropriate later time.

Control of the level of energy supplied to the extra-vascular compartment, also involves control of the level of cardiac activity under the particular circumstances prevailing at that time. The whole must then be coordinated to provide a flexible and sustained circulation, that can allow alterations of the balance between the energy required in the individual fluid compartments, and at the same time produce a mechanism reflecting this balance in the individual parameters involved in circulatory regulation.

The consideration of movement of fluid outside the vascular system must in turn include some assessment of the volumes of fluid that are transferred from one region to another. It soon becomes apparent also, that an appreciation of the relative volumes of fluid in each 'compartment' of the body must be involved, together with the influences which determine the distribution of fluid between one 'compartment' and another.

The relevant compartments are three in number. Fluid from the vascular system, the 'intra-vascular compartment', must be in some sort of equilibrium with the 'extra-vascular compartment' of extra-cellular fluid, which in turn must be balanced with the volume of the 'intra-cellular compartment', or fluid contained within the cells themselves.

In this distribution of fluid within the body, the extra-vascular compartment must occupy the central area, insofar that all fluid within the body must pass through it on the way to and from the intra-vascular and intra-cellular compartments. This implies a key role for the circulation of fluid in the extra-vascular region for the metabolism and fluid economy of the body as a whole. Some understanding of the mechanics of the fluid circulation in this area is therefore imperative, if the role of the circulation in bodily function is to be understood in any overall sense. It is from recognition of the crucial importance of the extra-vascular compartment and

its relationship with the pressure developed by contraction of the left ventricle, that the present volume draws its initial concept.

Because the extra-vascular space is in an intermediate position between the cardio-vascular system and the tissue cells, it is impossible to fully comprehend the factors that are important in the interchange of fluid, salts, nutrients, and metabolites between these latter two areas, unless those factors which control the volume and movement of fluid in the former are also understood.

Once there is a working hypothesis that enables one to estimate the relative volumes of fluid within the extra-vascular compartment and each of the other two compartments, and the relative interchange of fluid between them, it becomes much easier to appreciate the reasons for, and the significance of, fluid distribution between the three.

The required exchanges between these compartments take place at the sites where they are in physical contact, separated only by a membrane across which transfer of fluid and energy occurs, depending on the nature of the membrane and the distribution of physical forces across it. Because of its semi-permeable nature, the distribution of ions and molecules is different on each side of the membrane at any particular time, and under any particular set of circumstances that might alter its 'permeability'. Changes in the distributions of fluid, contained substances, and energy, are continually taking place, depending on such altered permeability. For this reason it is desirable if practicable, to examine the interchange in areas where it is possible to assess the effects under circumstances where conditions on at least one side of the membrane are controlled or determinable in advance. In many areas of contact between tissue cells and extra-vascular fluid, such assessments may be difficult, and it is necessary to concentrate investigation in those regions that offer the advantage of more controlled conditions. Similar problems present themselves in the development and transfer of fluid and energy between 'effector' cells and the intra-vascular circulation, and between the intra-vascular and extra-vascular circulations.

The regions that have been chosen for observation because of advantages they might offer, are the heart, the kidney, and to a lesser extent the general capillary circulation. In the ventricle of the heart, energy produced by the contracting muscle cell is transferred directly to the circulating blood. The amount of this energy, and its effect on the mechanics of the intra-vascular circulation, the extra-vascular circulation, and on the cells of more distant tissues and organs can be observed directly or at least implied by use of the circulatory model.

At the same time, it is the residual energy contained within the blood presented to the heart at diastole to produce 'ventricular filling', that determines the response of the muscle cells of the ventricle, and the amount of energy made available when contraction occurs. It is the level of energy in the blood returning from its close association with tissue cells, that determines the amount of energy which is in turn imparted by ventricular contraction to the blood returning to the site of cellular activity in the peripheral regions, and 'effector organs'. The interposition of the pulmonary circulation on the one hand, and the extra-vascular circulation on the other, complicates but does not invalidate the balance that cardiac activity and cellular function must exercise upon each other.

In the kidney, transfer of fluid and energy from the intra-vascular circulation to the extra-vascular circulation (represented by the glomerular filtrate), and then from the extra-vascular

fluid to the cells of the renal tubule (represented by reabsorption of solutes and fluid), allow the circumstances under which this transfer takes place, to be observed more readily than elsewhere.

Limited observation of the relationship of the intra-vascular with the extra-vascular circulation can be made using the finger plethysmograph to show volume flow patterns during the cardiac cycle and some use has been made of this technique.

Movement of fluid within the body is maintained for the most part by ventricular contraction. Although contraction is regularly followed by ventricular relaxation and filling of the ventricle during diastole in readiness for the next systolic contraction, this relaxation does not signal the cessation of fluid movement. The latter continues during both systole and diastole, though the amount of movement (and so the linear velocity of the blood) changes continuously during the cardiac cycle, being greater during systole than during diastole, but nevertheless maintaining flow at an adequate level over the whole period. This situation implies storage of energy in some form, so that part of the energy produced by ventricular contraction during systole, is available to maintain blood flow during diastole.

It has long been appreciated that some of the energy of systolic contraction is stored in the elastic walls of the aorta, and that by the end of diastole, the energy has been reduced by the fall in blood pressure from the systolic to the diastolic level, and the change in pressure is associated with pulsatile flow in the arterial system. Pulsatile flow beyond the arterioles is only seen on rare occasions, so that beyond the arterioles energy must either be stored in some other manner, or be totally used, in for example, maintaining flow while overcoming frictional resistance in the smaller blood vessels. Energy used in this way is lost so far as further movement is concerned, momentum is reduced and flow should soon be almost totally arrested. Indeed, the velocity of flow in the capillaries may be greatly reduced so that the linear velocity in this region is only a small fraction of the average linear velocity of flow of blood in the circulation generally. Once blood reaches the veins its linear velocity increases once more, but in order to achieve this increase in velocity, further energy must have been acquired from an extra-vascular source. Some energy comes from muscle contractions which compress the veins incidentally as the contracting muscles change shape. This is considered to be of importance in the limbs, where such muscle contractions within the fascial sheath combine with the action of venous valves to force blood upwards towards the heart. In some parts of the circulation, this arrangement of contracting muscles and strategically situated venous valves is not available, and another source for the energy of venous flow must be sought. If one considers that immediately following passage through the arterioles blood enters the capillaries, and from the arterial end of the individual capillary fluid passes to the extra-vascular space, then it must follow that this movement of fluid has kinetic energy associated with it. The contained energy must ensure that the extra-vascular fluid is in continuous movement, and that the velocity of this movement must depend on the volume of the extra-vascular compartment, and on the amount of energy transferred to it from the intra-vascular compartment with the extruded fluid. In other words, the energy in the extra-vascular compartment will be a function of the linear velocity of the fluid within the blood vessel and the volume of fluid that passes to the extra-vascular space. The formation of extra-vascular fluid with its associated energy is limited by the osmotic pressure of the plasma proteins. Haemo-concentration increases the osmotic pressure the plasma proteins are able to exert. With the rapid fall in velocity and lateral pressure that occurs over the length of the capillary, fluid is attracted once more into the venous end of the capillary

together with its kinetic energy, and this gives volume and velocity to the venous flow.

The simple mechanism outlined constitutes the extra-vascular circulation whereby a portion of the fluid that is normally part of the blood volume, bypasses part of the capillary circulation together with some of the energy provided by ventricular contraction. Both the fluid and its associated energy are then available to maintain the volume and the linear velocity of the venous blood. Now if simple control mechanisms can adjust the volume of fluid entering and that leaving the extra-vascular space independently, there is now a system which can store both fluid and kinetic energy after the manner of a flywheel in a reciprocating engine.

The size of the store of fluid and energy will in turn determine the balance of fluid exchange between the extra-vascular fluid and the cells, and between the extra-vascular fluid and the blood. Calculation of the relative amount of flow energy and/or fluid volume in each compartment then becomes a prime objective, if the exchange is to be fully understood, and given a quantitative value even if only in a relative sense.

There are then two ways in which energy produced by ventricular contraction can be stored in the circulation. While the wall of the aorta can store potential energy that is partly released later in the cardiac cycle in the form of kinetic energy, fluid in the extra-vascular space can act as a storehouse of kinetic energy, even while it remains a part of the circulation though remaining outside the vascular walls. The relative amount of energy stored in each area (i.e. the aorta and the extra-vascular fluid circulation) is a balance the cardiovascular system has to achieve in order to maintain the efficiency of the circulation. The transfer of energy into and between these two storage areas, manages to eliminate pulsatile flow from the circulation beyond the arterial system.

Energy stored in each area is then in a specific form. The aorta stores potential energy represented by pressure, though this energy is partly released as kinetic energy of flow, produced by conversion of the stored potential energy. In the extra-vascular compartment the stored energy is kinetic energy of movement. It is as kinetic energy that it leaves the capillary, and it is in the same form that it returns to the intra-vascular compartment. The difference between the two areas of energy storage largely exists in the form of energy which each conserves, and the comparison between them is similar to that of the ratio of potential to kinetic energy in the circulation generally.

Although 'at rest', storage of kinetic energy would involve passage of fluid into and out of the cells largely on a mechanical basis, once the cells become 'active' with depolarisation of the cell membrane, and altered permeability of the cell wall, fluid passes more readily to the extra-cellular space. Kinetic energy is provided by change in cell volume and the breakdown of high energy phosphate bonds, and this energy passes to the extra-vascular space, and with the extra fluid provided from the cell, increases the venous return, and becomes a significant factor in the increased circulatory activity that rapidly occurs. In this sense, cells of the 'effector organs' (particularly muscle cells) always have a 'store' of energy available to augment that in the extra-vascular space, immediately the cell becomes active. Replacement of this energy store, depends on repolarisation of the cell membrane, together with the replacement of high energy phosphate bonds by cellular metabolism as the muscle cell relaxes. Replacement of the fluid lost during contraction has to occur from the extra-vascular space, using the kinetic energy in that space,

which helps to re-extend the contracted fibres, and increase cell volume. The kinetic energy supplied is used in the re-extension as the muscle fibre relaxes, and is stored there by the attachment of high energy phosphate bonds, which enable the cell to maintain its relaxed state. Kinetic energy is then stored when the muscle cell is extended, and released again when the muscle contracts, when it again becomes available to the circulation.

Voluntary muscle is rarely completely relaxed at any time, some muscle 'tone' generally being present, and being represented as groups of contracting fibres maintained by the reflex activity of the nervous connections. Kinetic energy is constantly being absorbed and released between the circulation and the effector cells, and reinforcing the flow energy of the circulation depending on the level of activity of the 'effector organs'. This energy is in addition to that used to provide the force of contraction which for instance, approximates the two ends of the muscle, but as the energy of contraction is provided from the high energy phosphate bonds when they are disrupted, the energy provided for one function will be inversely related to that provided for the other. The speed of contraction then becomes a significant factor in determining the relative amount of each kind of energy provided.

Although the origin and re-appearance of kinetic energy associated with cell activity and metabolism is essentially in the form of fluid movement, 'storage' of this energy within the cells must involve conversion to potential energy linked to the cell volume and metabolic activity of the cell enzymes. Furthermore, 'storage' of energy of any kind, can only occur when more energy accumulates in the system during one time period than is returned to the vascular system during that period, and this presumes that the ventricle is producing more energy per beat than is required to provide the necessary momentum to maintain the circulation at its current level. The result must be an increase in the potential energy retained within the system, and reflected in the level of blood pressure that is currently sustained.

In brief then, the maintenance of blood pressure is largely determined by the balance between the kinetic energy supplied to the cells by the extra-vascular circulation on the one hand, and that returned to it as the result of cellular activity and metabolism on the other. Any variation in the ratio between the two, will be reflected in changes in arterial blood pressure, and if large or protracted, in pathological syndromes of greater or lesser degree. The virtue of the circulatory model is as an instrument to suggest how and why such variations might occur.

To assist in putting these ideas forward, I have employed a simple though possibly controversial device in order to simplify manipulation of variables that would otherwise be of daunting complexity. This device is the use of a theoretical value for each of the complex variables in the circulation that otherwise would be very difficult to determine by direct observation.

Each of these theoretical values is designated the 'average mean' value of that particular variable. This somewhat clumsy term is used to indicate the separation of three dimensions of space from one of time. A mean figure is estimated to give a representative value over three dimensions of space, and these mean figures are then averaged over equal intervals of time. The result is an 'average mean' figure which indicates a representative value over four dimensions. It is used in the energy calculations as though it were a readily determinable quantity. (It should be pointed out that it would be theoretically possible to determine these values accurately, given sufficiently sophisticated information and processing equipment, and that reasonable approximations can be produced fairly simply, provided it is accepted that the concepts are 'real'

and not imaginary. For example, if one defines 'l' as the 'average mean' length of each of the blood vessels in the circulation, estimation of its value can only be approximate; nevertheless the value of 'l' meaning the average distance travelled by each millilitre of blood in passing from the left ventricle to the right atrium must have a 'real' value and a 'real' meaning. The same reasoning applies to all of the 'average mean' values introduced, such as 'v', the average mean linear velocity of the blood in the circulation, or 'a' the average mean cross sectional area of the vascular bed, so that the product of 'l' by 'a' equals 'Vs', or the volume of the systemic circulation, and so on).

The value of this device is that it allows relationships to be developed between the observed and the presumed 'average mean' variables that are equivalent with respect to energy development and utilisation, and therefore to allow a general statement or 'Principle of Energy Equivalents' in the circulation, which greatly simplifies the interpretation of the significance of any observed change in circulatory parameters. The use of the 'Principle of Energy Equivalents' is of particular value in elucidating the reason for blood pressure changes that have previously been considered to occur because of some unknown pathological process or substance acting on the blood vessels. The 'alternative view' is that these changes are normal physiological adaptations that maintain an adequate circulation when function otherwise would not be sufficient to preserve the individual's continued existence at an adequate level.

Using the simplified model of the circulation constructed according to these principles, the result is to demonstrate that the major control of energy production in a particular circulation rests on the pulse rate and the 'average mean' length of the blood vessels in that circulation, while the efficiency of the ventricle also depends principally on a simple relationship between stroke volume and the volume of that particular circulation at the time. One function of the diastolic arterial pressure in this model is to modify and maintain the efficiency of the ventricle when the ratio of stroke volume to circulatory volume is varied.

When the ratio between stroke volume and circulatory volume is considered further, a similar ratio is found to exist between linear velocity of flow and the force of ventricular contraction, between peripheral resistance per unit circulatory volume and the systolic blood pressure, and between the duration of the cardiac cycle and the circulation time, and that each of these ratios has the same value and is therefore 'equivalent' to each of the others. This circulatory ratio becomes the basis for the circulatory model, and the conclusions which might be drawn from it.

The circulatory ratio, or ratio of stroke volume with the volume of the circulation to which it is added by each ventricular contraction, and its equivalent values, is the basis for the 'Principle of Energy Equivalents'. The algebraic model of the circulation results from manipulation of these equivalent values, and allows the expression of each circulatory variable in terms of other variables, despite the fact that 'numerical values' are not able to be directly assigned to them. While this ensures that the values of such variables remain abstract in concept, it opens the door to the possibility that ultimately some relationship can be derived which can be tested against observed data, and then give significance to the relationships on which it is based.

This principle is the basis for what follows. It is supported in some significant areas by direct experiments, which, though somewhat rudimentary in design, are considered to give credence to the conclusions reached. Used in this way the algebraic model becomes an important tool in helping to reveal the sometimes complex relationships on which circulatory and renal function

may be based.

While the importance of variations in diastolic blood pressure in modifying ventricular efficiency is an important conclusion of this examination, there are other results involving the control of liver temperature and alterations in carbohydrate metabolism, particularly of lactate metabolism and gluconeogenesis, and possibly also of protein metabolism.

Control of fluid balance, extracellular fluid, and circulating blood volume, are subjects that are being constantly investigated, and they are of enormous significance for the physiology of blood pressure maintenance. This wide field is not examined comprehensively in this volume, but the influence of mechanical forces on salt and water excretion by the kidney, have been the initiating factors in the compilation of this account, emphasising as they do the dependence of the chemical activity of the cells on the physical forces to which those cells are subjected. The similarity to the cells of cardiac muscle will be apparent. Put another way, the basic physiology of the circulatory and excretory systems is determined in the first instance by physical forces.

Superimposed on these, but not essential to their activity in a primary sense, are the nervous and hormonal controls, which though important, can be removed from the system without it ceasing to function, though that function might not then be as adequate as it is when the nervous and hormonal controls are intact.

There are then two different elements to the mechanisms involved in the production and maintenance of circulatory energy and organisation of fluid movement within the body. The amount of available energy depends on the physical dimensions of cells, and the permeability of their membranes that are varied by the concentrations of cell metabolites and gas concentrations. The overall energy produced is the result of large numbers of individual cells with different levels of activity, and different rates of energy production, each liberating energy according to their individual circumstances. There are mechanisms required to reduce the total energy to the equivalent of a single dimension, and of a single rate of energy release to represent the whole by requiring individual cells to conform to it. These give rise to an overall pulse rate representing the rate of energy release, and overall circulatory length representing the quantity of energy released. Overall energy produced is a function of cell dimensions related to the overall dimensions of the circulation, and the overall rate of energy release is represented by the pulse rate imposed on the circulation by hormonal and nervous mechanisms. Energy is directed in particular directions best suited to body needs at the time, by alterations of pulse rate and circulatory length within the limits allowable by the physical dimensions of cells and blood vessels.

Continuing vitality results from the application of the available energy modified by the regulating effects of hormones and autonomic nerves altering pulse rate and circulatory length to best utilise the energy, with the product of pulse rate and circulatory length remaining equivalent to the energy produced, but modifying its application so that the product of the concentrations of carbon dioxide and oxygen remains proportional to circulatory length through variation of cell and membrane permeability. The physical basis of vitality is the energy available from activity of individual cells co-ordinated into a whole to appear as pulse rate and circulatory length, whose individual values are further regulated by hormonal and nervous mechanisms, varying pulse rate with respect to length to modify the linear velocity of tissue fluid, and the volume pressure and momentum of other fluid compartments, to achieve

appropriate values of each parameter required for continuing function. Important as the regulating function is, it can only become effective when the appropriate energy has been developed according to the dimensions of individual cells, and the metabolic processes that determine them.

My point is that the nervous and hormonal controls are superimposed upon an already functioning system, and it is the primary forces concerned in the functioning of that system, with which this book is concerned in great part.

Until a clear understanding of the physical and mechanical basis of the circulation has been achieved, progress in circulatory physiology can only proceed on an empirical basis. Descriptive accounts of regulating mechanisms, without a readily discernible foundation in physical science (which must underlie all mechanical systems, whether their origins lie in biological material or not) can only remain descriptive accounts, with limited value for predicting future behaviour in the system.

Once such a basis founded on physical science is established, it can then be built upon more confidently, and the significance of any regulatory mechanisms, more soundly assessed.

It is the author's hope that the concept of continuous motion determining and dominating the distribution of body fluids will be seen by the reader as offering a logical extension of Harvey's original view of the circulation. It is only by analysis of the variables associated with this motion, that an adequate appreciation of the mechanical basis and functional capacity of the circulation of body fluids can be obtained. Whether or not this presentation is considered to be acceptable in this respect, there seems little doubt that the path of progress in circulatory physiology lies along this direction. The success of this book can only be judged by the regeneration of interest in such an approach which it is able to stimulate.

Summary.

The complexity of the cardiovascular response requires continuing variation in circulatory parameters to regulate speed of blood flow with respect to the resistance encountered, and impose the least distending pressure on individual vessel walls. The result is limitation of vascular volume by altered linear velocity of flow, and determination of both the size and arrangement of blood vessels in relation to the efficiency of energy production.

Vascular models to describe circulatory activity were proposed by or arose from the work of Harvey, Bernard, and later Starling, but the resulting models still remain inadequate to relate function of individual cells with the environment provided by circulating fluid, and the mechanics of fluid movement. Current investigations fail to fully illuminate the problem, mostly because they involve

clinical rather than basic physiological investigation. A further model based on an algebraic approach may provide a more comprehensive account through a more abstract analysis of circulatory function.

Movement of fluid between body compartments occurs through disturbance of the energy equilibrium required for the stability of their volume and concentrations. Changes arising from activity of muscles and other 'effector' organs are transmitted to other fluid compartments by movement of fluid between them.

Energy production in the 'effector' cells and in the heart, occurs mainly as the result of glycolysis, and oxidation of carbohydrate, and is governed by the relative levels of oxygen, carbon dioxide, and lactate persisting in body fluids, and which influence both the length and diameter of the blood vessels. In core organs like the liver, increased energy is produced in response to increased activity elsewhere. Fluid movement outside the vascular system is closely related to cell and circulatory activity, and exchange between compartments following energy differences, but this is complicated by energy 'stores' in the walls of the blood vessels, and in body cells, which temporarily remove energy from the system. Storage of kinetic energy also occurs through constant motion in the extra-vascular fluid, and this 'flywheel effect' both absorbs and transmits energy to and from the other compartments according to the levels of potential and kinetic energy available in each. Energy transfer also varies between 'active' and 'resting' cells, through alteration of cell and capillary permeability affecting fluid exchange, and the external work performed, compared with the levels of energy exchange and cell volume. Residual energy retained in each compartment is related with ventricular or vascular 'filling'. Fluctuations in residual energy occur with the cardiac cycle, and with energy 'storage' in fluid compartments under the influence of the osmotic pressure of plasma protein. Energy 'stored' in a specific form in a particular compartment, is involved in work capacity of cells and the level of blood pressure which is maintained.

In order to allow for the rapidly changing parameters encountered, a representative value for each during the cardiac cycle is assumed in the circulatory model, and allows relationships to be produced which give rise to the 'circulatory ratio' between circulating and stroke volumes, and other equivalent ratios leading to the 'principle of energy equivalents', on which the algebraic model becomes based. The basic physiology of the circulation, and distribution of body fluid, each depend on physical forces which produce continuous motion resulting in the distribution of body fluids.

Introduces the relationship which exists between energy production and fluid distribution in the body. It arises from the personal involvement of the author over a number of years, and the perceived failure of current investigations to fully illuminate this problem, mostly because they involve clinical investigation rather than basic physiology. Movement of fluid between body compartments occurs through disturbance of the energy equilibrium required for stability of their volumes and concentrations. The quantitative relationships governing equilibria is most readily shown by a model incorporating current information,

and following on those models proposed or originating out of the efforts of Harvey, Bernard, and Starling, and the application of sophisticated instruments to expand them. Changes arising from the activity of muscles and other 'effector cells' or organs are transmitted to other compartments by movement of fluid between them, i.e., by variation in momentum and linear velocity of flow.

Energy production in the effector cells and in the heart, occurs mainly as the result of oxidation, and is governed by the relative levels of oxygen, carbon dioxide, and the levels of intermediate metabolites, such as lactate, persisting in body fluids. These influence both the length and diameter of blood vessels.

In 'core organs' like the liver, energy is produced in response to increased activity elsewhere, and transmitted by circulating blood. Fluid movement outside the vascular system, is closely related both to cell and circulatory activity, and exchange between compartments occurs because of energy differences between them, but is complicated by the presence of energy stores, both in the walls of blood vessels, and within the body cells, which temporarily at least, remove energy from the system. Storage of kinetic energy may also occur through constant motion in the extra-vascular fluid, and this 'flywheel effect' both absorbs and transmits energy to and from the other compartments, according to the potential and kinetic energy in each area. Energy transfer also varies between 'active' and 'resting' cells, through alteration of cell and capillary permeability affecting fluid exchange, and the external work performed (e.g., by contraction) compared with the level of energy exchange and cell volume.

Calculations are based on 'average mean values', energy equivalents, and the circulatory ratio, allowing quantification of the energy produced by the ventricle.

Other subjects mentioned involve the effect of physical forces affecting the basic physiology of the heart and kidney, mechanical forces in salt and water excretion, dimensional changes in renal tubules related to renal function, and 'essential hypertension' and its origins.