CHAPTER 2.

ENERGY GENERATION IN THE CELLS AND CIRCULATION.

The production and later transfer of energy from the cell where it originates, to some other area either within the cell itself, or in its immediate environment, are essential characteristics of living tissues. The mechanisms which underlie this movement are those of immediate concern to the present enquiry.

The principle underlying this account is a simple one. Overall energy production by tissue cells is reflected in the energy which is made available in the circulating fluid to regulate fluid and energy exchange between intra-cellular and extra-cellular fluid compartments.

Although it might seem more economical to produce energy at the site where it is required for a particular purpose or reaction, the complicated nature of the intricate cross reactions within the cell, appear to make it more satisfactory to maintain a certain level of `free energy' which can be available in a general way to fuel the various reactions at a particular steady rate, which is optimal for that cell under prevailing circumstances. The measure of the level of `free energy' is the ambient temperature maintained within the cell, representing a pool of energy, which can be directed towards some particular purpose or set of reactions ,and maintained by either continued production of energy, or transferred from an `energy store' used to supplement `free energy' when necessary.

The success of the individual organism in maintaining a constant background of `free energy' is indicated by its ability to keep the body at a particular temperature. Although increased activity in one area might increase the energy level and heat produced there compared with another, movement between regions ensures a balance of available energy between them, and helps to coordinate all associated body functions in line with overall activity. These mechanisms become the norm for warm blooded animals, but they involve considerable organisational problems which have to be resolved for its successful implementation.

In the first place, increased activity in one area needs to influence that in another, to respond with altered activity of its own. It gives rise to a concept of `effector organs', where greater activity is initiated, and `core organs' which respond to this greater activity in an appropriate manner to complement and sustain it.

Secondly, it requires a system for transferring energy and metabolites between areas, while allowing one area to exercise `dominance' over the activity of another, through initiation of increased function in the `effector' organ.

This system of energy maintenance immediately introduces a number of questions requiring further explanation, such as the nature and control of the energy `store', as well as the optimal level of `free' energy, and the relationship to energy exchange with the surrounding fluid environment. For unless there are limits placed on the exchange, excessive gains or losses could well disturb the current energy level, and jeopardise that required for optimal cell activity. Unless a balance is maintained between `free' energy within the cell, and that in its environment, energy will pass from one fluid compartment to the other, limited only by the nature of the semi-permeable membrane which separates them.

The primary consideration is the amount of free energy present within the cell, which has to be balanced by an equivalent energy source in the immediate environment to maintain equilibrium after each cardiac cycle, and the relative fluid volumes on each side of the cell membrane. Stability is obtained within the system by maintaining a relatively constant ratio between the stroke volume expelled from the ventricle per beat, and the volume of blood contained in the systemic circulation. By maintaining the volume of fluid exchanged with the cells at an equivalent value with that expelled from the ventricle, stability is provided between the cell and circulatory volumes. The ratio between stroke volume, and systemic circulatory volume, has been called the `circulatory ratio', and it becomes a fundamental element in the structure and function of the circulation.

The problem of keeping this balance involves not only the amount of `free' energy maintained within the cell, and that presented at the cell surface, but also the changing permeability of the cell membrane. As a result, although the ratio of energy levels across the cell membrane remains as the essential feature determining the exchange of fluid and energy between these areas, the exchange with each individual cell is regulated by changes in permeability of the cell membrane according to metabolic activity.

The relationship between the energy level available within the cells, and that provided by the heart, and maintained in the extra-vascular fluid, is the foundation for energy development and distribution within the body.

As a consequence, the primary objective in the preparation of the present account, has been to examine the efficiency of energy production and distribution within the body, exemplified by fluid transfer between the circulation and the various organs and cells, in association with their related functions. The hydraulic system produced by movement of fluid and energy, allows motion in one area to exert a particular influence on all other regions connected with it, and the quantitative relationships which result, then become a basis for comparison between them. Because the amount of circulating fluid and the energy it contains is itself provided by contraction of the cells of the myocardium, the balance between the circulation and the peripheral cells is simply an extension of the relationship between energy developed by the myocardial cells, and that of cells elsewhere in the body. It is the manner in which these balances are maintained which is examined in the following pages. The metabolism of each effector cell is associated with movement of fluid and energy across the cell membrane, and it is the momentum generated through this activity which is fundamental to the continued function of fluid circulation in the body. Transmitted to venous blood, the total of all energy and fluid movement from the effector cells, produces the momentum available in venous blood returning to the heart, regulating the filling of its chambers, and the amount of energy given to the arterial blood. The latter appears as pressure and momentum, or potential and kinetic energy available to maintain its distribution to all areas of the body, including the cells from which the fluid first originated, where it replaces that previously lost from the cell, and provides flow energy of equivalent amount. In effect, the cell repeatedly contributes fluid to the circulation and receives an equivalent volume of fluid in return complete with nutrients and other essential materials necessary for its function, including the flow energy to re-expand its volume. The precision required to achieve the exchange indicates the close relationship which needs to exist between cell function and overall circulatory activity, and it is produced by adjusting the momentum in each area accordingly. Each individual cell must be able to adjust the exchange with its immediate environment according to need, and it is the total of all these individual adjustments which dictate circulatory activity at any particular time. The individual cells are able to control the exchange which is optimal for their function, but they must also be able to control the overall circulatory activity which provides the requisite conditions for continued function. Exchange with each cell depends on the momentum presented to it, the store of energy accumulated within the cell together with the free energy it has, and the permeability of the cell membrane which allows any exchange to take place at the required rate. The hydraulic system consists of the momentum provided to venous blood, which initiates an appropriate response from the heart including potential and kinetic energy to balance that within the cells, and also to provide energy to transfer fluid and energy across the cell membrane in appropriate amount regulated by cell permeability. Induced alteration in any of these parameters must then produce equivalent changes in each of the others, if the system is to operate in an optimal fashion. A satisfactory model to demonstrate the operation of the circulation, can only be produced by relating each stage of the operation to all the others by means of ratios showing the relative variations of one parameter with another using an appropriate mathematical method.

Commencing with the momentum provided to venous blood by cell activity, ventricular size and shape is adjusted in specific ways to accommodate the volume exchange with the cells, the power needed to overcome resistance to flow, and provide both the required increment in momentum, and the energy which accumulates in the cells associated with strength and work capacity. Power developed must also balance the `free' energy necessary in the cells to drive the system, and provide the venous momentum which initiates and maintains the circulation on a continuing basis. Each of these functions is intimately connected with all of the others, and the aim is to outline a circulatory model illustrating these relationships and their significance for overall function.

The immediate difficulty with this view, is the varying activities of different groups of cells with time, so that although the overall activity of the ventricular myocardium is always maximal for the circumstances under which it contracts in an all-or-none fashion , the tissue cells are much more individually variable, and a representative figure to represent their activity may not seem readily available. One solution which has been adopted, is to assume a theoretical value which is representative of all the varying energy levels from cell to cell. This `average mean' value represents a series of mean values for all cells estimated over three dimensions of space, and averaged over equal time intervals, and is used in the estimation of energy levels as though it has a readily determinable value, and the energy balance is calculated on this basis.

Each cellular exchange contributes to the total energy which finds its way into the venous system, and eventually determines the amount and energy of the venous return to the heart. The amount of the venous return becomes a measure of the total fluid and energy exchange which has occurred between the circulation and the cells, and becomes an important indicator of the required circulatory response to maintain this exchange.

That a balance between cellular and circulatory activity may be present under usual circumstances, is evidenced by the amount of `free' energy available in each area. By `free energy' is meant the uncommitted energy which is available to fuel the intricate cross reactions which constitute basic cell function, and which can most readily be measured by the prevailing temperature in the area. The relative temperature of the peripheral cells and that of the myocardial cells, indicates the `free' energy level available in each area. Provided the temperature in one area is stable with respect to that in the other, so will the production of `free energy' in each region remain related.

In warm blooded animals , these variations in temperature are relatively slight on most occasions, but they will indicate the basic activity of one area compared with the other, and the energy production or transfer which would be necessary to re-establish the balance between them.

The total energy developed by each cell includes, not only the `free energy' represented by the prevailing temperature, but also the energy exchanged with the environment, and the energy `stored' against future requirement for cell activity, but which is still part of the energy which must be balanced by that in the region surrounding it, derived from fluid circulating in the body, and originally from the external work provided by cardiac muscle as part of its own `energy exchange'.

The energy required in each area is then related to three different activities; the maintenance of `free energy', `stored energy', and `energy exchange' with the environment. The energy supplied must vary depending on the relative value of each of these compared with the `free energy' level, which the body is at some pains to preserve.

The implication is that the energy supplied by ventricular contraction must constitute three separate elements representing `free' energy, `stored' energy, and energy `exchange', and equivalent parameters can then represent energy production in both the cells and the circulation. Energy from the metabolic activity of the cells of the myocardium needs to be directed in these various ways, and each will lead to variation of the load on the myocardium in a specific way, to correspond with overall energy production in the cells, but allowing the `free energy' and temperature of the cells to remain at a relatively constant level.

The main variables are then `energy storage', and `energy exchange'. Of these, `energy exchange' is related to the volume exchange, or momentum which is linked with the stroke volume, while `energy storage' depends on the potential energy, or pressure per unit velocity, presented to the cell membrane, which maintains the `energy store'. While the level of `free energy' remains constant, so will the ratio of stroke volume/ energy exchange, and of potential energy/energy store in the cells. The activity of the myocardial cells then `balances' the activity of cells elsewhere, and gives rise to a series of equivalent ratios which express this balance. For this reason, expressions which describe energy production in the myocardium, have similar significance for energy developed in body cells elsewhere, and in particular in the cells of the `effector organs' (muscles, glands, and nerves).

The aim has been to develop a series of ratios or expressions which not only describe energy production in the myocardium, but which can be extended to the activity of other cells, and become useful in describing the energy exchanges derived from both cell metabolism, and the energy provided in the circulating fluid.

By developing ratios which are relevant to different aspects of circulatory and cellular activity, but which are equivalent to each other in terms of energy development, it becomes possible to produce an algebraic model to describe circulatory activity in terms of energy produced or used in each area or volume of circulating fluid. It is then a relatively simple matter to describe activity in one area in terms of activity elsewhere, and to allow development of a series of `energy equivalents', which govern this activity.

The response of the circulation to increased cellular activity, involves a change in the momentum of the circulating fluid, but this is modified by the resistance to flow presented by the `stored' energy level which needs to be maintained in the cells to achieve that increased activity.

It is the momentum present in the venous return which initiates this response, i.e., Vs.v is proportional to Q.l.PR . (where `Vs' is systemic blood volume, `v' is the average mean linear velocity of flow, `l' is the average mean circulatory length, `Q' is stroke volume, and `PR' is pulse rate per sec.) `Vs.v' represents the overall momentum of blood in the systemic circulation, which is greatest in the arterial system, and least as the blood re-enters the heart from the great veins. This momentum falls off with increasing vascular length. The cardiac output and venous return is closely related to the venous momentum, or `Vs.v / l' is proportional to `V venous'.`v venous', and `Q.PR'.

The linear velocity of flow given to the circulation by ventricular contraction is then, directly related to the length of the vascular system, and also to the diastolic length of the cardiac muscle fibres which determines the magnitude of the contraction. In other words there is a general relationship between circulatory length, and the initial length of the cardiac muscle fibres for a given ventricular output.

Because of the relationship between venous momentum and cardiac output, the volume and time factors in each are similarly related. If `Q' is related to `V venous', then `v venous' must be related to `PR' , provided `l / v', or circulation time, is unaltered. The relationship of linear velocity of flow with pulse rate, and of circulatory length with the force producing momentum in the circulation, would indicate that the force of ventricular contraction is proportional to `l.PR', giving momentum to the expelled blood proportional to `Q.l.PR', while the external work performed by the ventricle is momentum times resistance per unit velocity per ml., or `R.Q.l.PR' or `Q.APs' (where `R' is resistance per unit velocity per ml. of blood, and `APs' is the systolic blood pressure). The algebraic model of the circulation is developed from these relationships involving equivalent energy values, and based on the equivalent circulatory ratios, and the `Principle of energy equivalents', (q.v.).

In the development of these relationships, the pulse rate can be seen as exercising a dual function. The first of these is to limit the value of the stroke volume (depending on the elements which contribute to the momentum of venous blood), while the second is to vary the time elements involved in ventricular muscle contraction, and the power developed, or rate at which energy is produced. Both functions have a vital role in regulating energy production and utilisation in the circulation.

The circulatory ratio is the underlying relationship which regulates the size and functional activity of the cardio-vascular system, relative to cellular requirements for energy production. Its pervading importance in all circulatory function, enables it to be expressed in terms of many if not all of the parameters involved in the regulation of energy requirements in each area. The most readily comprehended form is probably the volume ratio, `Q/Vs', where `Q' represents the stroke volume, and `Vs' the volume of blood in the systemic circulation. The stroke volume can be shown to be related to the requirement of the tissues for oxygen and nutrients, and to the fluid and energy exchange with the cells, and it is determined by this requirement, which influences the momentum of the venous return. The volume of the systemic circulation is related to both circulatory length, and the cross sectional area of the series of vessels which allow the blood to flow with adequate momentum for tissue requirements, and without producing a work load on the ventricle which is unacceptably great on the one hand, or inadequate for maintenance of momentum from beat to beat, on the other. It implies a relatively constant number of ventricular contractions to completely fill the circulation, and a constant circulation time for constant pulse rate, for the current level of bodily activity. Because of these relationships, the circulatory ratio can also be expressed as a velocity ratio, as a pressure ratio, time ratio, or as a relationship between the concentrations of the respiratory gases, oxygen and carbon dioxide, maintained in the cells for optimal function of the respiratory enzymes, and there are other expressions which can also indicate the functional limits imposed by changing circulatory parameters. The equivalence of these ratios allows them to be equated with each other, and to allow expression of one variable with respect to the others in any particular section or area of circulating fluid and/or cell activity, and makes it possible to produce a `Principle of Energy Equivalents' which governs these relationships.

One considerable difficulty in comparing the variables involved in circulatory activity, is their rapid fluctuations with events during the cardiac cycle. Because changes in one variable compared with those in another may not occur simultaneously, it is necessary to eliminate them as far as possible. Simultaneous recordings and calculations to overcome these difficulties, would be a formidable if not impossible task, and the solution which has been adopted is to assume a representative value for each variable which can be used in calculation as though it was readily ascertainable, despite the absence of any absolute fixed value which can be assigned to it, although approximate values may be calculated fairly readily. These representative values are called `average mean' values. As already stated this rather clumsy term indicates a mean value estimated over three dimensions of space, and an average of these means over small time intervals, to give a representative figure over a particular interval of time (for example, over the duration of the cardiac cycle). An example would be `v', the `average mean' linear velocity of flow. Linear velocity varies continuously in different parts of the circulation at different time intervals. The value of `v' is a representative figure taken over the whole of the circulation and the whole of the cardiac cycle, which ignores these individual variations, but is still adequate for the calculation of the `average mean' momentum in the circulation. Nevertheless, the linear velocity will be greater during systole than at diastole, and in the arteries compared with the capillaries or veins, but the overall linear velocity during the cardiac cycle, is an estimate of the velocity which each ml. of blood would require in order for the whole circulatory volume to make a complete circuit from ventricle to atrium in the `average mean' circulation time. The symbols may not represent readily ascertainable values, but they none the less have a `real' meaning, and represent `real' values, which can be used to determine variability in other parameters. It is the use of `average mean' figures which converts simple arithmetical calculations into algebraic ones, and produces the algebraic model, by comparing ratios of variables in one area, with similar ratios elsewhere.

The energy supplied by the circulation to the cell environment, is in the form of kinetic energy represented as momentum, but before the circulating fluid can acquire this momentum, energy has to be expended in overcoming resistance to flow. The latter can be represented as a `momentum equivalent' which has to be supplied to each ml. of blood to be moved, over and above the required momentum, before any movement is possible. The resistance increases as the linear velocity of flow increases, so that the energy supplied must be related to `v', `R', and `Vs', or linear velocity of flow, resistance per ml. per unit velocity, and the total volume of fluid moved. After the energy exchange with the active cells which occurs with each heart beat, equilibrium is achieved between the cells and circulating fluid at diastole, and the energy present in the extra-vascular fluid, then represents `free energy' in the form of both the temperature level and linear velocity of flow, with the momentum present depending on the fluid volume and linear velocity, after supplying the energy necessary to overcome resistance to flow in the venous system; i.e.,`V venous. v venous. R venous'. The relationship with the total energy supplied will vary with the prevailing temperature, which in turn adjusts the size of the capillary bed, and so the `length' of the circulation, which changes with alteration of temperature. The relationship between the momentum supplied to the blood by the heart (Vs.v), and that present in the venous return as the blood re-enters the heart, then depends on circulatory length (affected by temperature and the effect on the total size of the capillary bed) so that `V venous'. `v venous' is proportional to `Vs.v / l'.
`Circulatory length' is then related to `free energy level', and momentum in the venous blood can only be maintained if circulatory momentum is increased proportionally with circulatory length. For the circulation to continue, `V venous . v venous' is equal to `Q . PR', the stroke volume depending on maintenance of `V venous', while the pulse rate needs to be related to the linear velocity of venous blood as it enters the heart at diastole.

The heart receives blood with momentum `V venous. v venous' (or `Q.PR'), and has to supply blood to the systemic circulation (after passage through the pulmonary circuit) which is proportional to `Q.PR.l', and the energy supplied must be increased by a factor proportional to `l', the circulatory length (which is also proportional to the `free energy' required in the system and the cells). The circulatory length is important, not only for the `free energy' level maintained, but also for the energy `stored', and for the energy `exchanged', and the total energy required then becomes proportional to `l cubed'.

In addition to the momentum necessary in venous blood to maintain the circulation, the venous return also contains increased metabolites, and altered gas concentrations, which each have an individual influence on the form of energy supplied by ventricular contraction.

The relationship between `circulatory length' on the one hand, and the diastolic length of the ventricular muscle fibres on the other, becomes the basis for the determination of ventricular muscle efficiency, in the sense that one indicates the work required from contraction of the muscle in maintaining the circulation, and the other, the energy which needs to be produced to achieve and maintain this level of ventricular work.

For this reason, a given level of ventricular efficiency becomes an important consideration in maintaining an adequate balance between cellular and circulatory activity, and therefore needs to be examined in some further detail, commencing with the relationship between venous return, linear velocity of flow, and pulse rate, which is fundamental in determining the required work level for ventricular muscle.

These relationships are more readily comprehended in terms of the algebraic model of the circulation, which involves the dynamics of the moving fluid, and is developed in succeeding chapters. The method adopted is to examine and analyse the familiar aspects of cardio-vascular function as illustrated above, and by finding common or related parameters, to relate one aspect of activity with another until a complete algebraic model of cardio-vascular function has been developed. Using the same methods, the model is then extended to extra-vascular fluid and the cell membrane, and to relate the findings to the cell activities, functions or metabolism, through common features with the surrounding fluid, and the exchange of similar amounts of energy or volumes of fluid with time.

The succeeding chapters outline the application of these methods, firstly to cardio-vascular function, extending later to the other areas, to produce a complete model of fluid and energy exchange between fluid compartments.

Summary.

> *The prevailing temperature indicates the level of `free energy' present in a particular area of the body, but energy is also present as `stored energy', or manifested as `energy exchange' with the environment. These three elements representing the necessary energy level, requires a functional balance across the cell membrane, which relates cell energy with circulatory energy, and that*

provided by ventricular contraction. Energy from metabolism of ventricular muscle cells must be directed in three different ways by the contraction; towards storage of potential energy, fluid or energy exchange, and linear velocity or momentum. It may be accomplished by alteration of the size and/or shape of the ventricle at diastole, which directs the released energy towards a particular mix of functions and muscle fibre lengths as may be necessary. In this way a balance is maintained between cellular and myocardial functions which coordinates their activities. The development of ratios and expressions which govern the activities of both myocardial and peripheral cells, leads to the `algebraic model'.