

## CHAPTER 27.

## CONCLUSION.

The most striking feature of the current examination of circulatory and renal physiology, is the emphasis which it places on the kinetic energy of flow, rather than the static concept of energy represented by pressure differences. In the overall picture of the circulation which emerges, energy is depicted as velocity and momentum, rather than in the more conventional pressure relationships which are more readily observed. For in the opinion of the author, the concept of the circulation is one of motion, a pattern of related velocities, which between them produce the conditions necessary for the continued existence of the whole organism. This is nowhere more noticeable than in the manner in which the continual motion of the fluid in the extra-cellular extra-vascular compartment, together with its significance for overall circulatory function, is conceived.

The most novel and interesting feature of William Harvey's view of the circulation, was that it focussed attention squarely on movement of the blood from one part of the circulation, the heart, continuously forward, until having traversed the arteries and veins in all sections of the body, it arrived once more at its original position. The concept of a constant internal environment put forward by Claude Bernard, was a startling innovation, which captured the imagination, and set the scene for the expansion of physiological chemistry which followed. Nevertheless it had one unfortunate consequence, in that it seemed to favour the somewhat static view of "normal levels" of the constituents of body fluids, as representing ends in themselves. Although it is in no way inherent in Bernard's conception, the internal environment came to be regarded as a rather stagnant pool of constant composition, maintained by minimal inflow and outflow of fluid, in which the body cells were suspended somewhat after the manner of bacteria in a liquid medium.

The present view is conceived as emphasising the Harveian concept with its concentration on the idea of motion. It represents the extra-vascular compartment as a vital section of the circulation, by means of which a considerable part of the kinetic energy of the circulation effectively bypasses the increased resistance presented by the capillary network, and allows the energy and the fluid (in which the energy is represented by motion) to transfer to the venous system in a relatively unhindered manner. The constancy of the internal environment is then seen as the result of the balance brought about by this transfer of energy, which determines the volume, velocity, and constitution of the fluid in the extra-vascular compartment.

The 'constancy' of the internal environment however, is only relative, its constituents varying with the level of cell activity, and the energy provided in the extra-vascular fluid, to balance that developed and maintained within the 'effector' cells. It is the activity of these cells, and the amount of energy development they initiate, which determines the overall energy levels within the body, as indicated by the observed body temperature. The volume and physical and chemical properties of the extra-vascular fluid is a reflection of the amount and nature of effector cell activity, and the circulatory response is required to be sufficient to balance it, and maintain the appropriate cell environment. The energy made available by effector cell activity, produces

movement of fluid within the body, and between its various compartments, and constitutes the basis for circulatory function. The latter commences with the movement of fluid and energy across the cell membrane; i.e., it results from the movement of a volume of fluid (related to blood viscosity and the stroke volume) at a particular linear velocity of flow. The basic circulatory parameters are those involving the kinetic energy which becomes available, and which can be quantified as momentum and linear velocity of flow, or those aspects of the circulation which Harvey perceived as its essential characteristics.

In other words, cell activity needs to result in movement of extra-vascular fluid commensurate with the level of momentum, and linear velocity of flow originating from energy production within the cell. Equating the energy balance between the cell and extra-vascular fluid, provides a basis for estimating the amount of energy required in each area, and this has been exploited to produce an algebraic model to describe the function required of the circulation as cell activity varies with time, and with the changing requirements for particular functions.

Cell activity produces energy related to three particular functions. The first is exchange of fluid and energy with the cell environment. Because it involves the amount of fluid exchanged, there is both a volume and a velocity component, which is related to cardiac output, and the latter becomes a measure of the exchange for all cells.

Secondly, the energy related to linear velocity of flow in the extra-vascular fluid, needs to be such that it balances the level of 'free energy' present in the 'effector cells', and measured by the temperature at which they are maintained.

Thirdly, any energy produced in excess of these requirements, can be 'stored' in appropriate areas until required for further use (e.g., in performing external work such as muscle contraction or gland secretion) but to maintain the 'store' requires extra energy in the circulation, which can be represented as 'momentum equivalent' (or the product of the volume involved and the resistance offered to unit volume at unit linear velocity, such as ' $V_s.R$ ', or vascular filling).

The product of 'energy exchange' and 'energy store' with systemic vascular volume represents the 'peripheral resistance' the circulation must overcome, before it can provide a sufficient volume flow for fluid and energy exchange with the cells. This product is directly proportional to the peak systolic pressure for a particular circulation, and the ratio between ' $v.R$ ' and the systolic pressure is one representation of the circulatory ratio.

The total amount of energy available within the cells, is the product of the energy for each of these functions, viz., the 'fluid volume exchange', the 'free energy', and the 'energy store'. This is balanced by the energy of ventricular contraction, and is directly proportional to ' $Q.R.l.PR$ ', though the composition and direction of application of the energy depends on the individual values of ' $Q$ ', ' $R$ ', and ' $l.PR$ '. The volume exchange, or ' $Q$ ', is directly proportional to ' $[CO_2].l$ '; the 'energy store' is proportional to ' $[O_2].\eta.l$ '; while the 'free energy' level depends on circulatory length and pulse rate,(or  $L.PR$ ).

For the 'effector cell', the relevant parameters for energy maintenance are ' $[CO_2]$ ', ' $[O_2]$ ', 'PR', '[lactate]', and the energy available from glycolysis, while for the cardio-vascular response, the corresponding values are ' $[CO_2]$ ', ' $[O_2]$ ', 'PR', ' $\eta$ ', and '(l cubed)'. Equivalence or balance between the two areas then depends on equivalence between '[lactate]' times a 'fraction representing free energy available within the cell', and ' $\eta$ .(l cubed)'. Maintenance of this balance becomes an essential feature of the circulatory response; any significant imbalance between the two resulting in functional disturbance, and if excessive or prolonged, it leads to functional disorder, or even to pathological states.

By pursuing further analysis of these relationships it is possible to formulate energy equivalents between variables, and this becomes possible because of two relationships or 'principles' which are seen as fundamental to circulatory function, and may be expressed as the 'Circulatory ratio' which governs relative circulatory size, and the 'Principle of Energy Equivalents', which relates the various parameters governing circulatory function depending on the contribution each makes to the energy produced or available for a particular purpose.

The circulatory ratio can be represented as the ratio of stroke volume and the volume of the circulation to which the stroke volume is added at systole, and from which it is withdrawn to produce ventricular filling at diastole, and it is a characteristic which becomes related to the particular 'size' of the circulation in question. It can also be depicted as a velocity ratio between linear velocity of flow, pulse rate and circulatory length, or as a pressure ratio between peripheral resistance per unit circulatory volume in the systemic circulation, and peak systolic pressure, or again as a time ratio between the duration of the cardiac cycle, and the mean circulation time. These ratios have values which are directly proportional to each other, and they are 'equivalent' to each other in terms of energy development and maintenance. By equating them with each other, each parameter may be expressed in terms of the other parameters for circulatory function, and this represents an underlying relationship between all such parameters encountered. It is the basis for the 'Principle of Energy Equivalents", which allows each parameter to be expressed as 'equivalent' in terms of energy to another or a combination of other parameters, which can then be manipulated to produce an 'algebraic' model of the circulation.

The important condition governing the circulatory ratio, and the Principle of Energy Equivalents is circulatory 'size'. In this context 'size' includes not only the circulatory volume, but also the 'shape' of the circulation in which the volume is contained, i.e., the relative length as opposed to the diameter of the containing vessels. Circulations of the same volume, but different 'shapes' have different characteristics for fluid circulation, insofar as the same amount of energy will produce different volume flows, and different linear velocity of flow in circulations of different dimensions (length and cross-sectional areas) although they are each of the same volume. Alteration of circulatory shape may then require change in the level of energy required to maintain that circulation; it will require some variation in the energy developed by the ventricle to maintain the same overall flow characteristics.

The problem is overcome by allowing ventricular 'shape' and diastolic fibre length, to vary with respect to ventricular volume, enabling energy to be differently applied as the shape varies in response to alteration of stroke volume, pulse rate, circulatory length, and the resistance to be overcome in the blood vessels and beyond. These changes are reflected in changed 'contractility' of ventricular muscle, involving altered 'inotropic state', 'active state', and 'energy transfer' from the contraction of the ventricular wall, to the fluid contents of the ventricle.

These concepts are combined in the 'Law of Ventricular Efficiency', specifying those parameters which together maintain ventricular efficiency, and requires lactate concentration to remain in proportion to the ratio 'cube of circulatory length' with the 'fraction of energy attributable to stroke volume', the latter balancing the 'apparent viscosity' or 'internal resistance to flow' of the circulating blood, so that ventricular activity remains optimal to balance the energy output of the 'effector cells'. Using these relationships as a basis, the energy exchange together with the volumes of the fluid compartments of the body, enable the regulation of the appropriate venous return. The filling conditions for the heart chambers, and the volume and pressure relationships between the pulmonary and systemic circulations are in turn determined by the venous return.

These parameters are modified by a certain amount of backflow in the inferior vena cava at atrial systole, which has the effect of regulating ambient liver temperature, and consequently its level of metabolic activity. This is perceived as an important regulator of gluconeogenesis from lactate. Its part in the control of blood lactate level, has significance for the lactate / circulatory length ratio, and circulatory function. The relationship between blood lactate concentration and circulatory length becomes necessary to 'balance' the increase in effector cell energy production when these cells become more active, and the production of lactate increases. Momentum in the extra-vascular circulation must be increased to 'balance' the increase in cell energy, with increased extra-vascular volume, and capillary filling. Capillary filling increases as  $l^3 \eta [CO_2, O_2]$ , while increased momentum requires increased ventricular energy output, and the latter occurs when [lactate] increases in coronary blood to produce the extra energy required as 'vascular filling' when circulatory length increases in the effector organs. Increased circulatory length in the core organs, and/or the integument, also requires increased energy in the circulation, but the extra cardiac energy then occurs from increased metabolism of short chain fatty acids, or derivatives, rather than from lactate, which tends to be diverted instead to gluconeogenesis. Because the relative levels of  $[CO_2]$  and [lactate] are reduced with fat metabolism, so are 'stroke volume', 'venous return', and the ability for 'work' by the effector organs, each of which can only be maintained by increased lactate production, and plasma concentration.

The 'power' which ventricular contraction must produce to maintain adequate momentum for fluid and energy exchange with 'effector cells', is indicated by the systolic blood pressure, and the pulse rate, and is related to the 'energy store' which the cell must maintain to ensure an adequate level of function. In order to increase the 'energy store', both local oxygen load, and circulatory length need to be increased, and so does the 'free energy' level in the cell (l.PR). In other words, an increase in systolic blood pressure (R.l.PR), and peripheral resistance (v.R.O).

Any reduction in these values implies a reduction in oxygen load required to maintain oxidative metabolism, and energy production, while the circulatory length and the pulse rate must also be limited.

The functional capacity of the oxidative enzymes must be optimal, otherwise both  $[O_2]$  and  $l^2 \cdot PR$  will increase. Limitation of both these parameters are necessary to limit systolic blood pressure, and the momentum of the extra-vascular fluid needed to accomplish fluid exchange with the cells. The concentrations of oxygen and lactate are both important for oxidative metabolism, and also for the permeability of the cell membrane. Some significant phenomena arise as a result of the importance of the tissue concentration of oxygen, and of the lactate/circulatory length ratio in blood pressure maintenance.

Metabolic considerations lead to the concept of 'lactate tolerance', and a tolerance test for administered lactate, can provide significant information regarding the elevation of blood pressure which can be observed in some individuals. The test is not without some inherent danger, and its place can be taken by calculating a simple ratio between systolic pressure and pulse rate which can be used to determine whether the blood pressure is elevated because of elevated oxygen partial pressure (and 'R') or because of elevated pulse rate, i.e., because of extra 'energy storage', or because of elevated 'free energy' within the cells. In either case, blood pressure may be reduced if the capacity for oxidative metabolism is increased, so that  $[CO_2]$  increases with respect to oxygen concentration and/or pulse rate, as the case may be. The ratios of  $[CO_2]/[O_2]$ , and of  $[lactate]/l^2 \cdot \eta$  are those of greatest significance for blood pressure maintenance, and are considered of such importance, that their influence in producing well known syndromes, or combinations of disturbed function, have been pursued in two chapters which examine each ratio, and its effect on the circulatory response.

This interpretation puts emphasis on momentum and linear velocity of flow, i.e., not only movement of fluid but also the rate of movement of fluid in the body. On the one hand the volume of fluid moved, and on the other the linear velocity of flow, are both important in determining the amount of the required motion, and the amount of energy which must be provided to produce it. The relative rate of movement between different fluid 'compartments' gives rise to balanced volume and pressure differences between these particular areas, depending on the rate at which energy is developed, which in turn affects the purpose or use to which that energy is directed. The rate of energy development or release is the 'power' available, and the chemical reactions and physical changes in a particular tissue will ultimately depend on the available power. As power alters, some activities are favoured over others for each particular power level. For example, when the power is increased, the movement of fluid between different areas may be greater, and the capacity for the performance of external physical work may be relatively less, while a reduction in the power provided, may decrease fluid movement, but favour the more efficient accomplishment of external work, by varying the ratio of 'internal' to 'external' work performed at a particular energy level.

The implication is that the composition of the internal environment depends on those chemical reactions which are most favoured by the energy levels persisting in the cells and the cell environment, and which is regulated in turn by the energy level maintained within the intra-vascular compartment by contraction of the heart on the one hand, and on the other, by the 'momentum equivalent' required to overcome circulatory resistance to flow of fluid into and out of the cells, and other fluid compartments.

The chemical reactions which proceed most readily at any particular energy level will depend on the activity and concentrations of the enzymes which are necessary for those particular reactions to occur at the required rate. If the available energy level is varied, the relative rates of different chemical reactions will also vary, leading to alteration in the concentration of substrates on which they depend, and the metabolites they produce, with a different balance of composition of the immediate chemical environment. If the energy level leads to variation not only of the chemical concentrations of the relevant substances, but also the permeability of membranes to water and its contained solutes, the balance of concentrations in the fluid environment will also be altered, and its final composition come to depend on the energy level which is available in the area. The physical basis of homeostasis, or control of the internal environment, then lies in the energy level which is provided by the interaction of the activity of cells and the circulating fluid in which the cells are immersed.

The algebraic model which has been employed to explain the functional activity of the circulation, would seem to indicate that a major mechanical activity of the heart and intra-vascular circulation, is to maintain a level of momentum in the extra-vascular fluid, which is adequate to maintain energy balance, fluid and energy exchange, and the 'energy storage' facility in the 'effector' cells (i.e., muscle, nerve, and glandular tissue) commensurate with their level of activity and metabolic capacity, and still allow the internal constitution and functional activity of the cells to be maintained. It is this balance between the activity of the cells and the cardiovascular system which determines the level of momentum required in the extra-vascular fluid, and the systolic blood pressure is an indication of the ventricular work required to maintain that level for a given stroke volume. In the algebraic model, the linear velocity of flow of the extra-vascular fluid is determined by intra-vascular volume (proportional to stroke volume for a particular value of the circulatory ratio), while the volume of the extra-vascular fluid is a function of linear velocity of flow of blood in the intra-vascular circulation (and so of the force of contraction of the ventricle). The momentum of extra-vascular fluid is the product of its linear velocity of flow, and the mass of fluid which is moved (represented by the volume of the extra-vascular fluid, if its density remains reasonably constant). While the stroke volume remains stable, the momentum is then directly related to the volume of the extra-vascular fluid. The amount of energy exchanged with the cells, together with the level of energy storage, and the balance of 'free' energy present in the cell to maintain its vital processes, are all dependent on the volume of the extra-vascular fluid, 'V<sub>x</sub>', and directly related to the linear velocity of flow of the blood within the vessels, while the volume of the fluid exchanged with the cells is related to the linear velocity of flow in the extra-vascular compartment, which depends on circulatory volume and the stroke volume of the ventricle.

The activity of the ventricle is varied by the size of each of the elements for which it has to provide the energy (viz., intra-vascular, extra-vascular, and cellular momentum, and fluid exchange). The total energy it furnishes to the circulation per beat, is the product of these three factors, each of which results from a different physical dimension of the ventricular cavity at diastole. In this way, not only the size, but also the shape of the ventricle has significance for the level of energy the subsequent contraction provides, as well as the form the energy takes (stroke volume, force of contraction and linear velocity of flow, and the momentum equivalent required to overcome the 'resistance' to flow, and 'storage' of energy in the cells, which resists the exchange of energy with the intra-cellular compartment).

The situation begins with activity occurring in the 'effector' tissues, which in turn requires increased metabolism, and ultimately increased oxidation processes. The facility with which the oxidative enzymes can use oxygen and produce carbon dioxide, is reflected in the partial pressures of these gases which are maintained locally, and in the other metabolites which are produced, e.g. whether there is an increase in glycolytic products as opposed to metabolites produced by oxidation. All of these substances, but particularly  $[O_2]$  and  $[CO_2]$ , have profound effects on the circulation locally, and if sufficiently widespread in their variations, they produce general effects, influencing the value of the stroke volume, blood volume, and resistance per unit velocity in the circulation. Together with the main variable influencing the release of energy by the left ventricle (I.PR), they are responsible for the variations in the ratio 'v/R', and this ratio in turn regulates the volume and velocity of extra-vascular fluid. In addition, the relationship of the stroke volume to  $[CO_2]$ , means a relationship between stroke volume and the alkali reserve, and between stroke volume and salt and water balance in the body. By means of these relationships, and the general relationships which have been indicated between general metabolism and the intra-vascular circulation, a dynamic balance is maintained which in turn provides a constant but flexible internal environment, responsive to general body needs. Similar considerations can be invoked to relate the composition and volume of the extra-vascular fluid to the activity of the kidneys. By these means the constancy of the internal environment which is maintained, can be seen to result from the balance of energy exchanges which relate the extra-vascular compartment to the remainder of the circulation.

Concentration on the importance of velocity as representing the concept of motion, leads to a change in the manner of thinking about pressure, and particularly about the pressure which resists motion in a system, and which is then called 'resistance'. This pressure consists of an element representing velocity, and also one representing 'resistance per unit velocity'. This separation gives the two elements 'v' and 'R', and the relationship between these two, plays an important role in relating blood pressure with motion in the circulation.

By representing the systolic arterial pressure as 'R.IPR', and pulse pressure as 'D.v.IPR/2', relationships become apparent which were not obvious previously, particularly between 'v' and 'R'. At the same time, the ratio between diastolic and systolic blood pressures can be expressed as a ratio of velocities, and similar ratios are involved which relate diastolic blood pressure to the mechanical efficiency of the ventricle, in the expression which has been named the 'Law of

Ventricular Efficiency'. This expression has very great significance for the determination of current levels of blood pressure as they exist for each individual.

The basis for this relationship is the ratio of left ventricular stroke volume, and the volume of the systemic circulation. Because of its close relationship with the values of the partial pressures of the metabolic gases ( $[O_2]$ ,  $[CO_2]$ ), which reflect the capacity for oxidation demonstrated by the active tissues, this ratio ( $Q/V_s$ ) is seen to pervade the whole energy structure of the heart and circulation. Closely associated with cardiac efficiency are the venous pressures, both pulmonary and systemic, and while the control of the former is seen as essential for efficient left ventricular function, the value of the systemic venous pressure has a part to play in regulating liver temperature and metabolism. Of particular interest is the effect which may be produced secondarily upon glyconeogenesis, a function which is of considerable significance when oxidative processes lag behind glycolysis in the immediate production of energy. The 'Lactate Tolerance Test' was introduced to demonstrate the effects this might have on blood pressure maintenance.

In an analysis of ventricular function, the role of stroke volume, resistance offered by the circulation per unit velocity, the functional length of the circulation, and the pulse rate are all shown to have a role. The relationships between these elements are examined to indicate the way in which arterial volume is influenced by the ratio of 'R' and 'I.PR', and the importance of this ratio for clinical hypertension. The manner in which these variables relate to each other during reaction to circulatory stress is briefly examined in the light of the relationships which have been developed. The conclusions which appear, particularly for pregnancy, as also the concept of raised blood pressure as an adaptation to delay the onset of ventricular failure, following difficulty in maintaining an adequate stroke volume, could prove enlightening.

The kidney is regarded as a special case or adaptation of the extra-vascular circulation, where the whole of the extra-vascular fluid is confined within the renal tubule for much of the time it is outside the vascular system. Although the renal glomerular filtrate (extra-vascular fluid) is subject to the same energy exchanges as the extra-vascular fluid elsewhere, the exchanges are modified by two further mechanisms to vary the linear velocity of fluid flow along the tubule. These are the renal nerve supply, and the relationship which regulates glomerular with tubular function for the production of urine.

This relationship was the subject of a special investigation which is reported for the first time in any detail, and is considered important for the regulation of salt and water excretion. The relationship has been named 'The Law of the Nephron', because of the variations it is able to impose on the energy exchanges of the extra-vascular fluid within the kidney. In examining the circulation in this fashion, two important flow regulators are seen in a different light. The arterioles have been primarily considered to control the level of blood pressure, and they do this by controlling the outflow of blood from the arterial system. Looked at from the point of view of flow energy, the arterioles control the volume of blood flowing to a particular area, but also the amount and form of the energy which accompanies it. On one side there is a large supply of

potential energy in the form of pressure, and on the other the energy is mostly in the form of kinetic energy appearing as linear velocity of flow. The arterioles control both the volume flow to a particular region, and also the amount of energy it is given. By controlling the linear velocity of flow, they also control the lateral pressure exerted on the vessel walls, which must be limited if vascular damage is to be avoided. In addition, blood leaving the arterioles is approaching a series of even smaller vessels, and as each unit volume of blood has a certain amount of energy (currently mostly kinetic), when it enters the capillary and the resistance to flow increases, this will slow down the blood and the energy will appear as pressure on the capillary walls, unless a mechanism is present which can remove energy quickly and without much pressure increase.

The mechanism employed is that involving the plasma proteins, which combine with the permeability of the capillary wall, to allow a certain portion of the blood fluid to pass to the extra-vascular compartment, complete with kinetic energy, but retaining sufficient fluid and remaining energy within the capillary to maintain the circulation, even though the velocity (and so resistance to flow) is greatly reduced, while the lateral pressure on the capillary walls does not become a problem for its continued integrity. This internal control mechanism for diversion of flow without excessive loss of energy during capillary passage, allows the energy to re-enter the capillary at the 'venous end', and the virtue of this mechanism was first perceived by Starling (1899). It represents the method for production of extra-vascular fluid both in the general circulation and in the special circulation of the kidney.

The ideas expressed in the foregoing pages, provide a possible physico-mechanical basis for the maintenance of the function of homeostasis in the internal environment of the body. As such it focusses attention on the constancy which results from the algebraic sum of continuing variations in bodily activity, and which is largely coordinated by these physico-mechanical factors. Regarded in this light, the level of blood pressure which is maintained is a reflection of the manner in which these mechanisms are functioning, and as such it indicates the adequacy or otherwise of the extra-vascular circulation in its role of homeostasis, both generally, and in the special circumstances occurring within the kidney.

The initiating factor in the generation of these reactions, is the metabolic activity of the functioning tissues, and this activity is responsible both for the variations occurring in the internal environment, and for the responses which occur to balance their effects. In the 'effector organs' (voluntary muscle, nerve tissue, and the main body of glands of external secretion) the alteration of cellular activity which gives rise to observable external effects such as muscle contraction, nerve conduction, or glandular secretion, begins with an adequate stimulus of a mechanical, chemical or electrical nature. An adequate stimulus is one which causes the polarisation of the cell membrane to alter or break down completely, and in the latter case, to spread in a wave like motion over the whole of the cell surface. Accompanying this wave of depolarisation is a change in permeability of the membrane, leading to destabilisation of the fluid volume and energy balance which characterises the resting cell, and allowing transfer of fluid and contained kinetic energy from one side of the membrane to the other. This transfer may be minimal and confined simply to the transfer of ions across the membrane in the case of nerve tissue, or it may involve larger transfers of fluid and energy with resulting changes in the volume

and shape of the cell, in the case of contractile or secretory organs. The metabolic activity which follows, produces the energy necessary to restore the polarisation of the cell membrane, together with the energy, volume, and shape of the cell in its 'resting state'.

The observable activity or 'external work' which the cell performs, depends largely on the magnitude of the fluid volume and energy which is transferred to the extra-vascular compartment. Together with the fluid loss, energy is permanently lost to the cell, and appears in the system in some other form. Some appears as force of contraction available to do external work in the case of muscle, and some will appear as heat produced by internal friction between the contractile proteins and other cell constituents, but much is available to increase momentum in the extra-vascular compartment, for later transfer to the venous blood in the intra-vascular compartment, where it augments the venous return. Restoration of the cell to its 'resting state' requires energy from two sources. The extended form of the contractile protein elements can only be sustained by an adequate level of high energy level phosphate bonds (eventually ATP) which is produced by the metabolic activity of the cell, finally involving the activity of the oxidative enzymes. In addition, fluid volume and kinetic energy of flow must be returned to the cell from the extra-vascular fluid, and retained there by the repolarised membrane. Energy is returned to the cell from the momentum present in the extra-vascular compartment, which is provided in turn by contraction of the left ventricle. The 'resting' muscle cell then contains a 'store' of energy, part of which is originally supplied by flow energy from ventricular contraction, and retained in the cell by an adequate level of high energy bonds, until such time as changed cell permeability allows these bonds to be ruptured, so that energy is released, partly in the form of external work as the muscle contracts, but also partly to increase fluid volume and momentum in the extra-vascular compartment, and ultimately to increase the venous return from the area. In this fashion, there exists a 'store' of energy which is available to boost kinetic energy and the venous return whenever the cell becomes active following an adequate stimulus. The mechanical activity on which the circulatory system depends, has its foundation in the level of momentum maintained in the extra-vascular compartment, and the exchanges which occur between the vessels and tissue cells, based on the 'permeability' of capillaries and cell membranes, and the mechanisms which regulate this 'permeability'.

The 'permeability' of the effector cells is a basic concept, both regarding the part it plays in the contractile process, and also for its importance in maintaining the 'resting' or non-contractile state. The factors which determine it are doubtless complex, but for descriptive purposes it can be considered as having two basic aspects, designated 'passive' and 'active' in the current account. "Passive permeability" is regarded as reflecting the inherent properties of the cell membrane, affected partly by its structure, which is inherited according to the genetic code, but also subject to the variability of the physical forces resulting from changes in cell volume, producing internal strains or stretching, which distort the crystal lattice by inducing stresses in the same plane as the membrane itself. Any variation in passive permeability is regarded as resulting primarily from the application of these physical forces and/or from changes in the chemical environment presented to the external cell surface, and allowing fluid and energy to move into the cell. "Active permeability" on the other hand is regarded as representing any alteration in permeability which might follow changes in the chemical environment within the

cell, which is produced by metabolic processes, and which results in changes in the energy level contained therein, with subsequent changes in the physical forces acting at right angles to the plane of the membrane, so that fluid and energy move out of the cell. Changes in active permeability reflect the metabolic activity of the cell at the time of observation. It would ordinarily be difficult to separate the individual effects of variation of these two forms of permeability. Cell volume and cell metabolism both vary continuously, and both affect the resultant permeability. But in the kidney, by a fortunate circumstance, 'active permeability' varies in a linear fashion, while 'passive permeability', resulting from stretching forces in the cell membrane, can, at least on some occasions, appear as quantum jumps from one level of permeability to another. This allows the separation of the metabolic aspects of permeability from the physical aspects, which follow changes in the volume and shape of the tubule cells, and it is this separation which permits the results on sodium reabsorption and oxygen consumption on which 'The Law of the Nephron' is based.

As the stability of the internal environment remains an essential condition for the continued existence of the organism, an adequate understanding of these mechanisms is a vital prerequisite for anyone contemplating the therapeutic interference which might become necessary to preserve that continued existence. Because it might prove of assistance to any who would wish to understand these processes more fully, the implications of the author's views have been included in general terms.

The main thesis which this examination of the extra-vascular circulation proposes, is that the constitution of the internal environment depends primarily upon the linear velocity of the fluid in the extra-vascular compartment. This velocity, together with the linear velocity of fluid in the intra-vascular compartment, is varied in response to the metabolism of the active tissues, which interact with the surrounding extra-vascular fluid, according to the principles which have been set out. Variations of blood pressure are also involved, depending on the ratio of ' $v/l.PR$ ' (which determines the level of diastolic pressure required to maintain left ventricular efficiency), and on the ratio ' $v/R$ ' or ' $PPs/D.APs$ ', for the systolic and pulse pressures, in the manner which has also been described.

A similar principle applies to the special 'compartment' of extra-vascular fluid within the renal tubules, where the constitution of the intra-tubular fluid varies from that of the extra-vascular fluid generally, depending on the ratio of ' $v_t/v_x$ '. This ratio can be varied by special mechanisms within the kidney, so that the constitution of the intra-tubular fluid increasingly deviates from that of the remainder of the extra-vascular fluid, until it is eventually excreted as urine. The mechanism which plays a major role in varying the ratio ' $v_t/v_x$ ' is that which has been outlined as "The Law of the Nephron", so called for this reason. If the value of ' $v_t$ ' approaches that of ' $v_x$ ' throughout the course of the renal tubule, the composition of urine comes closer to that of the extra-vascular fluid, but as ' $v_t$ ' decreases, the volume of urine and its composition is varied accordingly, and deviates in greater degree from the composition of protein free plasma.

Oxygen concentration in the effector cells is kept at a constant value under ordinary circumstances. Increase in oxygen load and lactate concentration does not increase oxygen

concentration if it is possible to increase oxidation energy (i.e., L) instead, with development of hypertension as the alternative, the more usual result of increased oxygen load. But if 'L' cannot be increased, or if it is decreased, cell oxygen concentration, and cell volume may increase leading to neoplasia (i.e., increase in cell divisions, and a reduction in active state). If oxygen load is reduced with reduced lactate concentration, then carbon dioxide load needs to increase with increase in carbon dioxide concentration leading to the onset of an asthma attack. Asthma occurs when there is reduced lactate concentration and oxygen concentration with increase in carbon dioxide concentration to maintain the value of 'L', or oxidation energy, at an adequate level.

Circulatory dynamics is regulated by the concentrations of the respiratory gases oxygen and carbon dioxide. Oxygen concentration is dependent on the oxygen provided from the atmosphere, while carbon dioxide is derived from metabolic activity, partly from oxidation of carbon, and partly from glycolysis of carbohydrate available from foodstuffs, to produce [lactate] (circulatory oxygen load) carbon dioxide load (momentum of extra-vascular fluid and elevated cell temperature) & allowing a rise in circulatory energy, part of which then becomes available to promote the resynthesis of glycogen from accumulation of these metabolic products when their concentrations are elevated sufficiently as a result of accumulation from both oxidation and glycolysis. Glyconeogenesis becomes an essential element to limit circulatory activity when the available energy is increasing with the rising kinetic energy of flow either by increased oxidation, or excessive glycolysis, both of which must be limited as carbon dioxide concentration accumulates, compared with that of lactate.

Accumulation of energy may be as a result of either oxidation or glycolysis, and the total kinetic energy is the product of energy from oxidation and glycolysis, but limited by resynthesis of glycogen (i.e., permanently stored energy in liver and kidney cells). (see Figures 8.9 & 8.10). The permissible limit of mechanical energy is that available as 'augmented stroke volume'  $\propto Q.v.PR$ , and any excess energy beyond this limit then appears as 'cell heat', or 'free energy' that is then absorbed into glyconeogenesis, after suitable provision has been made for 'genetic activity' from the rise in cell temperature.

Oxidation energy  $\propto R.PR^3$ , while glycolytic energy is  $\propto L.PR^3$ , and the ratio between them is  $\propto L.[O_2]$  equivalent to lactate concentration or 'oxygen load',  $R.PR^3 \propto v.PR^2$ , or  $Q.v.PR$  when one factor of PR is converted to Q by the factor of  $[O_2]$  as it is converted by passage from tissue fluid to venous blood.  $L.PR^3$  times  $L.[O_2]$  likewise becomes  $R.Q.PR^2$  or  $v.Q.PR$  by crossing the capillary membrane, so oxidation energy and glycolytic energy become equivalent, and kinetic energy becomes  $R.L.PR^6$  after glyconeogenesis removes excess lactate and carbon dioxide and free energy from the system

It becomes desirable to separate the effects of oxidation energy from those of glycolysis because oxidation energy reflects energy related to 'R' or stored energy, while glycolytic energy is related to 'L' or 'free' energy (heat), so oxidation energy reflects mechanical energy, and oxygen

usage, while glycolytic energy reflects heat energy, and cell 'genetic energy'(L.PR), including momentum of tissue fluid, without any effect from oxygen, which would increase 'v' or R.PR instead. Increase in genetic activity requires heat energy while oxidation energy is available for mechanical activity rather than heat energy, and activity of genes ceases in the absence of heat energy produced from glycolysis alone. As heat energy is reduced, energy in the cell is restricted to increasing cell volume rather than heat, and neoplastic activity rather than genetic function.

Oxidation energy is related to multiples of 'L', and involves both oxygen and carbon dioxide concentrations, to provide mechanical energy from shortening of ventricular muscle fibres, as well as increase in carbon dioxide concentration with the increase in carbon dioxide concentration through combination with oxygen. Glycolysis releases carbon dioxide from disintegration of carbohydrate molecules, with release of energy, but without involvement of oxygen in the metabolic process as the molecules break down. Energy is released as metabolism progresses, and accumulates as heat available to accelerate chemical activity of other processes such as genetic activity, which would otherwise slow down and eventually cease unless it is produced from another source, in this case from glycolysis, in advance of the oxidative metabolism that usually follows. If stimulated by 'L.PR', rather than 'R' or ' $L^2$ ' representing cell stored energy from effector cells, the energy available is furnished as the square of 'L' if it is stored energy, when it is made available from the cell store, or 'R.L.vx'(i.e.;v)when it goes on to mechanical activity as 'L.PR', together with a further factor of 'L.PR' appearing as 'free energy' and momentum of tissue fluid, but coming from glycolysis on this occasion. The two together provide cell power, equivalent to 'R.PR.PR' which is the limit for development of mechanical energy(i.e.;'v.PR') with one factor of 'L.PR' appearing partly as heat because of the factor 'vx' or 'linear velocity of tissue fluid', indicating its origin from glycolysis rather than oxidation.

Energy from glycolysis is necessary to maintain genetic activity, by increase in 'vx', or linear velocity of tissue fluid, indicating concentration of carbon dioxide compared with that of oxygen, and this difference is transmitted to effector cells, and so to the ratio of gas concentrations, limiting oxygen concentration, but increasing carbon dioxide, and the energy difference between the cell contents, and tissue fluid, with fluid and energy passing between them, and restricting cell volume, but increasing cell energy as heat content, to maintain the exchange.

Oxidation energy appears as mechanical energy to maintain physical activity, while glycolytic energy increases cell temperature, and momentum of tissue fluid, overcoming the additional energy used in moving the oxygen load (i.e.; concentration of lactate, that then needs to be removed by conversion to glycogen, and increase in carbon dioxide load, or stroke volume) Interference with this energy distribution becomes the basis for neoplastic disorder which appears when glyconeogenesis is restricted, allowing increased oxygen concentration at the expense of carbon dioxide load, and increasing cell volume as the stroke volume is restricted.

The most important conclusion is that the dynamics of the circulation depends on only two variables, and these variables must regulate metabolic processes and energy development. The

variables are oxygen and carbon dioxide concentrations maintained in the effector tissues which control dynamics and so volumes and metabolic processes, regulated by the ratio of carbon dioxide concentration and that of oxygen, and equivalent to the ratio of carbon dioxide with oxygen cubed, if the concentration of oxygen is constant to maintain normal function. Although oxygen concentration remains constant for normal function, the oxygen load ( $L.[O_2]$ ) can still alter changing the mechanical efficiency of the circulation as 'L' alters but  $[O_2]$  remains constant (and  $[O_2]^3$  must also remain constant) while the only variable for normal function is the concentration of carbon dioxide, which regulates cell temperature, genetic, and functional activity, while oxygen concentration regulates cell volume and multiplication, and oxygen load increases the efficiency of ventricular contraction, as an alternative to changing oxygen concentration and effector cell volume.

The energy required in the circulation per beat is proportional to  $R^3 \times PR^6$  as power available, i.e.,  $L^6 \times PR^6$ , or  $L^2 \times PR^2$  in each of three dimensions at right angles. The power needs to be accurately sufficient in toto at each beat to ensure there is no difficulty or hold up with the accumulation or the resistance that needs to be overcome with each beat; i.e.,  $L^2$  for residual power and oxidation energy in each cardiac dimension, together with  $PR^2$  to produce  $(L \times PR)^6$ . It indicates a necessity for exactly  $L^2 \cdot PR^2$  per beat, or L.PR in kinetic energy, with L.PR in overcoming internal resistance to flow and heat provided as resistance is overcome. (It includes  $PR^3$  from oxidation as well as  $PR^3$  from glycolysis, and there has to be an exact balance if  $PR^2$  remains constant so that glycolysis and oxidation each provide the same energy per beat from oxidation and glycolysis to prevent circulatory disaster.

If they are not exactly the same there will be either excessive carbon dioxide or excessive oxygen which will accumulate as oxidation or glycolysis is progressively greater. Such levels are precluded by the Pasteur and Crabtree effects which prevent it. Otherwise an increase in carbon dioxide concentration destroys the local pH, or an increase in oxygen concentration may produce neoplasia if in sufficient amount, or an increase in glucose (or hyperglycaemia and so Type II diabetes) and becomes potentially destructive. An adequate level of these gases is essential if 'R .PR' is to maintain adequate linear velocity, or 'v', while 'v.PR' produces 'power' and 'v.PR<sup>2</sup>' gives augmented stroke volume, and effector cell 'energy store'.

Adequate power is proportional to  $v^3 \times PR^3$ , or v.PR in each of three physical dimensions in the ventricle, equivalent to  $R^3 \times PR^6$  when increased by  $PR^3$  from glycolysis producing  $v^3 \times PR^3$ , or total circulatory energy overall with  $R^3$  from oxidation, and  $PR^6$  (from oxidation and glycolysis which are accurately balanced).

Increased  $\frac{[O_2]}{[CO_2]}$  produces neoplasia, and  $\frac{[CO_2]}{[O_2]}$ , if excessive, produces increased pH which is difficult to survive without the likelihood of asthma and if prolonged, progressing to peripheral

failure. Eventual failure of functioning oxidising enzymes leads to either (1.) neoplasia (subacute oxygen poisoning) or (2.) Type II diabetes and circulatory failure, or if there is attempted patient adaptation, to essential hypertension with raised oxygen load and eventual heart failure.

These conditions can only be avoided by 1. Maintaining oxidation energy (preserving oxidation activity and prevention of subacute oxygen poisoning or neoplasia) or 2. Maintaining pulse rate at an adequate regulated beat (e.g. with a pacemaker) and avoidance of alteration of lactate concentration (oxygen load) and /or carbon dioxide load as long as possible to prevent cardiovascular failure.

Effector cell reproduction is proportional to oxygen concentration.. The key to cell activity is the provision of 'vx and 'L'( or cell reproduction times protein for cell function is proportional to ventricular diastolic fibre length). Genes require energy proportional to 'vx' as an overall energy source for functional activity and 'vx' operates as a main switch for 'functional' activity. Once energy proportional to vx is supplied to the cell, genetic activity is able to regulate the amount and 'direction' of energy given to any activity as genetic function. i.e., the amount of energy supplied, and the direction in which it acts for any particular function. The overall genetic key is 'vx'. And multiples of vx up to vx cubed, but the keys for specific function are genetic.

The specific genetic activity for each gene or group of genes gives specificity to cell and tissue function after 'vx' supplies the overall energy for cell 'function'. Each gene or group of genes acts as a switch (or group of switches) to direct energy to a specific 'function' of cell or tissue after 'vx' supplies the energy for cell function.

Oxygen from 'messenger RNA' transmits activity to an area of 'DNA' which 'fits' with the origin of DNA from which RNA originally appears and acts as a key to activity of the respective genes for 'structural' or 'anatomic' proteins which produce structural or anatomic changes to body bulk or size with increased size or number of body cells. The effect of the genetic code is to produce proteins under provision of instructions from DNA, activated by RNA to reproduce individual structural proteins, and become a continuing part of the body structure.

On the other hand, the essential 'function' of effector cell activity is to maintain provision of proteins required for the living state of cells to persist, and become involved in that persistence. Oxygen concentration is essential for both structural proteins and cell reproduction, while carbon dioxide concentration is essential for continuing cell function, or synthesis of 'functional' proteins. Cell function and cell reproduction are related both directly to maintain effector cell length, and inversely to maintain 'vx', or cell function. The relationship of structure and function all depends on the relationships of concentrations of carbon dioxide and oxygen.

Functional activity is improved with 'training' and this improvement is shown through reduced pulse rate, and so reduced pulse rate multiples, with physical training; i.e., increased mechanical efficiency leads to reduced pulse rate for a given activity, with reduced energy for a given level of activity, and reduced pulse rate for a particular protein synthesis (requiring less 'L.PR' ) as a

result, while reduced cell heat (i.e., temperature) becomes required for a fixed amount of functional protein synthesis.

It follows that if training is reduced or absent, pulse rate is increased and the increased efficiency that is otherwise present is lost again with increasing pulse rate, which becomes an indicator of relative functional efficiency for cell activity.

Increased provision of carbon dioxide concentration is then available from augmented stroke volume to maintain synthesis of 'functional protein', while increased oxygen concentration is needed for synthesis of structural protein which results from 'messenger RNA'. Increased oxygen concentration with  $vx^2$ , then produces  $\frac{PR}{[O_2]^2} \times [O_2]^2 \propto [CO_2]^2$ , or pulse rate, which indicates

structural protein production, and increased body bulk as pulse rate, and 'R.vx' increases by 'vx' to produce  $R.vx^2$ , or  $PR^2$ .

The spiral double helix of genetic 'strands' provides several functions.

1. It allows increased RNA to be developed from an appropriate site on one 'strand', and then progress to the area of DNA which lies 'directly opposite' to the position of the genes which regulate structure and function in a particular body site. The arrival of RNA from this area of DNA produces increased oxygen concentration and structural protein synthesis with inhibition of functional proteins (metabolic enzymes) and restricted metabolism from its loss. There is increased 'anatomical' protein for tissue growth and replacement, while the increase in oxygen concentration continues, and carbon dioxide concentration within the cell is reduced.

2. It is associated with uniform change in direction of dimensions of the structure of 'genetic strands' with the uniform shape of the area between the strands altered from a distorted rhomboid to an even more distorted shape 'controlling' the activity of the recipient DNA from the presence of increased oxygen concentration. It changes the specific alteration in activity with specific regulation of shapes and sizes, from the irregular changes produced in the 'neoplastic' state with continued reduction of 'vx', and the associated irregularity in 'anatomic' tissue production to form 'new growths'. The spiral double helix form enables the direction of produced energy to be restricted, and allow reduction of the three dimensions of energy (between zero and the maximal value) over a total of 360 degrees for a full cycle, and allows restriction of the reduced oxygen concentration, to one cycle of the helix. The effect of segregation is increased by the insertion of 'functionally restricted sections' between active genes in the strands of DNA. It implies that the two 'strands' of DNA have separate functions, with one strand determining 'functional protein', and % 'vx', while the other determines the amount of 'structural protein', under the influence of increased oxygen concentration provided from 'RNA' as 'L' increases compared with 'vx'; and diminished 'functional' protein generation as structural protein is increased locally.

THE DIFFERENCE BETWEEN OXYGEN 'POISONING' (OR NEOPLASIA).AND NORMAL REPAIR AND INCREASE IN TISSUE BULK, AND CELL NUMBERS THROUGH INCREASE IN RNA

Both functional protein activity, and that of structural protein, need to be continually changed with altered metabolic conditions, as the present values of carbon dioxide and oxygen vary with prevailing conditions, and body requirements. There is also change in the overall requirements for functional and anatomic changes with the ability of the body to maintain changes with time, with a maximal improvement in body development on the one hand, and a steady decline in capacity with increasing years, so reduced capacity for change in both functional activity, and anatomic change, depending on declining capacity, until the body ceases to maintain viability, and resulting in ultimate death. In effect there is loss of the capacity to maintain function and anatomic repair and replacement as 'augmented stroke volume' and adequate RNA become reduced as the gas concentrations also reduce with time, to produce the changes of increasing age, with reduced values of 'L'; and ventricular efficiency, as an inevitable result. The changes occur because of reduced capacity for oxidative capacity to reduce function, and reduced RNA to limit anatomic repair if the alteration of each is equivalent, although sudden loss of function, or abnormal anatomic proteins leading to absent or abnormal structural activity may also happen, or also even body wasting or 'neoplasia'.

Increased provision of carbon dioxide concentration is then available from augmented stroke volume to maintain synthesis of 'functional protein', while increased oxygen concentration for synthesis of structural protein results from 'messenger RNA'.

DNA leads to production of 'functional' proteins. These proteins (essentially enzymes) are necessary for continuing functional activity, while RNA leads to production of 'structural' protein, and 'anatomical' changes including cell numbers and volumes, but inhibiting functional activity of cells, until the effects of oxygen concentration provided by RNA (as it alters to DNA once more) have been eliminated, allowing production of functional proteins to again become the main genetic function, while reducing 'anatomical' activity to a diminished level, as oxygen concentration is reduced and that of carbon dioxide again increases in the relevant chromosomes.

The change from 'structural' to 'functional' protein depends on the ratio of 'vx' as this ratio between carbon dioxide and oxygen ratios is altered by the changes between pulse rate and effector cell volume (oxygen concentration squared) as production of messenger RNA equivalent to 'oxidised DNA' is altered. by loss of oxygen.

If 'functional' protein becomes insufficient for maintenance of cell activity, the concentration of carbon dioxide falls, and the necessary level of functional protein is also reduced, and soon falls below the concentration necessary for continuity of cell function as cell temperature declines. The processes required for continuation of the living state cease unless the concentration of oxygen is increased to maintain 'diastolic length of ventricular muscle' cells. If oxygen concentration increases, 'functional' protein is replaced by further production of 'structural' protein with associated increase in effector cell volume and increased cell numbers. Increased glycolysis is necessary to increase carbon dioxide concentration once more from increasing pulse rate, but involves increased oxygen load (lactate concentration) and is accompanied by increased blood glucose concentration unless there is increased glucose metabolism and oxidation. There is then the necessity for increased glucose oxidation to limit the level of blood glucose, and TypeII

diabetes, unless the glucose is metabolised with further production of carbon dioxide, leading to a resumption of 'functional' protein production.

Functional protein needs sufficient 'vx' to maintain it, while structural protein needs the value of 'L' with 'vx' to increase structure; i.e., 'vx' times 'L' or pulse rate, with 'vx' from DNA, and oxygen from RNA with constant value of 'O' (or systemic blood volume), and PR (L.vx). Pulse rate then depends on the size of the body structure, and the level of function provided..

Functional protein is proportional to 'vx', while structural protein is proportional to 'L.vx' or pulse rate (vx from tissue fluid velocity, and 'L' proportional to vascular length). Structural protein depends on the concentration of lactate as well as 'vx'(from DNA, that is, it increases as pulse rate increases) but needs 'vx'(which is no longer available for functional protein synthesis as well as genetic function) and is inhibited when structural protein increases because it uses the energy from 'vx' to produce 'L.vx'(i.e., 'L' from diastolic length, as well as genetic activity. 'vx', but reverts to functional protein production when oxygen and 'L' decrease with reduction of 'L' needed for functional protein production. The whole of energy from 'L.vx' is needed for structural protein synthesis, and body growth, which depends on increased pulse rate required for increased body bulk, and number of body cells, and is proportional to the square of systemic blood volume.

This implies that increasing pulse rate for a particular energy requirement (or 'L.PR' for the 'resting state') must lead to increasing body bulk (volume) and reduction of tissue function, and metabolic activity, until there is renewed production of 'vx' compared with 'L' and so increased functional state compared with cell reproduction, and reduced cell volume from structural protein compared with functional protein, and increasing metabolism. There will then be increased body size rather than increased body function until the relationship between the two is reversed, as the relationship between 'vx' and 'L' returns to a more satisfactory or usual level.

Alternatively it may not be possible for the living state to continue for any period unless pulse rate is increased to maintain functional protein, when there is associated production of structural protein and tissue bulk also required. In any case increased pulse rate, and so increased effector cell temperature are both needed for function and structure to persist simultaneously, and allow the living state to continue without interruption. Increased body bulk may then only be possible if pulse rate is also increased. It suggests that increased pulse rate may indicate increasing body size compared with increasing body function under prevailing conditions.

Increase in body size is only possible if it becomes possible for function to increase at the same rate as there is increase in body size, so that both function and structure increase at the same rate, and each is increased at the same speed, or pulse rate, to preserve body activity, which then becomes proportional to the square of pulse rate, with 'L' and 'vx' becoming proportional to each other; only possible if oxygen concentration remains constant in value, and 'L' and 'vx' each equivalent to carbon dioxide concentration. Body activity is then proportional to ' $PR^2$ ' cubed, or  $PR^6$  over three dimensions, and representing glycolysis and oxidation for production of pulse rate for each. It requires oxidation and glycolysis to each provide equivalent amounts of carbon dioxide by

different chemical processes, and for an accurate balance between them, to provide the same amount of carbon dioxide by each..

Increased functional proteins together with increased structural proteins may then only co-exist if there is an additional supply of 'vx' available as well as that required for functional protein production, or that required to produce 'contractility', or 'vx squared' with each ventricular contraction. It also requires 'oxidation energy', or 'R' to be available with 'contractility', for function to continue as well as 'structure' for continued cell activity. This would allow both structure and function to co-exist, for continued cell activity at a 'normal level', and maintain both at the required level, along with momentum of tissue fluid. It suggests that 'contractility' must be adequate for normal body activity to continue, and that 'abnormal' cell function might result from its absence, with increased likelihood of 'neoplasia' as 'L' increases with respect to 'vx,' and structure replaces 'function' in body cells. Maintenance of contractility requires both 'active state' and 'inotropic state'(L) to be regulated for production of 'vx squared', if neoplasia is to be avoided.

If it is accepted that circulatory activity depends on the relationship of oxygen and carbon dioxide concentrations to maintain it, then both functional and structural changes are also dependent on these gas concentrations in active tissues. If changes occur in both structure and function at the same time, then the requirement is for alteration in 'L' and 'vx' simultaneously to produce both increase in 'L' and ' $vx^2$ ', or 'PR.vx' (PR and tissue 'bulk' with linear velocity of tissue fluid and 'vx')i.e.,  $L.vx^2$  for both functional and structural protein production) and 'normal' tissue activity. If structure improves individually, there is increased body bulk without increase in functional protein, while increase in functional protein without increasing body bulk increases functional activity without alteration in body size (i.e., increasing physical fitness but not bodyweight). This emphasises the importance of 'contractility' in body function under normal circumstances, and the effect on body bulk if physical fitness is unable to match increase in body size which needs to increase as well as the diastolic length of ventricular muscle fibres .Contractility needs to increase as well as the diastolic length of ventricular muscle fibres for maximal physical performance to produce improvement in any particular field of endeavour.

Active state is proportional to  $vx^2/L$ , and if 'L' increases with respect to ' $vx^2$ ', there is reduction in 'active state', and an increased likelihood of development of 'neoplasia', as the generation of proteins, both functional and structural, is restricted, and structural protein can only be maintained by increase in 'L' to maintain PR (L times vx) when 'vx' diminishes. Pulse rate then has different significance with change in ' $vx/L$ '. If 'vx' increases but 'L' restricted, pulse rate may be the same, but production of functional proteins increased while structural protein production is maintained, but if 'vx' is diminished and 'L' increased, structural protein may continue to be available, but its effects might alter with increasing 'L', while 'vx' becomes unobtainable in adequate amount.

As the value of 'vx' decreases, there is decrease in 'functional protein' activity, and increased (but abnormal) structural activity from changed 'active state' ( $vx^2/L$ ) and these changes reduce functional protein activity, and increase in abnormal structural changes if oxygen concentration from increased RNA leads to increased pulse rate but an increased value of 'L' and fall in ' $vx^2$ '

with the threat of 'neoplasia' occurring with 'new growths' plus reduced functional activity in affected cells. This situation can only be reversed through reconstitution of 'vx', or increased carbon dioxide concentration compared with that of oxygen. When 'vx' is reduced it indicates an increase in oxygen concentration locally (from increased RNA in the local segment of the chain of DNA) providing increased oxygen concentration as RNA gives up oxygen and reverts to DNA once more.

For adequate protein synthesis, both 'structural and functional',  $vx^2$  or contractility must be adequate, with respect to 'L', for continued 'activity and maintenance'. If not the loss of protein synthesis leads to inadequacy, or 'ageing' of tissues, and the increased possibility of 'neoplasia' and death. In order to increase protein production there must be increased 'vx' (and  $vx^2$ ) with increased temperature of effector cells, increasing pulse rate, and reduced 'L', or if 'L' is maintained, to reduced pulse rate, but increased efficiency and unchanged  $vx^2$  as efficiency increases. But if efficiency does not increase and pulse rate does not increase but remains unchanged, there results increased cell volume and body bulk.

Increase in 'vx' on a continuing basis is necessary for maintenance of both functional and anatomic protein, with the latter also requiring the presence of 'diastolic length of ventricular muscle fibre' as well as 'vx'. However increase in 'L' is needed on a restricted basis for production of increased structural protein in limited areas of the body structure where only a small area of structure may need alteration in response to changing functional activity as determined by alteration of the level of RNA in a small area of DNA, limited by changed direction of energy production as the DNA chain rotates through 360 degrees over a restricted length, so restricting energy distribution to a small length of the 'chain', or to 'individual genes'. It is only in this region that 'functional' protein needs to be limited while structural protein production is increased, and functional protein continues to be produced on a general basis through further production of 'vx' to maintain the living state. Protein production in the two areas of function and structure then requires two factors of 'vx', or contractility, for normal activity to continue the life process, which needs both 'L' and  $vx^2$  or 'PR.vx.L' to persist. But if functional proteins do not keep pace with increasing body bulk there will be further difficulties. To increase functional protein activity requires further energy from diastolic fibre length of ventricular muscle, or a further factor of 'L' to be available, and total energy for protein activity proportional to  $R^2.vx^3$ , equivalent to  $LPR^3$  to provide protein function on an adequate level, as well as structural protein increase, for each value of pulse rate squared, allowing them to be of equivalent value.

Structural protein and functional protein both vary during the ventricular cycle, with increase and decrease in the value of each during the cycle. As one increases the other decreases so they remain inversely related at all times, and this relationship depends on fluctuation of the gas concentrations with these variations of size and shape and function, with alteration of activity compared with time, to regulate the living state with changes in cell function, essential for life to continue. The variations in cell activities change with altered protein concentrations to regulate function and structure. Functional protein alters with cell temperature, while structural protein

changes with alteration in cell size and shape, or cell dimensions with time, and associated with changing gas concentrations. The two are then of equivalent size, each proportional to 'L.PR', and the product of the two is ' $L^2.PR^2.vx$ ' or 'power' developed by each 'dimension' of the ventricle, with 'L' 'vx' proportional to pulse rate (if 'L' diminishes with any increase in 'vx') or ' $R^3.PR^6$ ', for the whole body activity, and equivalent to ' $v^3.PR^3$ '. Functional protein is proportional to 'R.vx' (i.e., L.PR, while structural protein is proportional to  $vx^2.[O_2]^2$  times 'L' or 'PR' times 'L' times 'vx' through the provision of oxygen from RNA. and is confined to the small segment of DNA defined by the 'twisting' of the genetic strand to limit the 'dimensions' to that area.. The difference in the two factors of 'L.PR' lies in the significance of 'L' or diastolic length of ventricular muscle fibres, and 'vx', proportional to functional protein provision by cell temperature regulation, and the resistance offered to internal' resistance to blood flow, producing 'free energy' in associated. tissues. Functional protein is regulated by 'R.vx', while structural protein is proportional to ' $R.vx^2 \times [O_2]^2$ ' to again produce 'L.PR', but increased by a further factor of 'vx' to become '%  $PR^2$ ', and indicate that functional protein must increase by this factor to become equivalent to structural protein as the two both increase in value with increasing activity. In addition,  $[O_2]^2$  (from R.N.A) and 'L' from diastolic length of ventricular muscle fibres, from 'stored energy' of effector cells before depolarisation, must also be supplied as well as 'contractility' for provision of structural protein

The total protein produced is the product of the two, or '% L. $PR^3$ ', or the kinetic energy of the systemic circulation, which is then proportional to the total protein produced per beat, to maintain circulatory function in the systemic circulation. Structural protein can only increase with respect to functional protein if ' $vx^2$ ' is available to replace 'vx' in functional protein, to produce 'structural protein' instead. Structural protein then requires 'contractility' to be available before it can replace 'functional protein' in the provision of total protein for functional as well as structural protein to maintain body growth and maintenance as well as body function, and in this it needs both to be produced as the result of kinetic energy maintenance, with 'L' from oxidation energy, and  $PR^3$  from glycolysis to maintain kinetic energy.

The validity of this account of the mechanics of fluid and energy distribution in the mammalian circulation, depends entirely on assumptions which while not directly proven, are nevertheless consistent with the available evidence. These assumptions concern the concentrations of respiratory gases provided to effector cells by circulatory function, and providing the distribution of fluid volume, and its contained energy, required for continuing activity. The respiratory gases are oxygen available from the atmosphere, and carbon dioxide from both glycolysis of carbohydrates, and oxidation of carbon residues, which together with oxidation of hydrogen, produce the energy for bodily activity and tissue maintenance on which the individual depends for its continued existence.

The assumptions are concerned with permeability of cell membranes for fluids and associated energy content available from the atmosphere in the case of oxygen, or provided from ingested

foodstuff by ingestion and absorption, until they are combined with oxygen to produce water and carbon dioxide, with production of energy and volume changes, between fluid compartments of the body. In the case of oxygen, its concentration supplied to the cell membrane, determines the rate of absorption, and consequently the volume and energy content it represents, to maintain the 'stored' energy the cell accumulates, as the result of 'passive' permeability which allows cell volume to change, depending on the concentration of the gas supplied to it.

Carbon dioxide on the other hand, is produced by glycolysis of carbohydrates, and/or oxidation of carbon residues to produce water and carbon dioxide, together with oxidation energy. Fluid volume with carbon dioxide and released energy is moved from the cells to tissue fluid by 'active permeability', associated with cell metabolism and released energy.

Passive permeability and oxygen concentration increase cell energy while 'active permeability' and carbon dioxide concentration reduce cell energy and fluid volume, which pass to extra-cellular volume, and produce fluid circulation within the body.

Movement of fluid and its associated energy from extra-cellular fluid then passes into the cell through 'passive' permeability with increasing cell volume, then movement out of the cell from 'active' permeability or metabolic activity, results from increased carbon dioxide concentration. The association of oxygen concentration with carbon dioxide concentration therefore initiates the movement of fluid into the cell and then expels it once more to maintain movement in the extra-vascular fluid and venous system to effector cell volume through ventricular contraction.

The forces concerned with linear velocity of fluid and blood, and the capacity for muscular work then all depend on the permeability of cell membranes, the flow into and out of effector cells, and the kinetic energy it represents, with effector cell volume % oxygen concentration, and reduced cell cross sectional area proportional to carbon dioxide concentration, while  $[O_2] \times [CO_2] \propto L$  (or diastolic length of ventricular muscle fibres and the energy of contraction of heart muscle {Starling's Law}).

If 'L.PR.vx' represents structural protein (body bulk), and 'R.vx' represents functional protein production, then if 'L' is increased with respect to pulse rate, there is increased structural protein with respect to 'vx' with increase in the relative amount of structural protein (and body bulk), and restricted functional protein, while if 'vx' increases with respect to stored cell energy (or 'R') there is increased functional protein, but inhibited structure and body bulk, or 'L'.

As functional protein increases relative to structural protein, there is increased genetic function, but reduced body size, while if 'L' increases compared with pulse rate, body size increases, and function is reduced. Increased functional protein leads to reduced body bulk (and cell volume), while if structural protein is increased compared with pulse rate, cell function and genetic activity is reduced. In the former case there is restricted body bulk, but increasing metabolic rate (and pulse rate during activity) while in the latter there is reduced metabolic rate but increased body bulk, when 'resting' pulse rate is increased but 'active' pulse rate is reduced.

This is the state of 'neoplasia' with increase (but 'disturbed' increase) in cell volume with limitation of 'functional efficiency', while there is a greater level of increased pulse rate with 'activity', but reduced pulse rate during rest periods (or functional increase in efficiency).

Preservation of the 'correct' balance between functional protein and structural protein requires 'L.PR.vx' to be equivalent to 'R.vx', with this balance preserved at all times to maintain 'normal' activity, and equivalence between 'L' and 'vx', or between '[CO<sub>2</sub>]' and '[O<sub>2</sub>]' for equivalence between structural protein and functional protein, and so provide 'normal' body activity, which depends on this equivalence over the longer term of the 'living state'. The life process can only persist through preservation of this balance between the concentrations of oxygen and carbon dioxide, over the whole life cycle.

If the balance between functional and structural protein production is disturbed, there are profound alterations in body functions which must be corrected for continued life processes. Increased structural protein is required to allow the production of cell dimensions such as the diastolic length of ventricular muscle fibres or 'L', before contractural energy of heart muscle can be made available for each beat, and this is the basis for cardiac energy production. In its reduction or partial absence, there is development of 'asthma', which requires increase in the value of 'L' for continued physiological function, and to maintain circulatory function compared with functional protein activity. It requires an increased value of 'L' to maintain the balance with functional protein for continued activity. It can be replaced initially by increase in carbon dioxide concentration as a temporary measure with 'asthmatic' symptoms, but if prolonged it results in reduced functional protein and circulatory failure. If, on the other hand there is reduction of 'vx', and functional protein synthesis, 'vx' is reduced with respect to 'R', tissue function is soon disturbed, and may cease altogether with subsequent death unless corrected by increase in the efficiency of circulatory activity (as a result of increase in lactate concentration and hypertension) as a temporary measure. Otherwise there is reduced cell temperature and genetic function, as carbon dioxide falls compared with oxygen concentration, with increase in tissue cell volume and 'neoplasia'. Either of these states soon leads to loss of function, and death, unless it is urgently corrected. The values of 'L' and structural protein production must be closely regulated compared with 'vx' and functional protein availability, for continuation of the living state, with varying degrees of interference leading to functional disability such as asthma, hypertension, or type II diabetes, with circulatory or other cell failure, altered effector cell volume, or 'neoplasia' developing.

When 'L' increases compared with the resting level of pulse rate there is increased structural protein production, and resulting increase in resting pulse rate, with increased 'body bulk' unless the resting pulse rate is reduced. The relationship between increased body bulk and resting pulse rate as a result of increasing structural protein production can be a basic cause of excessive weight gain in individuals who do not maintain physical fitness with reduced resting pulse rate, to increase functional protein at the same rate as structural protein by increasing 'vx' at the same level as 'diastolic length of ventricular muscle fibres, or 'L', on a continuing basis.

Kinetic energy available to the systemic circulation is proportional to  $L \times PR^3$ , composed of 'L.PR' i.e., 'functional protein' produced, and also 'free energy' or temperature of 'effector cells' times  $PR^2$ , or momentum of tissue fluid, and equivalent to the energy used to produce 'structural' protein, while the production of functional times structural protein together require kinetic energy available in the systemic circulation, or 'L.PR' times  $PR^2$  (i.e.,  $L.PR^3$ ) with the ratio of the two proportional to 'vx', or  $\frac{[CO_2]}{[O_2]}$ .

Functional protein production is proportional to cell 'free energy' or heat, and structural protein production is proportional to kinetic energy of tissue fluid, and the ratio of the two is proportional to '1/vx' (where 'vx' is the extra factor contributed to 'L.PR' to produce ' $PR^2$ ') which has to be contributed to 'L.PR' to produce ' $PR^2$ ', and maintain the balance between functional and structural protein production as the size of the body increases (%vx).

Functional protein increases with body temperature, and structural protein increases as the momentum of tissue fluid increases, and the amount of each is related %'vx'. If vx diminishes the ratio between functional and structural protein production is also diminished, so 'vx' must be maintained to keep the balance between functional and structural protein production directly related (or 'vx' must be maintained to keep the balance between functional and structural protein production, and 'vx' has to be preserved in value.) The temperature of 'effector cells' is controlled and related to the momentum of tissue fluid to maintain the balance between functional and structural protein production, and 'vx' has to be preserved in value to maintain the living state, and the 'balance' becomes an essential factor in maintaining the gas concentrations. Total protein production is proportional to the product of 'internal resistance to blood flow' times the momentum of tissue fluid, i.e.,  $L.PR \times PR^2 = L.PR^3$  (the kinetic energy available in the systemic circulation).

R.PR % v' or ' $v/[O_2]^2 \propto PR^2$ ', % 'structural protein production', or *DPs/effector cell volume*  $\propto$  '*structural protein production*' or the limitation of structural protein % the ratio of 'DPs /cell volume', so increased diastolic blood pressure is required to maintain both structural protein and effector cell volume simultaneously. Diastolic blood pressure increases as effector cell volume or pulse rate increases for a particular value of R (stored cell energy) to limit effector cell volume (oxygen concentration squared) by increase in diastolic blood pressure. Limitation of DPs occurs through a fall in PR to modify the effect of increased 'R' DPs is controlled by limitation of structural protein. As structural protein is increased so is DPs unless PR is limited ; i.e., tissue bulk is increased unless PR is limited. **Increased tissue bulk will occur unless resting pulse rate is limited, and functional protein increased.**

Contractility is proportional to vx squared or pulse rate over oxygen concentration squared; i.e.,  $\frac{[CO_2]^2}{[O_2]^2} \% vx^2$ , and the ratio varies with changing gas concentrations. If vx increases in value so

does the concentration of carbon dioxide compared with that of oxygen, and 'L.PR' compared with PR squared, and 'functional protein' compared with 'structural protein', while if 'L.PR' is reduced compared with ' $PR^2$ ', so is functional protein compared with structural protein. This is the basis for control of the two levels of 'functional' and 'structural' protein which depend on the relative values of the gas concentrations (oxygen and carbon dioxide) present in the body tissues. and controlling production of body protein between 'functional', and 'structural' activities, and so between body function and body size, which are mutually restrictive.

Functional protein is related to glycolysis, and 'vx', while structural protein is related to oxidation (and 'R'. $vx^2$ , while these two activities are also mutually restrictive), and so control the concentrations of protein production (Pasteur and Crabtree effects) and the relative production of functional and structural proteins, and their effects on body activity.

The relationship of ' $vx/L$ '%  $1/[O_2]^2$  or  $1/\text{effector cell volume}$ , and effector cell volume increases as L increases with respect to 'vx', and structural protein with respect to functional protein, and this relationship regulates the relative levels of these proteins, and cell function compared with body bulk ( $\%vx / L$  with vx proportional to functional protein production, while L is proportional to structural protein level, and this ratio regulates the production of each., and the critical ratio which is essential for body activity to perform in a normal fashion to maintain the living state). Effector cell temperature %'vx', and functional protein, and structural protein (body bulk) to 'L', while their ratio regulates body size and shape, and body form and functional activity.

If 'vx' is increased or decreased, increase or decrease follows in both 'functional and structural protein' by a factor of 'vx', with increase or decrease in kinetic energy of systemic blood flow in some degree, but with functional protein and structural protein which remain in the same relationship as before, proportional to the concentration of 'vx' in relationship with the 'ageing process'. However if 'L' increases with respect to 'vx', relationship between the two protein classes will be distorted, with ' $L > vx$ ', and change in the shape of the 'genetic chain' as 'vx' is altered with respect to 'L', and structural protein altered with respect to functional protein, resulting in 'neoplasia' with increased amount but altered constitution of structural protein, and reduced functional protein, eventually of sufficient degree to disrupt the relationship and pattern of overall protein production, as oxygen concentration increases with respect to that of carbon dioxide.

The alteration of apparent mechanical efficiency, allows increase in 'L' compared with unaltered 'vx' in the short term, allowed by some possible apparent functional adaptation in the short term, but with the adaptation overcome in the longer term by increased 'vx' with increased cell temperature and glyconeogenesis.

If 'L' is increased compared with pulse rate cubed (or the sixth power of carbon dioxide concentration) it implies increased protein production with increase in oxygen concentration compared with carbon dioxide concentration, and this needs to be prevented with the adaptation

that increases apparent efficiency when there is increase in 'L', otherwise there is increased oxygen concentration compared with pulse rate (or glycolysis) and reduced 'vx' compared with 'L' (and functional protein compared with structural protein) appearing as 'neoplasia' when 'vx' diminishes with respect to 'L'.

It implies that glycolysis is increased compared with oxidation as carbon dioxide concentration is increased compared with that of oxygen to maintain the ratio of 'vx', although this adaptation must have an 'upper limit' after which oxygen must increase again relative to carbon dioxide with further reduction in 'vx' and increasing effector cell volume.

As 'vx' falls and oxygen concentration increases once more to reduce 'vx', increase in glycolysis will increase also with increased glucose concentration in the blood and this gives rise to Type II diabetes, which appears as increased glycolysis appears compared with oxidation. Increased glycolysis and blood glucose levels result in increased oxygen concentrations and the level of structural protein production.

Any interference with these relationships will alter functional activity compared with body structural formation, and lead to restricted function and altered body form, and eventually to 'neoplasia' as a terminal event, to finally eliminate the life process.

The mechanics of circulatory and tissue activity all follow from this outline .

It is hoped that this publication, whatever the final judgement on its conclusions might be, may act as a stimulus to continued enquiry along similar lines to those it has attempted to initiate.

The only 'real world' of which we have experience is completely dependent on kinetic energy which results when energy increases or decreases with altered 'entropy' availability, to make life possible. The absence of 'mass/ energy' would mean the loss of kinetic energy, and also the loss of material substance, and so the absence of a 'material environment' of the type which supports a continuing life process, and the material world we experience, together with any form of 'life cycle' in that environment.

The presence of continuing kinetic energy of the systemic circulation is the ultimate basis for the 'life cycle', and so the living state, and the experience of the physical environment necessary for it to persist and continue. In other words the conditions for the physical universe as we know it, and that we regard as the 'ultimate reality' that our living state permits us to experience.

We are only able to experience that world by ourselves developing kinetic energy that allows us to take part in it for the relatively short time of our individual life cycle ( the only period during which we experience the 'material' environment, and so the only period when the environment is available to personal experience, though an historical account and material artefacts might still exist from a previous time frame and become integrated with our own personal experience of the 'present' as 'here now'.

Kinetic energy of the systemic circulation provides the energy for development of functional and structural protein, and must always be present for continuation of the life process. In addition, genetic activity requires activity of individual genes which need to be 'turned on' or 'off' as a result of other environmental conditions, e.g.:electromagnetic irradiation, and increased sunlight and power, and changes in carbon dioxide and oxygen concentrations from metabolic changes, as well as 'L' and 'PR'(or "R' and 'vx'(cell temperature) and changing external temperature; i.e., by change in energy supplied to skin, or change in chemical energy in excessive or reduced amounts, leading to change in 'vx' or 'contractility', and essentially to alteration of the provision of 'functional' and 'structural' protein levels, and the conditions for persistence of the 'living state'.

Disturbances of protein production and kinetic energy of the systemic circulation are responsible for the changes leading to 'neoplasia' and the presence of 'new growths', with eventual termination of the life process.

Protein metabolism %kinetic energy of the systemic circulation ( $L \cdot PR^3$ ) and fat metabolism is proportional to 'R', while carbohydrate metabolism (and effector cell activity) is regulated by the momentum of systemic blood flow ( $Q \cdot v^2$  or  $R \cdot L \cdot PR^3$  i.e., ' $L^3 \cdot PR^3$ '), and the level of metabolic activity is linked to the metabolism of the different foodstuffs presented by the circulation, depending on the region where activity is required, or the tissues which become involved with any particular parameters of metabolic function. If kinetic energy in the systemic circulation is altered, there is a requirement for altered protein production in both functional activity and structural or anatomic changes. Altered activity of core cell metabolism on the other hand needs changed metabolism of lipid metabolism with altered values of 'R', and the circulation to the core organs (liver, kidneys, lungs, or gut) and required changes in the circumstances in which they operate to maintain their activity. Changed effector cell activity requires modification of glycolytic function, to be followed by changed metabolic and structural changes to cell dimensions, and functional adaptations to effector cells, with the modifications of size and shape necessary for the changed conditions, and altered function required.

The suggestion is that effector cells require carbohydrate metabolism, while core cells respond with changes in fat metabolism, and change in kinetic energy of the systemic circulation leads to essential changes in protein metabolism necessary for continuation of the living state, and the functional changes such as cell temperature, and the alteration of cell size and shape necessary for continuing cell function, and body activity.

The energy required for bodily activity is 'diastolic blood pressure cubed', times 'pulse rate cubed', or 'the cube of oxidative energy times the cube of the pulse rate'. These ratios are essential elements for continuation of the normal life process, and their values alter with changing 'life processes'

Carbohydrate metabolism is necessary for activity of effector cells, but is connected with protein and fat metabolism, which require an equivalent level of energy availability. Carbohydrate metabolism needs energy proportional to ' $R \cdot L \cdot PR^3$ ', and protein uses energy equivalent

to 'L times PR cubed', with fat metabolism 'R', (or a similar energy availability for protein and fat together to become equivalent to 'L times PR cubed', with fat metabolism equivalency to 'R', (or a similar energy availability for protein and fat together to become equivalent to that used for carbohydrate or effector cell activity)

Energy availability seems to be distributed according to these proportions, to maintain a correct level of energy usage by each of the three sources of metabolic activity, i.e., carbohydrate, protein and fat, which is limited accordingly, by changing energy parameters, and eventually by changing concentrations of carbon dioxide and oxygen, though that of oxygen must be kept at a constant value for 'normal' functional activity. Changing oxygen concentration may rapidly lead to cessation of adequate protein metabolic function unless immediately corrected.

The development of energy in each area of 'core' cells', effector cell energy', and protein development for cell function', and cell structure, have as their common factor 'R', or core cell energy, which is required as a factor for multiple factors that link the levels of activity in all three areas. Effector cell energy is proportional to 'R cubed' times 'vx cubed', and protein development is proportional to 'R cubed' times 'vx cubed', because protein development is proportional to 'R squared times 'vx cubed', although 'core cell energy' is proportional to 'R' as a single factor, which maintains the relationship between the energy development in the three areas. This factor is essential to all energy development, where it occurs in each as 'R' (for fat or core cell function) 'R squared' for protein availability, or 'R cubed in effector cell energy', with 'vx cubed' combined with the multiple values of 'R' to produce fluid movement, or momentum.

In each case 'R' or a multiple of 'R' is combined with 'vx cubed' as necessary, so that 'R' is the essential factor which associates the energy levels for energy requirements for the whole body, and must become the most significant factor in its development at each level. As the multiples of 'R' are reduced, the energy level is reduced, and energy increasingly returns towards the initial value of 'R'. As this reduction takes place, the basic energy is reduced and if appropriate, the animal approaches towards the state of hibernation, or most limited level of physiological function possible with a continued living state, for which the value of 'R' becomes the continuing factor, after the individual has temporarily largely lost the capacity for independent activity and function. The value of 'R' then becomes the required energy for the continuing living state. It represents a factor of 'L' (diastolic length of ventricular muscle fibres), and a further factor of 'L' as a similar factor of equivalent value, but signifying the 'length of effector cells (cells with a potential difference across the cell membrane) or energy available to the circulation from altered cell size and shape, with the two factors producing 'R', making 'R' proportional to 'core cell energy' to maintain metabolism of 'fat' for 'core cell' metabolism.

Core cell metabolism becomes the initial requirement for provision of metabolic activity in each metabolic region, which cannot initiate unless the core cell metabolism is first increased with a greater value of 'R', or fat metabolism, before other parameters can become involved. The basic value of 'R' signifies lipid metabolism, particularly with 'glyconeogenesis' in liver and kidney, to assist with carbohydrate metabolism, but it also becomes necessary for linear velocity of blood flow in the lungs (R.PR) which is required to maintain efficiency in the systemic circulation.

With other metabolic parameters, multiples of 'R' appear to maintain kinetic energy in the systemic circulation (for R squared) and 'Rcubed' for metabolism in effector cells, with development of both potential and kinetic energy in those cells, and 'functional' and 'structural' protein development associated with increasing energy in the systemic circulation. In a similar way, 'R.PR' is proportional to 'v', or diastolic blood pressure, while 'R.PR squared' indicates circulatory power for each dimension of the left ventricle, as well as effector, and core cells. .

In each case, provision of 'R' or fat metabolism, indicating equivalent provision of values of carbon dioxide and oxygen (related values of 'passive' and 'active' permeability of core cells) is the initial metabolic activity which makes further metabolic change possible, and is the forerunner of development of subsequent energy development, and in this sense, the basis for all further metabolic activity, and the basis for the living state to commence, and then continue while lipid metabolism persists.

Nevertheless, the secretions of endocrine glands can greatly affect metabolism of carbohydrate, fat, and protein, as an added factor to energy supply and regulation, to both stimulate and/or inhibit effects produced by the physical forces available in tissue and organ metabolism.

Hormones have functional effects that constantly vary the effects of physical metabolism, to influence the factors of cell size, shape, and function of body cells, influenced by nervous activity of the autonomic system as well as endocrine activity, which exist as overlying controlling systems to produce more rapid change in function than the comparatively slower effects of cell energy development, and are able to change the rate and extent of these mechanical changes to produce the overall structure and function of body cells.

It overlays the metabolic activity of the living state, and the existing features of physical vitality, and is able to lead to the existence of each living individual. By producing strict balances between opposing functions, it leads to more balanced levels of stable parameters as required for example, for the blood sugar in the living state, by constant presence of factors which increase as well as reduce the final value of each. Examples would be the secretions of pancreatic islet cells producing insulin to limit the concentration of blood glucose on the one hand, but the secretion of the anterior pituitary gland which has the opposite effect, increasing blood sugar levels, and increasing diabetes on the other, with the overall effect of a more constant blood sugar between the two. Similarly lactate concentration to maintain 'oxygen load' and oxygen concentration in effector cells, with the opposite effect of increased cell oxygen concentration from increased adrenocortical hormones in effector cells to prevent 'asthma', and also increase blood sugar when [lactate] falls; the secretion of the thyroid to increase metabolic rate, but internal resistance to systemic blood flow (or increase in 'stroke volume'), to limit metabolic activity; the secretion of testosterone by the testis to increase strength; and the increase in concentration of carbon dioxide to reduce strength but increase work capacity. A final example, is the effect of 'R' indicating 'core cell' energy and fat metabolism as the basic 'metabolic activity' which influences metabolism of effector cells (and carbohydrate metabolism ('vx' cubed times 'R' cubed) with PR cubed times 'L' (or 'L' to the fourth power times 'vx' cubed) for protein production and 'kinetic energy of the systemic circulation', but both depending on the value of 'R', and so affecting their

relationship with 'core metabolism', with each increasing and reducing with changing values of 'R'. As core cell metabolism and fat metabolism increases in metabolic activity of core cells, with increase in value of 'R' or its factors, so must the metabolism of effector cells and protein metabolism for continued body function, with increase in activity in all three areas linked with fat metabolism as the basic activity, as in physiological states such as pregnancy (see Chapter 14).

The development of energy may be little affected overall by these regulatory effects of hormone secretion, or autonomic nerve activity, but the distribution of energy may become altered, for a more economic overall result. It is the underlying metabolic activity for the living state, and the essential feature for persistence of physical vitality, leading to the continued existence of each living individual, to which the value of 'R' contributes in the most essential fashion, to determine energy production on a continuing basis.

If the factors required to produce energy for metabolism of fats, protein, and carbohydrate are examined, they may be condensed to two, or 'R' and 'vx', i.e., involving 'core cell' activity, and 'linear velocity of tissue fluid'. In order to produce energy for carbohydrate metabolism, there must be a contribution of energy from core cell metabolism over and above that necessary for basic cellular activity (or 'R') and the extra energy is required for carbohydrate metabolism to take place, which means extra energy from core cells (or fat metabolism). A total contribution to carbohydrate and protein metabolism from 'core organ' activity is required for their metabolism equivalent to 'R squared', which has to come from 'core organ' metabolism to maintain usage of carbohydrate and protein. Metabolism of core organs has to be enlarged to 'R cubed' times 'vx cubed' for protein metabolism, or 'R' to the sixth power times 'vx' to the sixth power overall, to maintain overall metabolism of all three types of nutrients, for normal performance.

It would allow carbohydrate usage (and effector cell activity) to become equivalent to (L.PR) cubed, or ('R' cubed times vx cubed), and ('R squared times vx cubed) for protein metabolism, while core cell metabolism provides stored energy equivalent to 'R' for their essential fat metabolism.

The origin for energy change comes from 'storage' of energy equivalent to increased 'R' in effector cells as the initial feature necessary for the energy (functionally provided by metabolism of 'fat') to maintain 'core cell activity, and metabolism, with multiples of 'R', required for protein availability with increasing 'L' (and maintenance of kinetic energy for the systemic circulation) together with carbohydrate metabolism requiring 'R.L' as factors for development of 'R squared' needed for additional energy with metabolism of protein and carbohydrate in addition to fat metabolism. Metabolism of fat is the basic initiative necessary for metabolism of protein and carbohydrate, which require fat metabolism to initiate their own metabolism.

*The basic need for 'R', or resistance per unit volume, per unit velocity of blood flow, i.e., 'L.O' times oxygen concentration'.*

Oxygen concentration needs to remain constant in value, to allow 'R'.'vx' %'L.O' (stroke volume and/or internal resistance to blood flow), and is also a result of 'fat' metabolism, with the latter proportional to stroke volume, but also to internal resistance to arterial blood flow. As a result 'R' is proportional to stroke volume while oxygen concentration remains constant. The initial effect of the core circulation is the provision of 'stroke volume' and internal resistance to systemic blood flow.. As a result 'R' is proportional to 'L.O' while oxygen concentration remains constant. The initial effect of the core circulation is the provision of 'stroke volume', and internal resistance to systemic blood flow. 'R' becomes the basic requirement for origin of the systemic circulation, but becomes proportional to 'L.PR', and the amount of functional protein, with structural protein also proportional to 'L.PR'. And pulse rate squared. This requires 'R' to become necessary for 'stroke volume', 'internal resistance of the systemic circulation' and protein metabolism (kinetic energy of the systemic circulation) as well as the metabolism of 'effector cells'(proportional to L.PR). It becomes fundamental for provision of all three forms of metabolism (fat, protein, and carbohydrate, and the initial factor for all metabolic activity, and the generation of mammalian life forms. .