

Geography and the heart

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Geography brings to mind the physical formations of the earth, mountains and rivers, plains and deserts, oceans and bays. Presently climate, winds and currents enter the mental picture. In contrast, the heart ticks on within the inner sanctum of the body, unseen and unheard. The connection between the world without and the heart within is scarcely apparent. Does the heart sense geographical events? Does it leap up before the rainbow in the sky?

Physical geography

The 'motion of the heart' which struck Harvey not only circulates blood but also maintains a constant internal milieu which contrasts sharply with the changing external environment. The constancy of the internal milieu is nowhere as striking as in the regulation of body temperature in homeotherms. A fresh cadaver will equilibrate its temperature with that of the environment in proportion to the difference between their respective temperatures. A homeothermic animal, however, will maintain the difference by spending energy in proportion to its surface area and $2/3$ power of its total mass (Figure 1). But mice and men differ in their methods for the regulation of body temperature. While the mouse counts on hair-coat erection and metabolic rate as its prime biological weapons, man lacks a hair coat or a vigorous metabolic response (Figure 2). He responds to thermal stress by different mechanisms. When air temperature rises from 6°C to 50°C at a relative humidity of 50%, his total peripheral resistance steadily drops as the temperature crosses 28°C with associated sweating (Figure 3). Notice that the peripheral resistance increases as the temperature falls from 28°C to about 15°C . It is clear that heating produces vasodilation whereas cooling causes vasoconstriction. If the experiment is repeated with a relative humidity of 90%, peripheral resistance drops drastically and the subject collapses at 40°C on sitting or standing up (Figure 4). To maintain normal blood pressure against such fluctuations in peripheral resistance, the heart raises its output in the heat and lowers it in the cold. The cardiac output curve is virtually a mirror image of the curve for total peripheral resistance. The rise in cardiac output is effected by increments in stroke volume and heart rate. It may go as high as 20 litres per min from a resting level of 5 litres to meet the extra

demand of skin circulation in a hot, humid zone. The skin senses the environmental temperature and signals the heart, which in turn responds by an increase or decrease in its output.

As one moves from temperature to pressure, the heart seems to respond less to higher environmental pressure and more to lower pressure. Atmospheric pressure above one in the depth of the sea evokes an elaborate response from the respiratory system; but the heart scarcely takes note of it. Adaptive circulatory changes are seldom seen in caisson workers¹. It is a different story at high altitude, where the atmospheric pressure drops to less than one atmosphere. At 14,000 feet, air density is decreased, temperature and humidity are low, and, as a consequence of reduced barometric pressure, the partial pressure of oxygen in the inspired air is low. The result is that the haemoglobin passing through the lungs becomes less saturated with oxygen, the tension of the oxygen in solution drops, and diffusion and utilization of the gas at the tissue level suffer. Cardiac adaptation to high altitude has been intensively studied because man has learnt to live at such altitudes for over 9000 years by natural acclimatization which goes beyond acquired adjustment and involves genetic

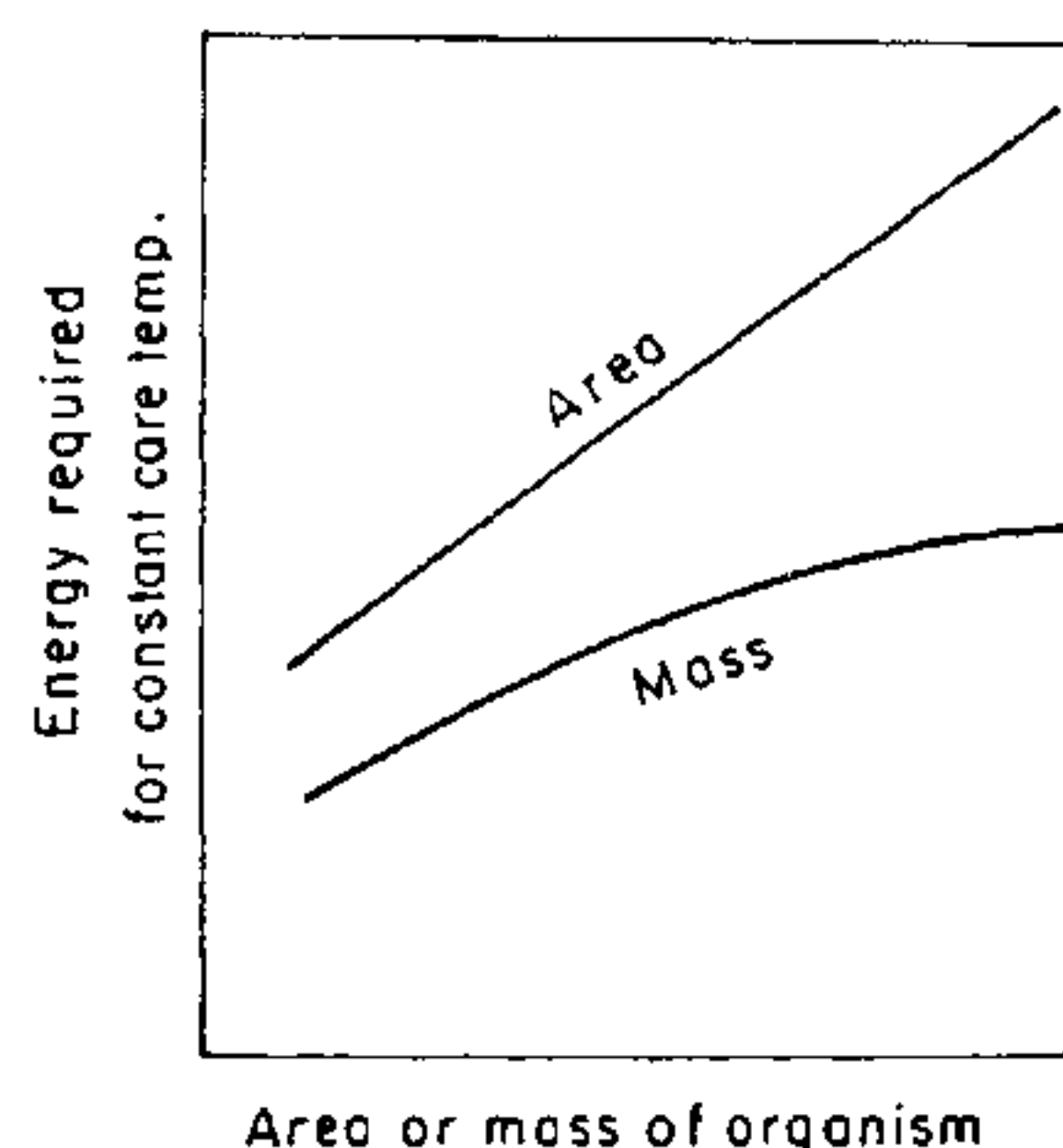


Figure 1. Energy expenditure in relation to surface area and mass.

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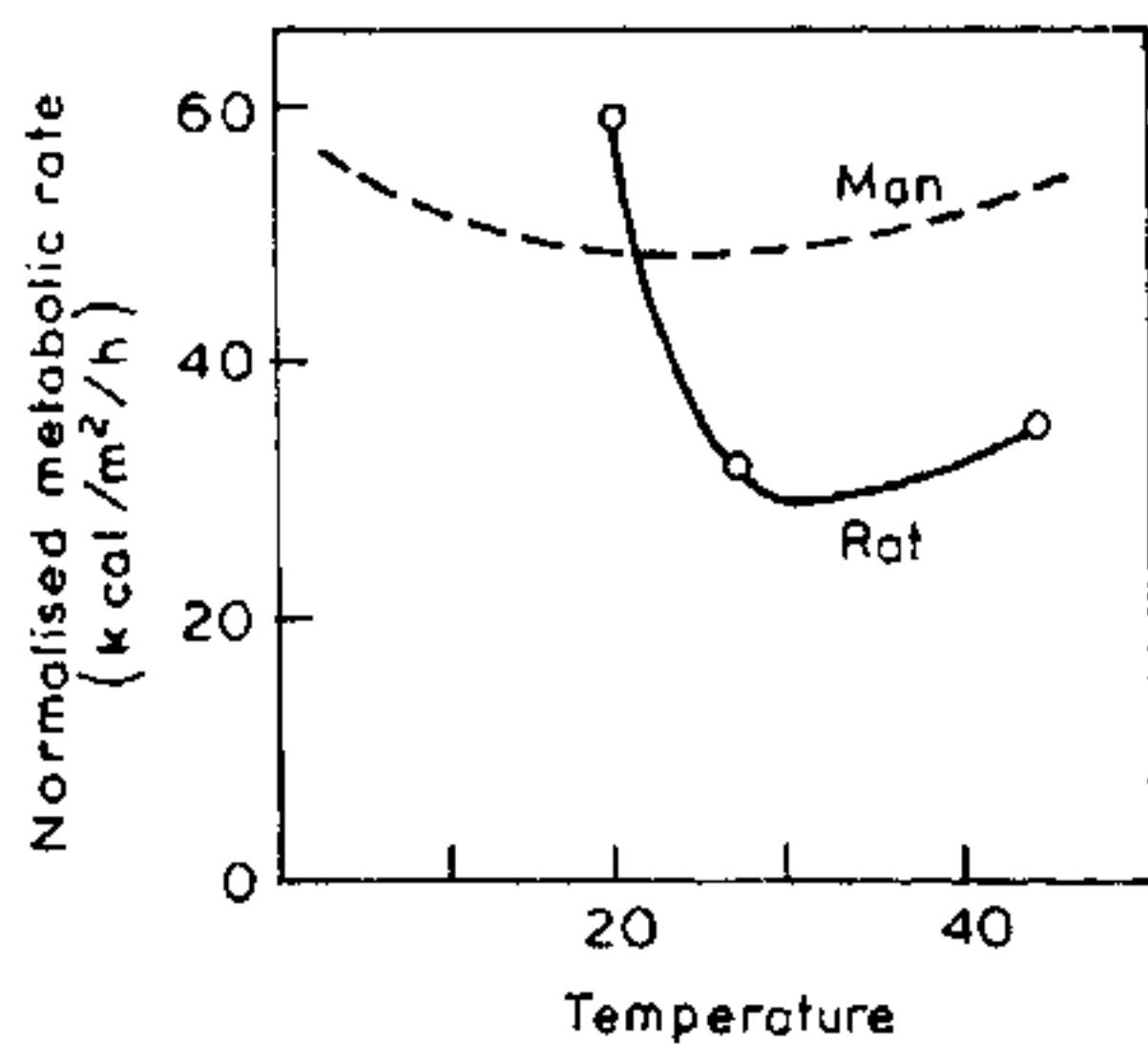


Figure 2. Metabolic response in relation to environmental temperature.

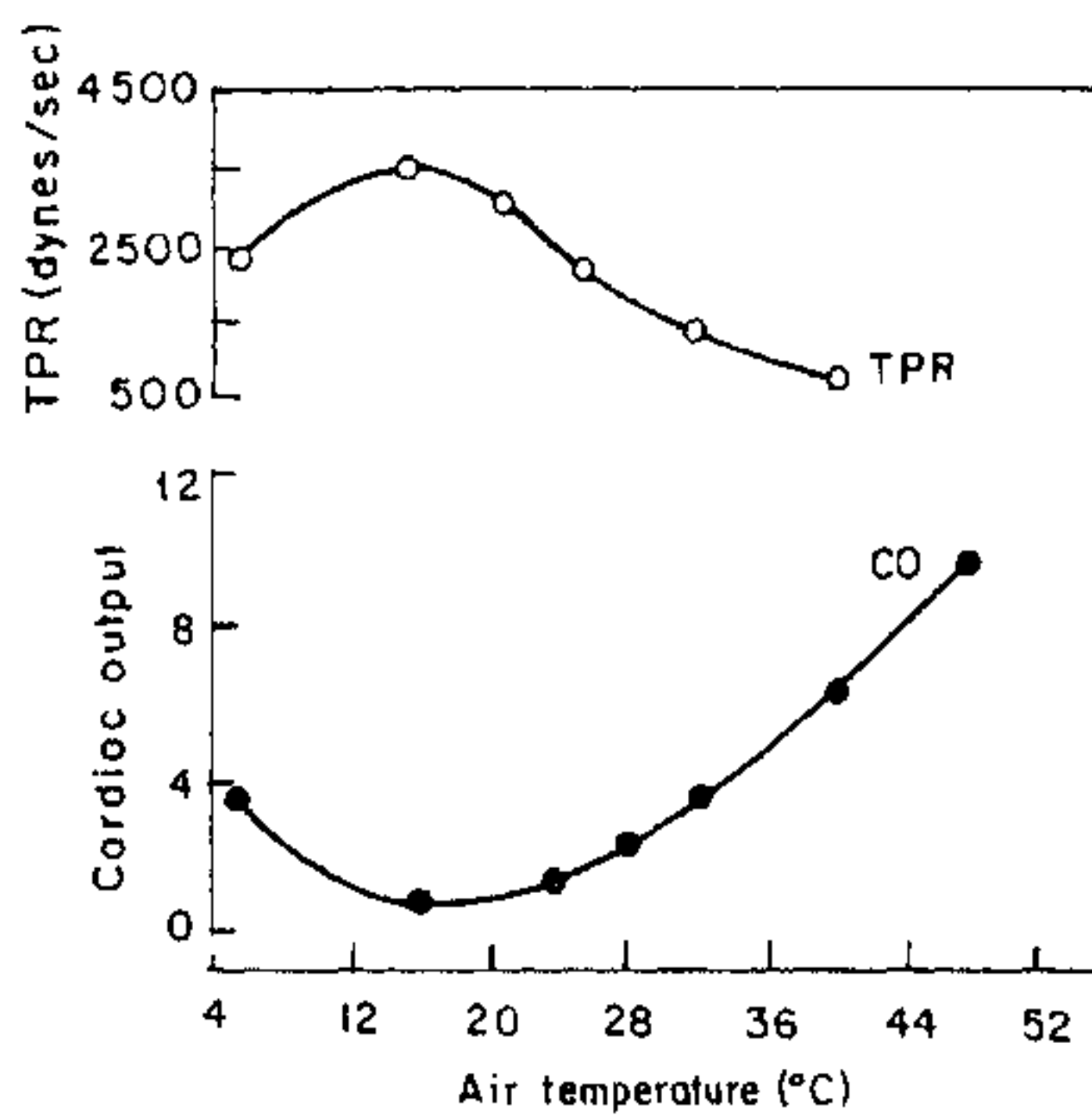


Figure 3. Cardiac output and total peripheral resistance in a nude, resting young man in relation to environmental temperature.

adaptation. How does the heart adapt for working at high altitude?

Contrary to general belief, blood supply to the heart muscle or coronary flow per unit time and per unit mass is lower at high altitude than at sea level². The lower flow is not compensated by raised haematocrit or arterial oxygen content and the oxygen supply to the heart does fall. Nevertheless there is no anaerobic metabolism and the heart cells, through a special metabolic process, seem to spare oxygen. Since the work of the heart remains undiminished, it obviously performs with less oxygen and increased efficiency. In parallel, new branches sprout in the coronary tree³. In short, at high altitude, the heart responds to the challenge of hypoxia by boosting its pumping efficiency. This is a far cry from its response in the hot, humid plains where the peripheral resistance drops and the heart raises its output at high energy cost for regulation of body temperature.

Leaving behind hot, humid plains and high mountains, we now move to the icy regions of the northern hemisphere. To tide over the bleak winter, subarctic

zone mammals allow their body temperature to drop to a few degrees above freezing point and enter a phase of deep hibernation. In the ground squirrel and wood chuck, heart rate and metabolic rate decline before the body temperature actually begins to drop. The thermoregulatory mechanism is passively abandoned and the heart rate reaches its lowest value in about nine hours while the body temperature continues to decline. As the parasympathetic system modulates the dropping heart rate, skipped beats and periods of asystole are common during cooling. Once the lowest heart rate is reached in deep hibernation, the parasympathetic influence on heart rate is no longer significant. The heart rate drops linearly in response to the low environmental temperature, and it is on this curve that nervous and other influences play during the progress of hibernation. The decline in heart rate is accompanied by a reduction in systolic and diastolic pressure. The reduced level of blood pressure is maintained by rise in peripheral resistance, which is caused in turn by increased blood viscosity and vascular tone. As the animal curls up into a ball to conserve heat at a body temperature of 4°C, the warmest part of the body becomes the area around the heart, which may beat 10 times or less per minute to maintain minimal perfusion of tissues (Figure 5). Entry into hibernation is, on the whole, a tranquil and low-energy-cost phenomenon. But cardiac somnolence in hibernation is light because the heart wakes up and boosts the rate in 2-3 sec following pharmacologic or electrical stimulation. Natural arousal, which does not differ from artificial arousal, is marked by violent shivering, high expenditure of energy, and sharp rise in cardiac output.

Chemical geography — role of elements

The response of the heart to high altitude, humid heat and the bleak subarctic climate provides examples that belong to the physical province of geography. In

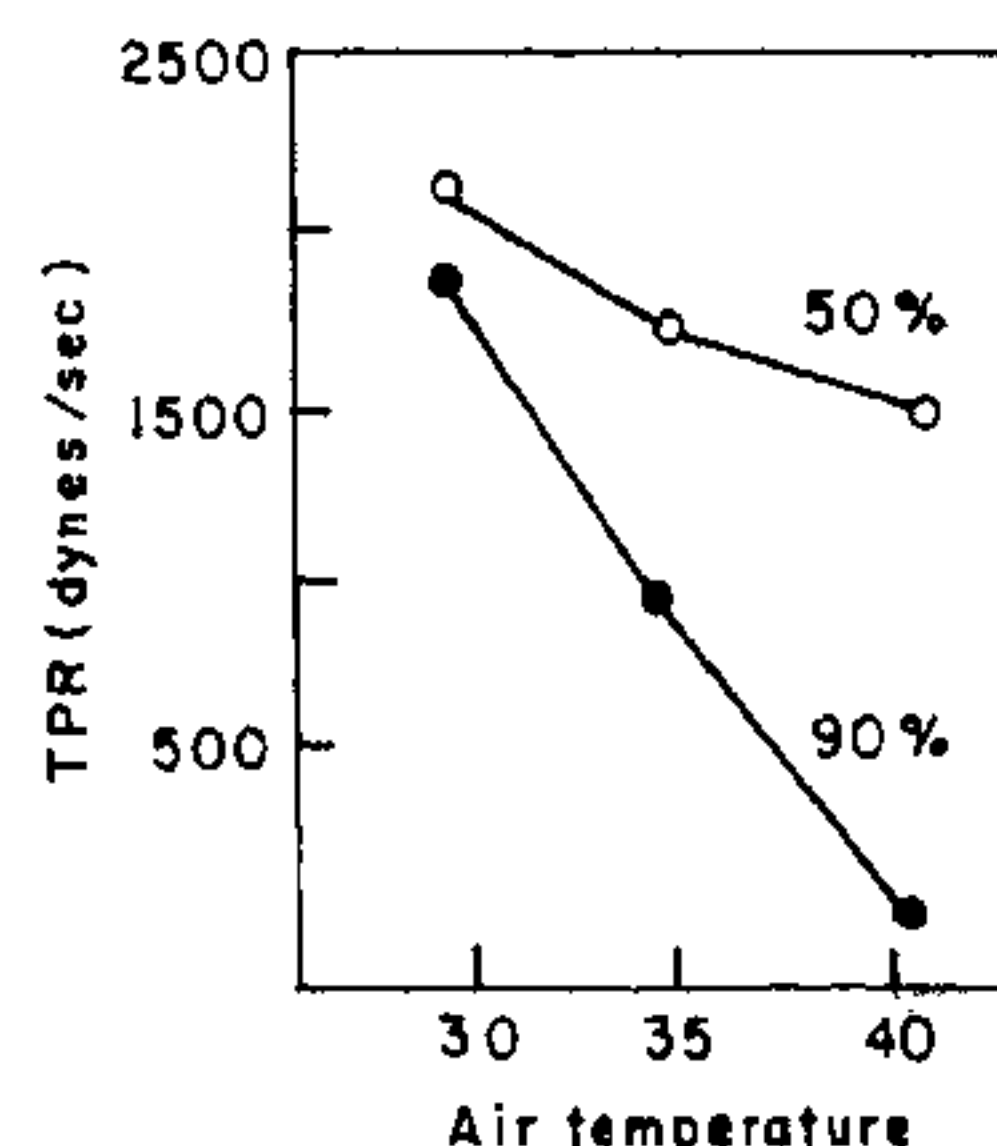


Figure 4. Total peripheral resistance in a nude, healthy young man in relation to environmental temperature and different levels of relative humidity.

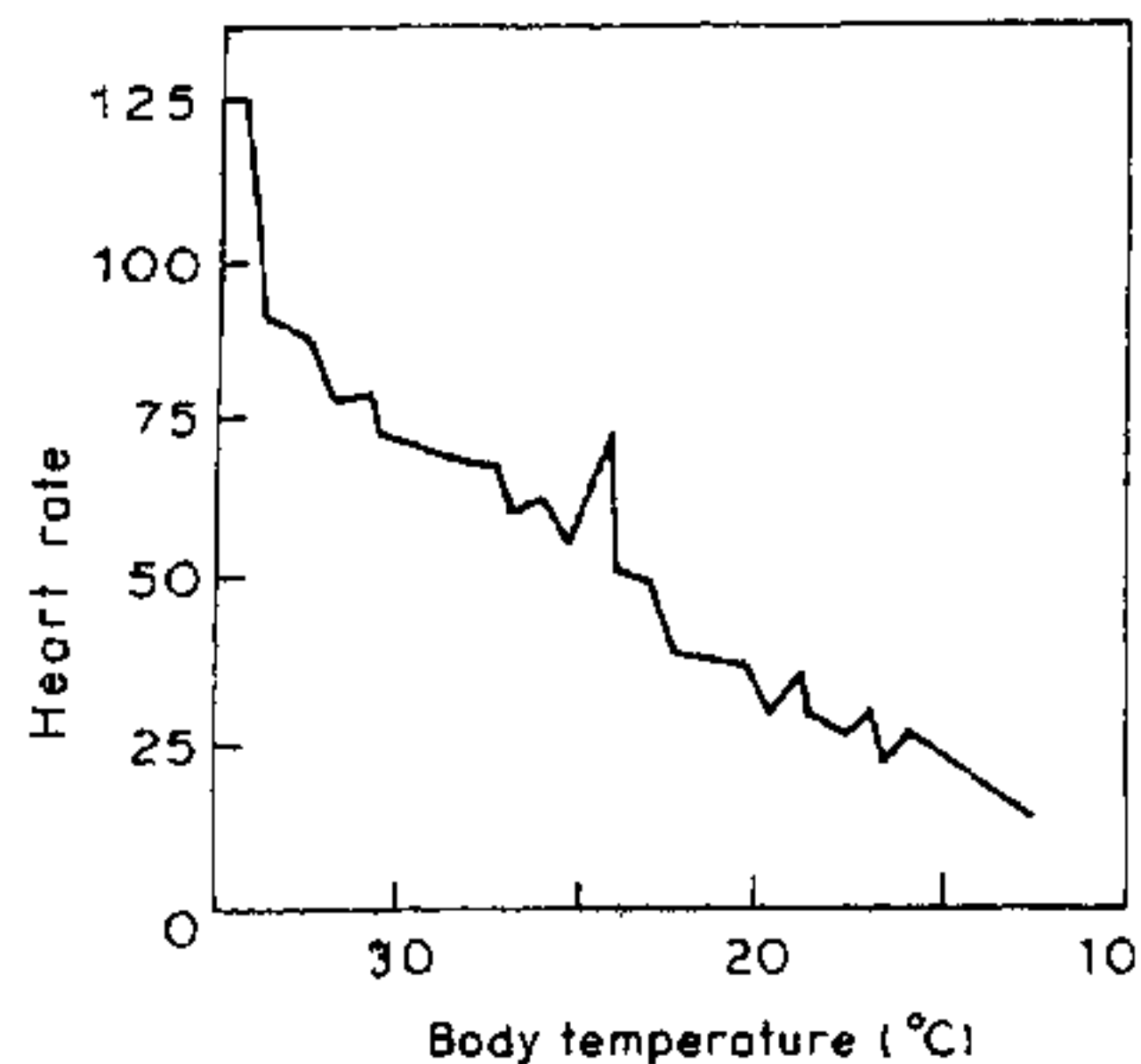


Figure 5. Heart rate of woodchuck during hibernation.

the chemical domain, cardiac molecules are composed of elements that were once synthesized inside many long-dead stars. Elements may excite, they may slow or even wreck the heart. In chemical cardiology, the theme song belongs to elements. Carbon and hydrogen form the bulk elements of which the heart is made; calcium excites the heart, but its effect is blocked by magnesium; and sodium and potassium modulate the normal stream of cardiac contractility. The elemental music is perfect for all seasons except when a regular player is missing or his place is taken by an impostor with no music in his soul. We would however recognize impostors better for having known the score of regular players because the knowledge of physiological elements is the very means for coming upon the role of harmful elements that lurk in our geographical environment.

Consider potassium and sodium. Potassium is the main intracellular cation in the heart; sodium is largely excluded. Intracellular potassium remains around 151 meq per litre of fibre water, sodium concentration being a mere 6.5 (ref. 4). The asymmetry of ion distributions across cell membranes is a central fact in cellular physiology. The cell is however far from a simple pouch filled with potassium solution. Potassium may be bound to proteins, its exchangeability may be determined by temperature, and its distribution within the cell may be non-uniform. Nevertheless, the bulk of potassium behaves as if it were in free solution and it exchanges fully under physiological conditions.

The sodium ion has low permeability through the cell membrane. Entering the cell during an action potential, it needs a mechanism of active transport to make an exit. A steady state exists in which sodium diffuses into the cell at a rate determined by the membrane permeability for sodium and the electrochemical gradient of sodium across the membrane; it is then pumped out by an active transport system (Figure 6). During excitation, membrane permeability to sodium suddenly increases with an inward rush of sodium.

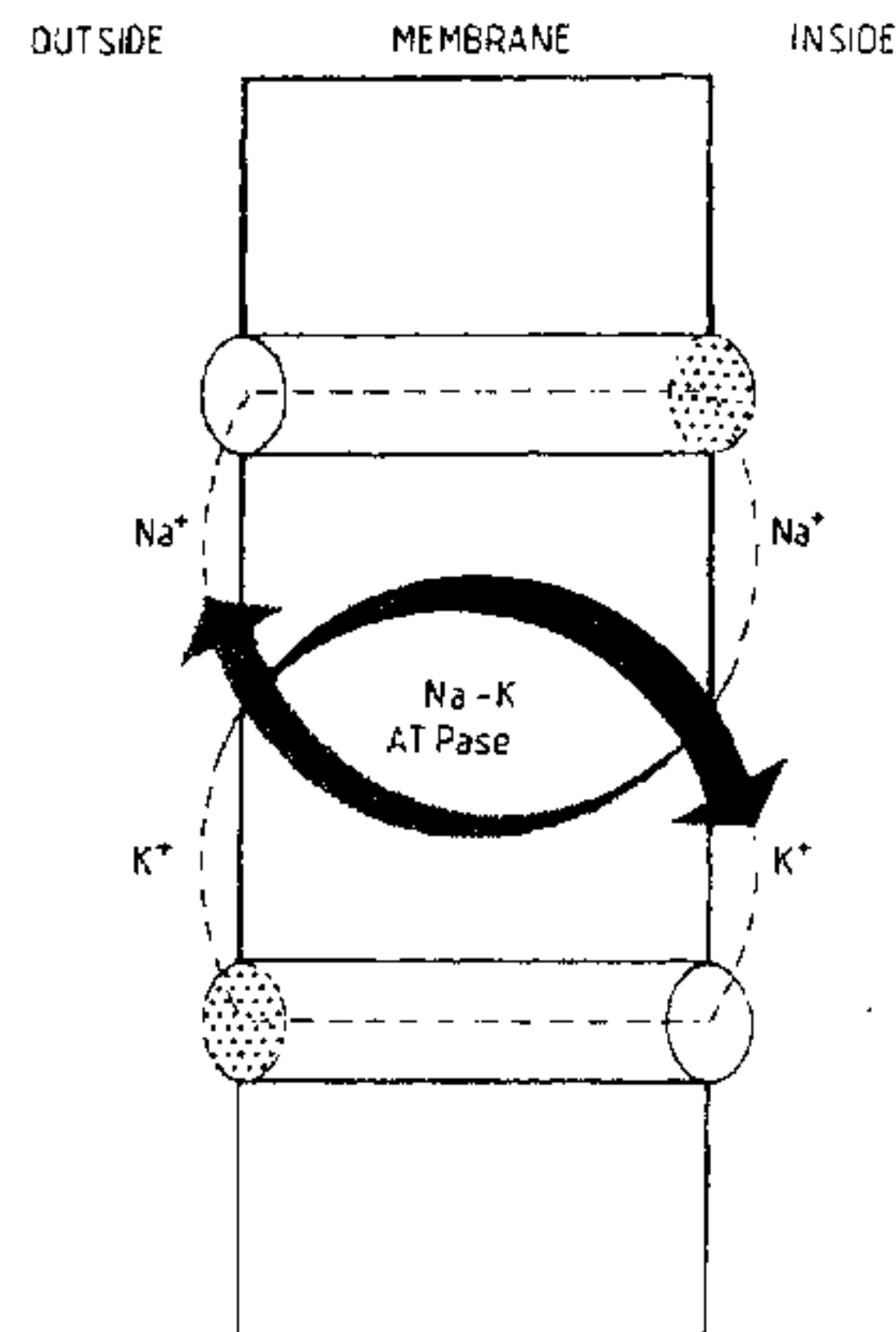


Figure 6. Mechanisms of active transport of sodium and potassium through the cell membrane.

When excitation is over and repolarization begins, ionic charge moves in the opposite direction in the form of potassium migration outside the cell. At this point the cell has gained sodium and lost potassium: active transport of both ions becomes necessary to restore the original set of conditions.

Alterations in the extracellular concentration of sodium and potassium evoke changes in the contractility of the heart. Increase in extracellular potassium causes a decrease in contractility until the heart arrests in flaccid dilation. Conversely, the response of the heart to a decrease in potassium concentration is enhanced contractility. Variations in extracellular sodium produce similar reactions. What influences contractility is not a ratio between these monovalent cations but the sum of their intracellular concentrations. What could be more important for contractility is the number of ions available per contractile protein unit. The absence of monovalent-cation specificity in intracellular reactions is a recurrent theme in cellular cardiology.

Lithium, for example, is an alkali earth metal that biochemically resembles sodium, but has no physiological role. Both may inhibit a group of enzymes that need potassium for activity⁵. Substitution of sodium by lithium in the culture medium for kidney slices causes marked inhibition of potassium uptake and severe inhibition of respiration. This is not all. Once inside the cell, the efflux of lithium is ten times slower than that of sodium. Whereas sodium can be transported outside the cell against an electrochemical gradient a lithium-loaded muscle cannot dislodge lithium into an outside solution. Even though the action potential of muscle due to the inward movement of sodium is mimicked by

lithium, the poor capacity of cells to pump out lithium leads to the slow intracellular accumulation of lithium and a stony heart.

Similar is the relationship between rubidium and potassium, which are chemically similar. Rubidium causes depolarization initially; this is followed by a further and slower decline in membrane potential due to the accumulation of rubidium. The membrane transport mechanism distinguishes poorly between rubidium and potassium so that both ions accumulate in the cell. Since the membrane permeability for rubidium is lower than that for potassium, intracellular concentration of rubidium will soon exceed that of potassium⁶. Rubidium however cannot substitute for potassium in the animal economy and the replacement of potassium by rubidium causes the death of rats in a few weeks.

The theme of an essential element being replaced by nonphysiological elements continues in the calcium story. Calcium towers over all elements in the study of cardiac muscle response to stimulation. It is the main link in the excitation-contraction coupling. A frog heart will cease its contractions in a calcium-free solution and restart promptly when calcium is added to it. Once the contraction has begun, the addition of calcium will cause an increase in twitch tension. Vital for the normal function of the excitable membrane, calcium does not govern resting membrane potential; its effective role is reserved for excitation, spike and repolarization phenomena of the cardiac muscle cell. It interacts with several elements, magnesium being foremost among them. The blockage of neuromuscular transmission by magnesium, for example, is reversed by calcium. While magnesium and calcium have little effect on the contractile response of the skeletal muscle to electrical stimulation, they produce opposite responses in the cardiac muscle. Apart from being 'nature's calcium-channel blocker', magnesium has other effects on the heart. When deficiency of magnesium occurs in man owing to poor diet, chronic alcoholism or gastrointestinal disorder⁷, it not only damages the cardiac machinery but also seemingly yields its place to other elements in the heart.

Unlike magnesium, which blocks calcium, barium and strontium resemble calcium in prolonging the terminal phase of repolarization. Strontium has been used extensively to replace calcium in experimental studies on muscle contractility. The lack of ion specificity in several of these elemental phenomena suggests the presence of a chemical site on the excitation-contraction mechanism for which barium, strontium, calcium, magnesium and other cations can compete. This site must have stronger affinity for physiological elements than for nonessential elements. In the absence of physiological elements, other elements are free to reach the site and evoke a response which may be stimulatory

to begin with, but turn destructive in the end. When accommodating toxic instead of physiologic elements, the heart muscle 'is clinging to a poisonous plant taking it for a sandal tree' (Bhavabhuti). This concept derives support from recent findings in relation to endomyocardial fibrosis—a heart muscle disease—of the tropics.

Geochemical clues in endomyocardial fibrosis

Endomyocardial fibrosis is a disease of the heart muscle, with the highest prevalence in countries within 12° of the equator. Claiming children and young adults from the poorer strata of society as its victims, the disease advances by the progressive growth of fibrous tissue within the ventricles of the heart (Figure 7). What follows is the gradual obliteration of the chambers, entrapment of the atrioventricular valves, valvar insufficiency and heart failure (Figure 8). The disease is invariably fatal with less than 30% patients remaining alive five years after the onset of symptoms⁸. Surgical treatment, drastic but more effective, consists of the excision of the fibrous tissue and replacement of the incompetent valves⁹. The cause of the disease remains unknown; the theories of causation have ranged from viral infection to eosinophilia with autoimmunity thrown in for good measure. None of the theories has taken note of the cardinal preferences of the disease for the equatorial zone, for the poorest among the young, and for the heart. Nor have they provided supportive evidence, the passage of decades notwithstanding. If the old theories are lacking in evidence, the causation must lie elsewhere, and an obvious factor to look at is the geography of patients.

A recent analysis of the cardiac tissues of patients, in fact, showed high concentrations of cerium and thorium in conjunction with a deficiency of magnesium, the difference in the levels of cerium and magnesium in



Figure 7. Heart in endomyocardial fibrosis. Notice the shrunken ventricular chamber below and the dilated atrial chamber above.

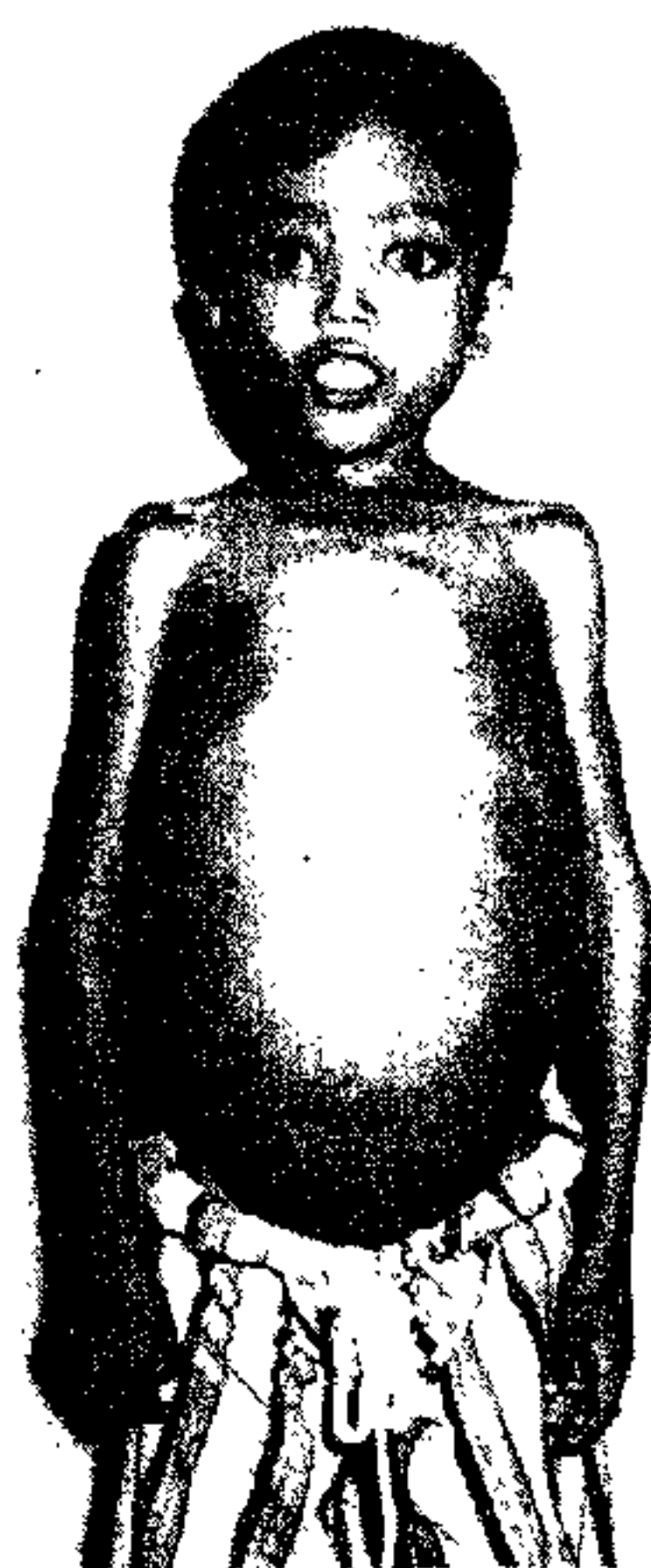


Figure 8. A child with endomyocardial fibrosis in heart failure.

comparison with those of controls being statistically significant^{10,11}. Given the fact that monazite—abundant in the lateritic soil of Kerala and other areas of the tropics—is essentially a phosphate of cerium, which forms 28.5% of its weight, the presence of cerium in the cardiac tissues of patients would suggest a geochemical clue to the causation of the disease. If geography underlies the presence of cerium, it is poverty and the consequent nutritional deficits of patients which cause the observed deficiency of magnesium. Magnesium deficiency is, in fact, a common accompaniment of malnutrition in children whose low intake and poor gastrointestinal absorption are compounded by their growth needs for the element. The question arises whether the presence of cerium is functionally coupled with the deficiency of magnesium and whether their conjunction holds the key to the riddle of endomyocardial fibrosis.

From the symmetry of reactions at the cellular level for elemental pairs such as sodium/lithium, potassium/rubidium and calcium/strontium, lack of metal-ion specificity stands out as a major feature of bio-inorganic phenomena. Zinc and cadmium, iron and gallium are other pairs that illustrate the same principle. The basis of experimental reactions which deliberately replace magnesium and calcium by lanthanum and strontium is no different. Lastly, the substitution of magnesium at critical enzyme and regulatory sites by the toxic species of aluminium, Al^{3+} , is of allied interest because of its bearing on Alzheimer's disease¹². Therefore the case for elemental interaction in the genesis of endomyocardial fibrosis is not

unprecedented in human pathology. The problems that call out for investigation are whether the deficiency of magnesium promotes the concentration of cerium and, secondly, whether the replacement of deficient magnesium by cerium will produce endomyocardial fibrosis.

To determine whether the deficiency of magnesium promotes the concentration of cerium, an experiment was carried out in a tuber crop—*Coleus parviflorus*—in culture. The plant model was chosen because tuber crops are consumed by patients regularly and they have been reported to concentrate monazite elements like thorium. The data clearly showed that cerium levels are enhanced by the deficiency of magnesium¹³. In a corroborative study *in vitro*, thorium and cerium catalysed the non-enzymatic hydrolysis of adenine and guanine nucleotides and both elements promoted the binding of creatine kinase to Cibacron Blue F3G-A, a substrate analogue of the enzyme, even in the absence of Mg^{2+} , the physiological cofactor¹⁴. Moreover, the inhibitory effect of cerium on protein synthesis, including that of myofibrillar proteins, by cardiac myocytes in culture is enhanced when the culture medium is deficient in magnesium¹⁵. These observations would imply that cerium can mimic the functional effects of magnesium under given conditions. As differences in physical characteristics such as atomic number, charge, radius and electronic configuration between magnesium and cerium do not prevent cerium from functioning as an analogue of magnesium, it is possible that properties such as charge/radius ratio, which is similar for magnesium and cerium (3.03 and 2.90), determine their interaction. The strong forces exerted by charge/radius ratio on the charged sites of biological macromolecules have already been observed by other workers¹⁶. Unlike magnesium, which forms reversible linkages and maintains the dynamic conditions of the cell, cerium probably forms irreversible bonds with biological ligands. This could trigger cellular dysfunction and death and mark the onset of cardiac lesions in endomyocardial fibrosis¹⁷.

The second question remains, whether the combination of magnesium deficiency and the presence of cerium can reproduce the morphological changes of endomyocardial fibrosis. Experimental induction of the disease in animals alone can solve this final riddle and open the possibility of preventing endomyocardial fibrosis by dietary supplementation of magnesium.

Conclusion

The heart came into existence millions of years ago like other evolving organs to deal with pre-existing imperatives. Emergence of a four-chambered design, separation of systemic and pulmonary circulations, and the growth of the coronary tree are reminders of the

evolutionary compulsions on cardiac structure. So are the functional traits that enable the cardiac pump to respond to the pull of geography, no matter whether it concerns high altitude or the chemistry of the soil. As the theatre of life expanded from water to earth and air, the heart learnt to grapple with diverse climes and elements by physiological adjustment in the short run and genetic adaptations over the long haul. Lessons learnt millions of years ago endured and supplied the heart with a rich repertoire to meet new challenges of geography. The greater efficiency of the cardiac pump at high altitude and the lack of ion specificity for several cations in the myocardium are mechanisms that the heart learnt long ago in its effort to move with evolution. A built-in capacity to boost output and the ability to handle more than one element would confer no small evolutionary advantage on the heart. Inherited from ancient days, these patterns of function could nevertheless cause injury if, for example, the muscle cell mistook a toxic element for its physiological cousin. However such injuries are no more than aberrations, or diseases, of evolutionary adaptation. On the whole, the range of cardiac responses has ensured our survival in varied climates and geographic locations. They represent a legacy of life which came on earth long before us.

The synchrony of the heart with geographical events is not a new concept. Heart as a cosmic resonator had found an echo in the *Chandogya Upanishad*, which declared: 'Even so large as the universe outside is the

universe within the lotus of the heart. Within it are heaven and earth, the sun, the moon, the lightning and all the stars. Whatever is in the macrocosm is in this microcosm also.'

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