Advances in Myocardiology
Volume 5

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Preface

The Eleventh World Congress of the International Society for Heart Research 1983 provided an opportunity to review some of the growing points in our knowledge of the structure and function of the myocardium. Those at the meeting will recall how London suddenly went tropical. Yet a series of scintillating reviews held over six hundred scientists captive in the lecture halls of Imperial College. There were sessions on nuclear magnetic resonance, the molecular basis of electrophysiology, calmodulin, protein synthesis and degradation, oxygen free radicals, the structural components of the myocyte, sarcolemmal sodium exchange, and the influence of lipids on membranes.

Here we have gathered together, as quickly as possible, a number of the presentations of the speakers invited to the symposia. They give, we believe, a striking picture of the diversity of technology and scientific enquiry which underlies this immensely active domain of modern cardiology. If only our clinical colleagues were more aware of it!

Peter Harris
Philip A. Poole-Wilson

London

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Evolution, Cardiac Failure, and Water Metabolism

Presidential Address

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Abstract. In this essay, I take the liberty of doubting the widely held view that congestive cardiac failure is due to an inability of the heart to provide enough oxygen for the needs of the body. Instead, the syndrome is best explained by an inappropriate and prolonged stimulation of the neurohumoral defense reaction that developed during evolution to support exercise and preserve life.

DIFFUSION AND CONVECTION

Theology and science alike are agreed that life had its origins in the sea. In these primeval waters, the first cells floated freely. Special devices were developed to transport molecules across the cell wall, but the movement of substances toward and away from these was by diffusion, aided by the random currents of the outside world. As multicellular organisms developed and increased in size, they needed to impose their own convective streams on the surrounding water in order to ensure an exchange of materials that could no longer be achieved by simple diffusion

Many simple organisms, such as the sponges and coelenterates, use the water in which they live as the sole means of convective transport. This system serves the combined functions of respiration, ingestion, and excretion. In more complex organisms, the transport distances within the body became too great to be maintained without the development of a mechanically propelled internal convective system. In the fishes, the function of the external convective system is still mixed. In addition to being used for the exchange of respiratory gases, it is used for the excretion of ammonia, the chief end-product of nitrogenous metabolism, and, to a variable degree, for ingestion.

The motility of the body as a whole is also a mechanism of external convection. This is so even in a unicellular organism such as paramecium. Does it just stir the water, or is it swimming? And what is the purpose of locomotion except to renew the environment? Many fishes have to swim in order to ventilate the gills. Predators rely on movement to capture food.

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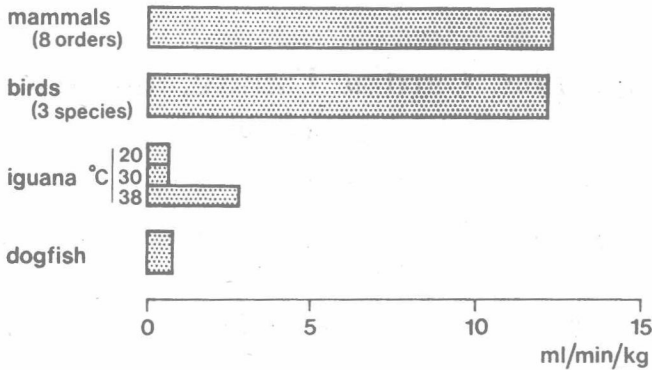
Figure 1. Basal oxygen uptake of mammals and birds compared with that of the iguana and the dogfish. Data from Altman and Dittmer [1].

And we all walk away from our own excrement. In this way, locomotion takes its place as a form of external convection.

This essay considers three great convective systems of the body: the flow of air, the flow of blood, and the flow of urine. They do not work in isolation, and when the heart is diseased, both the lungs and the kidneys suffer. The combined system is under greatest strain when locomotion, the fourth convector, comes into operation. We shall see how the demands of physical exercise have necessitated the development of a specific neuro-hormonal response and how the inappropriate and prolonged evocation of this response leads to the clinical syndrome of cardiac failure.

EVOLUTION OF THE LUNGS

Life began without oxygen, and the primitive pathways for the anaerobic production of high-energy phosphate groups persist to this day in every cell of our body. The bath of oxygen in which we now find ourselves is the result of the activity of photosynthetic organisms. With the arrival of oxygen, op-portunistic forms of life took advantage of the greater efficiency with which biologically useful energy could be derived from the combustion of hydro-gen, and this process has been a dominating evolutionary force. It is probable that the mitochondria invaded the primitive eukaryotic cell as parasitic mi-croorganisms in past eons and have stayed there ever since.

A survey of the oxygen consumption of the vertebrates leads us to the first of a group of "evolutionary jumps" that coincide with the development of warm blood (Figure 1). The oxygen consumption of mammals and birds is many times that of the cold-blooded vertebrates and is not due simply to the higher temperatures of the body (Figure 1). It was accompanied by an equally striking jump in the cardiac output (Figure 2).
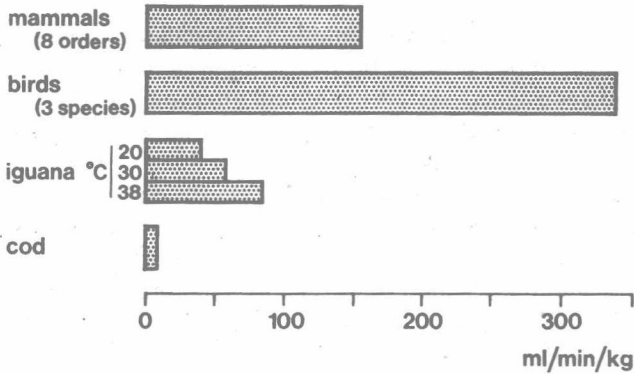
Figure 2.   Basal cardiac output of mammals and birds compared with that of the iguana and the cod. Data from Altman and Dittmer [1].

At the same time, radical changes were occurring in the design of the cardiovascular and ventilatory systems. In the fish, a single ventricle pumps blood first to the gills and subsequently to a second capillary network in the body. The mammals and birds developed a two-pump system, one pump being responsible for respiratory exchange with the outside world, the other for supplying the tissues of the body. The amphibian heart is a halfway step between the two.

With the emergence of life onto the land and into the air, the ventilatory system became converted from water to air. The use of air carried two bonuses. Oxygen is poorly soluble in water, so that air allowed an impressive reduction in the volume of ventilation (Figure 3). At the same time, air is
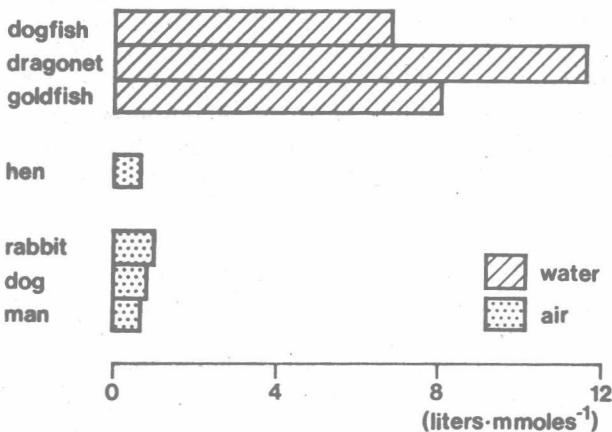
Figure 3.   Ratio of ventilation to oxygen uptake in various fishes, in the hen, and in mammals. Data from Dejours [4].

much lighter than water, and this allowed an oscillatory ventilatory system to be developed in place of the flow-through system of the gills.

The two redesigned systems of circulation and ventilation met in the lungs. This was to be the organ on which the dominating success of the warm-blooded animals would depend. It allowed the massive increase in the uptake of oxygen that was required during exercise and released the organism from the need to remain at the water's edge. A complex arborization of air tubes emerged from a single in-pouching of the pharyngeal ectoderm and ended in a vast and gossamer-thin exchange membrane. The alveolar membrane was less than a micron thick and would cover the area of a squash court, and yet it had been organized within the volume of a football.

The design was brilliant, yet it carried with it the seeds of disaster—a susceptibility to flooding. Pulmonary edema could never have occurred in the fish. It is one of the prices of evolution.

ECONOMY OF WATER

The threat of flooding came more from within than from without. The pulmonary extravascular space is as susceptible as the systemic to changes in water balance.

Economy of water affects cells as well as the extracellular liquids. Within each cell, there are some 2000–3000 different enzymes, each with one or two substrates and many with cofactors. If all these molecules were present in simple solution, the cell would be impossibly big.

Very early in evolution, a number of devices were developed that allow the cell to contain within a small space the vast number of molecules necessary to its function. Fuel may be stored in an insoluble form such as glycogen or triglyceride. Enzymes may be embedded in membranes so that only their active sites stick out into the watery phase. Most enzymes operate at a low K_m so that the concentration of substrate does not have to be high, and K_m values tend to be similar in a sequence of enzymes so that the product of one reaction may be fed into the next without large fluctuations in concentration. Finally, the formation of activated compounds such as the thioesters of coenzyme A drastically reduces the concentrations at which a reaction can occur.

The economy of water in the extracellular space is no less important. This has been greatly helped by the development of a closed circulatory system. In the crustaceans and the molluscs, the arteries deliver blood directly into the intercellular spaces, from which it returns to the heart through ostia. The relatively closed circulatory system of the vertebrates has led to a considerable reduction in the volume of extracellular liquid.

Despite all these economies, both inside and outside the cells, the body is still predominantly water.

EVOLUTION OF RENAL FUNCTION

The overall control of body water rests largely with the kidney. It seems likely that the primary function of this organ was to rid the body of excess water. According to Homer Smith [11], the fishes had their origin in fresh water. The problem that faced these progenitors of the vertebrates was the same problem that faces the freshwater fishes of today—a surfeit of water that was continually absorbed by osmosis into the gills. The kidney disposed of water by a process of filtration followed by the reabsorption of salts. This devious system was necessitated by the universal inability of the vertebrates to design a pump through which water could be actively transported across cell membranes. At this stage in evolution, the kidney was not used for the excretion of nitrogenous waste, which was eliminated as ammonia by simple diffusion across the gills.

Migration into salt water brought opposite problems. Now the sea drew water out of the circulation by osmosis through the gills. The kidney was useless; in many marine species, its tubular system is rudimentary, and in some it has lost its glomeruli. To counteract the loss of water, most species drink the seawater, which is reabsorbed in the intestine. The reabsorbed salt is then removed by chloride cells in the gills. Once again, the body uses the active transport of sodium or chloride ions; the movement of water is passive.

With migration onto land, the ingestion of water was intermittent, and the main concern was its conservation. At the same time, it became no longer possible to eliminate nitrogenous waste as ammonia through the gills. Ammonia is toxic above a very low concentration, so that it had to be converted to a more acceptable form. For this purpose, the mammals chose urea, while the birds and reptiles chose uric acid. The kidney now took on the responsibility for both water and salt balance and for the excretion of nitrogenous waste. It was now required not only, on occasion, to produce a highly dilute urine in the way it had originally functioned, but also, on other occasions, to produce a highly concentrated urine in order to conserve water. To provide this latter function, the kidney developed the concentrating mechanism associated with the loop of Henle. The overall control of water and salt balance was the responsibility of a neurohumoral mechanism that comprised the sympathetic nervous system in coordination with renin–angiotensin, aldosterone, and vasopressin.

At this stage, we come across another remarkable evolutionary jump—a great increase in the glomerular filtration rate (Figure 4). Such a high rate could be achieved only by a high flow of blood through the kidney, since the colloidal osmotic pressure of the plasma sets a limit to the filtration fraction. Thus, in man, the kidneys receive as much as one quarter of the output of the heart.
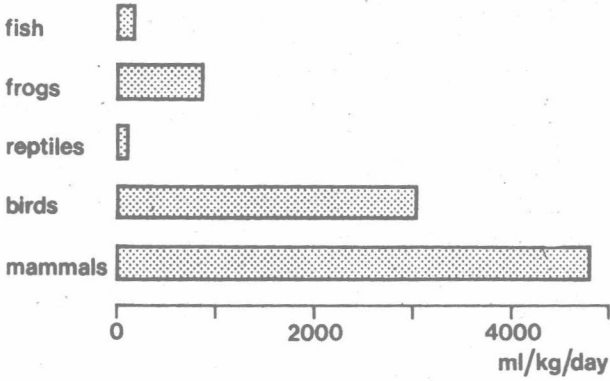
Figure 4. Average values for the glomerular filtration rates of various classes of vertebrates. Data from Schmidt-Nielsen and Mackay [10].

DISTRIBUTION OF THE CARDIAC OUTPUT·

The necessity for such a large flow of blood to the kidney is, as we have seen, the mechanical requirement of filtration and not a metabolic requirement for oxygen. The case is similar for the skin, where a large flow of blood is required for the dissipation of heat. Thus, these organs receive a share of the total cardiac output that is disproportionately high in relation to their requirement for oxygen. It follows that the rest of the body has to be content with less than its share (Figure 5). Such inequalities lead to wide discrep-
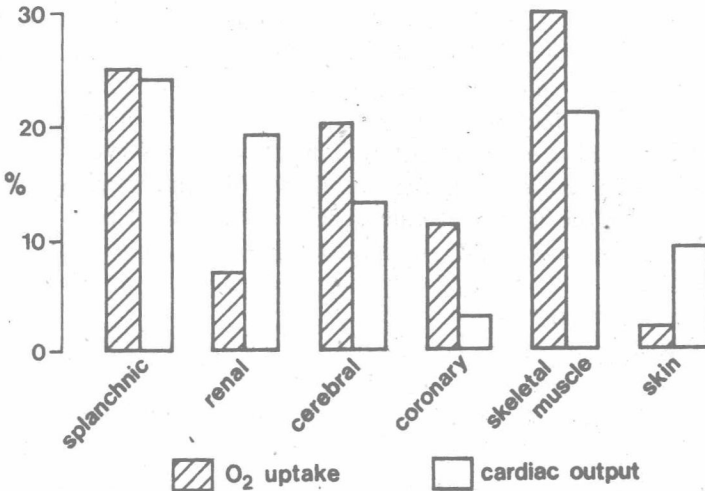

Figure 5. Percentage of total oxygen consumed and percentage of total cardiac output received by various organs in a normal person at rest. Data from Wade and Bishop [12].

ancies in the arteriovenous differences for oxygen. Of these, the most notable is that for the myocardium, which extracts two thirds of the oxygen brought to it. Skeletal muscle is affected in a similar way.

During physical exercise, the oxygen uptake of skeletal and cardiac muscle may increase many times. To support this increase, they have been endowed with a powerful and overriding local vasodilatory mechanism. At the same time, activation of the sympathetic nervous system constricts the blood supply to those parts of the body that are not immediately necessary for the purposes of exercise [12]. This vasoconstriction particularly affects the kidney.

Thus, during evolution, the mechanical necessity for a high renal blood flow has, in this indirect fashion, caused the myocardium to be utterly dependent on local vasodilatation during physical exercise. The consequences are tragic when the coronary arteries are rendered rigid by atheroma in a population that has outgrown the age during which the forces of natural selection have operated.

THE BLOOD PRESSURE

An important factor underlying the development of atheroma is the level of the blood pressure. We do not need epidemiology to tell us this; we each carry our own control. Atheroma is limited and late in the normal pulmonary circulation, but becomes prominent when, in disease, the pulmonary arterial pressure reaches the level of the systemic. And here we meet our last and most striking evolutionary jump (Figure 6). The systemic blood pressure of fishes, amphibians, and reptiles averages about 30 mm Hg. But all mammals have a blood pressure similar to ours, and birds average somewhat higher. Why this has come to be so has nothing to do with standing upright, although advantage is taken of the mechanism for this purpose [6].

CONGESTIVE CARDIAC FAILURE

We start with a semantic disadvantage. The difficulty is that the term carries its own definition. To take a recent example [3], congestive cardiac failure is:

> The pathophysiological state in which an abnormality of cardiac function is responsible for failure of the heart to pump blood at a rate commensurate with the requirements of the metabolizing tissues.

The heart can fail only in pumping enough blood. But enough blood for what? The metabolic requirements of the tissues. Then what are those requirements? Oxygen, glucose, free fatty acids? Only for oxygen does the entire cardiac output pass through the point of entry into the body. But, if