

## Full Review

# The evolution of blood pressure and the rise of mankind

Kevin Schulte, Uta Kunter and Marcus J. Moeller

Department of Nephrology and Clinical Immunology (Internal Medicine II), RWTH Aachen University Hospital, Aachen, Germany

Correspondence and offprint requests to: Marcus J. Moeller; E-mail: mmoeller@ukaachen.de

### ABSTRACT

Why is it that only human beings continuously perform acts of heroism? Looking back at our evolutionary history can offer us some potentially useful insight. This review highlights some of the major steps in our evolution—more specifically, the evolution of high blood pressure. When we were fish, the first kidney was developed to create a standardized internal ‘milieu’ preserving the primordial sea within us. When we conquered land as amphibians, the evolution of the lung required a low systemic blood pressure, which explains why early land vertebrates (amphibians, reptiles) are such low performers. Gaining independence from water required the evolution of an impermeable skin and a water-retaining kidney. The latter was accomplished twice with two different solutions in the two major branches of vertebrate evolution: mammals excrete nitrogenous waste products as urea, which can be utilized by the kidney as an osmotic agent to produce more concentrated urine. Dinosaurs and birds have a distinct nitrogen metabolism and excrete nitrogen as water-insoluble uric acid—therefore, their kidneys cannot use urea to concentrate as well. Instead, some birds have developed the capability to reabsorb water from their cloacae. The convergent development of a separate small circulation of the lung in mammals and birds allowed for the evolution of ‘high blood-pressure animals’ with better capillarization of the peripheral tissues allowing high endurance performance. Finally, we investigate why mankind outperforms any other mammal on earth and why, to this day, we continue to perform acts of heroism on our eternal quest for personal bliss.

**Keywords:** blood pressure, evolution, kidney

### INTRODUCTION

In some Aboriginal parts of our world (e.g. the African Kalahari, the northwestern parts of Mexico or Australia), humans

still outrun antelopes—or even the cheetah, the fastest land animal [1]. ‘Persistence hunting’ requires that humans run for ~2–5 h over some 25–35 km (16–22 miles) until their prey is too exhausted to continue [2–4]. Out of all mammals, only humans are able to deliver such high physical performances over such prolonged periods of time.

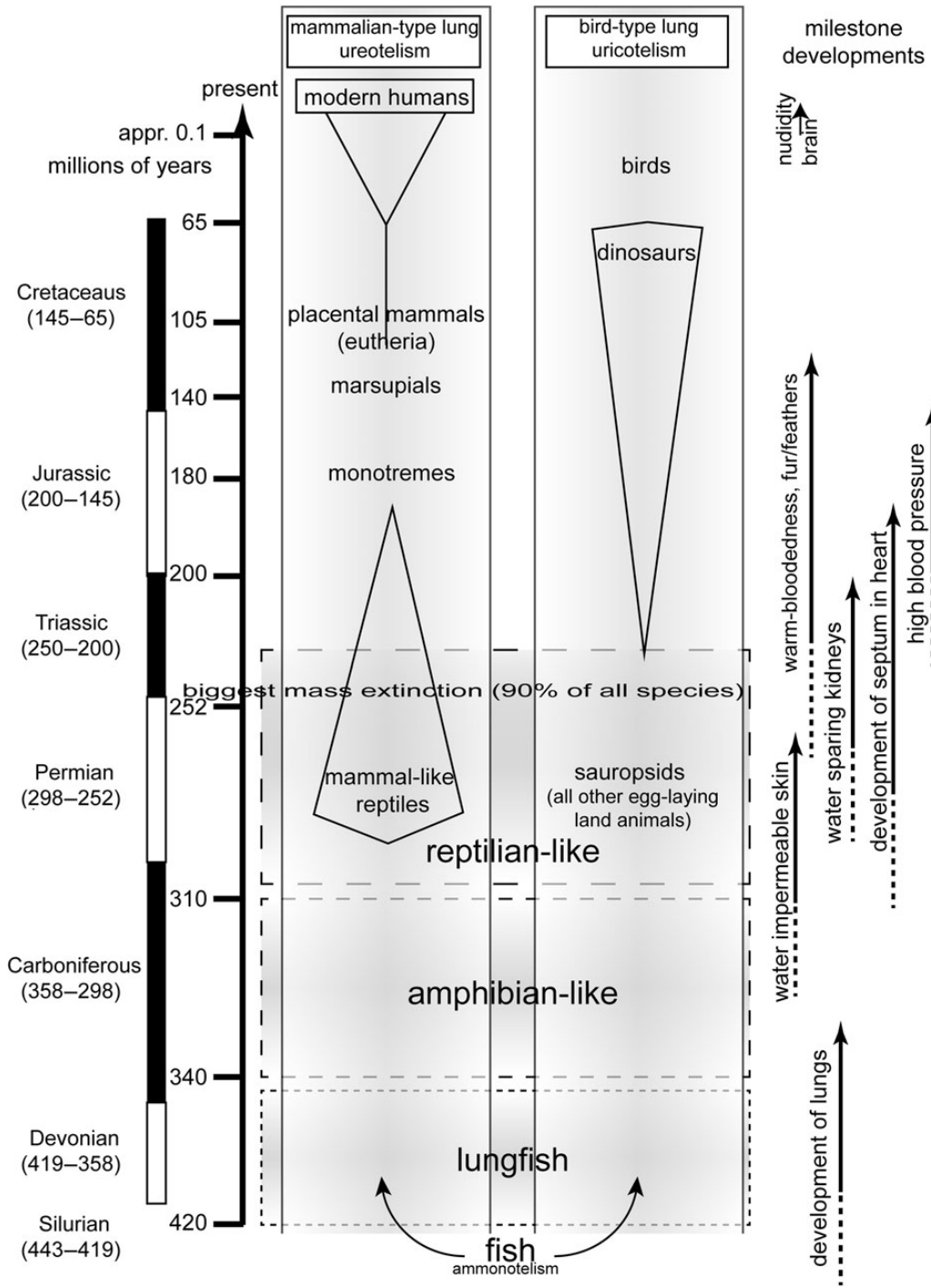
Today, running a marathon has become a popular sport among modern humans; the average finishing time has remained quite constant (~4.5 h) over the past decades. Unlike the first official marathon runner, the messenger Pheidippides, who according to the legend collapsed dead after exclaiming victory to the Athenians in the Battle of Marathon in 490 BC, the mortality rate does not increase significantly from running a marathon. In a recent analysis of more than a million marathon runs, the mortality rate was only 0.00075% within the first 24 h [5].

In the present review, we will investigate why humans are such extraordinary long-distance performers and why apparently only our species persistently delivers heroic acts. Special emphasis will be placed on the central role of the kidney on our long and ever-lasting pursuit of personal bliss.

### THE PRIMORDIAL OCEAN WITHIN US: INVENTION OF THE KIDNEY

We will begin our journey towards personal happiness with the fish, which evolved ~500–350 million years ago (Figure 1). As already well illustrated by Homer W. Smith [6], one of the major novel inventions of the fish was its capability to actively stabilize its internal milieu. Remarkably, the relative ionic composition (sodium, potassium, chloride and calcium) of the extracellular fluid is virtually identical in fish as well as in all subsequent animal species (including amphibians, reptiles and mammals) [7] (Table 1).

Because the salt concentration of the ocean has increased steadily over time, saltwater fish have a hypoosmolar internal



**FIGURE 1:** Chronological overview. From fishes, two major continuous separate evolutionary pathways can be traced which lead either to mammals (including humans) or to birds (including dinosaurs). Both branches show similar phenotypic stages of development (e.g. the stages of the lungfish and amphibian-like and reptilian-like animals). However, as evidenced by the different anatomy of the lung, the evolution of both branches was separate, even though similar (convergent) developments occurred (e.g. water-impermeable skin, separation of the pulmonary circulation, high blood pressure, warm-bloodedness etc.). The position of each animal klades (species) indicates the approximate time point of the 'last most common ancestor' [8]. Each transition of the geological ages (indicated on the left) was accompanied by mass animal extinctions and a subsequent rise in novel animal klades (species). Examples for *monotremes* and *marsupials* are the platypus and kangaroo.

milieu and lose water constantly to the hyperosmolar environment. To cope with this problem, saltwater fish drink up to 25% of their total body weight per day [9, 10]. To excrete the electrolytes of the ocean water, most of the sodium and chloride is excreted in an adenosintriphosphate-dependent process

via the gill epithelium [11, 12]. From an evolutionary perspective, one might say that fish 'invented' the kidney. In fact, glomeruli and tubuli evolved independently and were combined only later into a single functional unit, the kidney. The kidney's predominant role in saltwater fish is the excretion of

**Table 1. Extracellular electrolyte concentration of the major inorganic ions in vertebrates in comparison to the salt concentration of the ocean**

	Sodium	Chloride	Potassium	Calcium
Ocean	100	116.4	2.17	2.19
Fish	100	89.6	1.95	1.87
Amphibians	100	91.6	3.03	1.74
Reptiles	100	68.5	4.15	2.22
Mammals	100	71.4	2.85	1.78

To enable the comparison of the chloride, potassium and calcium concentration, sodium was standardized to 100 mmol/L, and the same correction factor was applied for the other ions.

divalent ions (especially magnesium) [7, 13]. Saltwater fish essentially form only the equivalent of the proximal tubule; thus, their urine osmolarity is always similar to the serum osmolarity [13].

When the fish conquered freshwater, the situation was reversed: the internal milieu of the fish was of a higher osmolarity with respect to freshwater, resulting in potential hyperhydration. The problem was solved in part by increasing the glomerular filtration rate (GFR) and with the development of a distal tubulus. Freshwater fish are capable of excreting a hypoosmolar urine relative to plasma (the first—but inefficient—salt-retaining kidney). This is why thiazide diuretics (targeting the distal tubule) induce more of a saluresis rather than an aquaresis (i.e. the relative loss of salt in the urine exceeds that of water). In addition, the urinary bladder and the gills also reabsorb sodium and chloride in freshwater fish [14, 15]. The GFR is quite variable in fish. In saltwater fish, up to 90% of the glomeruli may not actually be filtering [16]. The glomeruli may be reactivated in states of hydration. This phenomenon is called ‘glomerular intermittency’ and is relevant particularly in fish transitioning between salt- and freshwater.

In summary, from our early days as fish, we have taken the primordial ocean with us. The kidney was developed to maintain a standardized internal milieu within us.

## THE CONQUEST OF DRY LAND AND THE EVOLUTION OF THE LUNG

The next major step in our quest for personal bliss was the conquest of dry land. This transition required the ability to breathe. In shallow and warm waters, the oxygen tension is already considerably reduced and gills may no longer be sufficient to supply the body with oxygen. This appeared to be a rather common problem. In fact, the ability to extract oxygen from the air was developed independently >50 times in the course of evolution [17]. The electric eel (*Electrophorus electricus*), for example, gulps air into its mouth and extracts oxygen via capillary beds in its buccal mucosa [18]. The armoured catfish (*Hoplosternum littorale*) swallows air into its highly vascularized intestine, if the partial pressure of oxygen drops [19]. Therefore, it is not surprising that the actual lungs developed as an evagination from the upper gastrointestinal tract.

Any lung has the major limitation that it absolutely requires a low perfusion pressure. This is because the barrier between air and blood has to be very thin to allow sufficient gas

exchange by diffusion (~1 µm). Such a thin air-blood barrier limits the pulmonary perfusion pressure to less than ~30–40 mmHg (407–543 mmH<sub>2</sub>O). If the perfusion pressure were higher, significant pressure-driven filtration of fluid into the alveoli would occur. The consequences of even a minor increase in pulmonary pressure are illustrated in clinical practice in patients with myocardial failure. These patients characteristically develop pulmonary oedema and respiratory distress because of increased pressures within the pulmonary veins and subsequently impaired gas exchange.

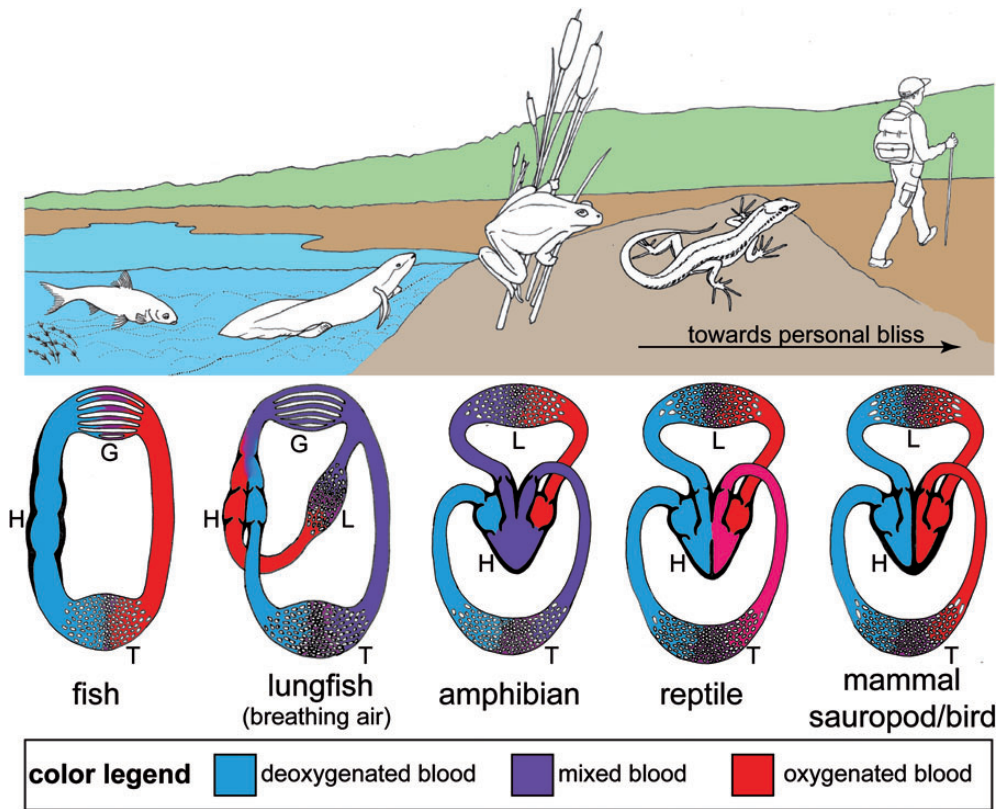
Because the lung developed from the front gut, its blood supply was first identical to that of all other tissues (Figure 2). For this reason, the systemic blood pressure had to be relatively low in early air breathers (i.e. lungfish, amphibians, reptiles). As evolution proceeded, the circulatory system of the lung was gradually isolated from the systemic circulation. An incomplete septum separating the heart ventricle first introduced the advantage that oxygen-rich blood could be diverted into the systemic circulation. When the animal was holding its breath (e.g. when diving), the lung could be shunted. This is because pulmonary vasoconstriction occurs when oxygen tension in the lung is low. The venous blood is diverted directly into the systemic circulation via the gap in the septum of the heart (Euler–Liljestrand mechanism [20]). Hypoxic pulmonary vasoconstriction is evolutionarily preserved due to various additional advantages. However, it is also the reason for pulmonary oedema in mountaineers at high altitudes.

## WHY FROGS ARE NOT GOOD RUNNERS

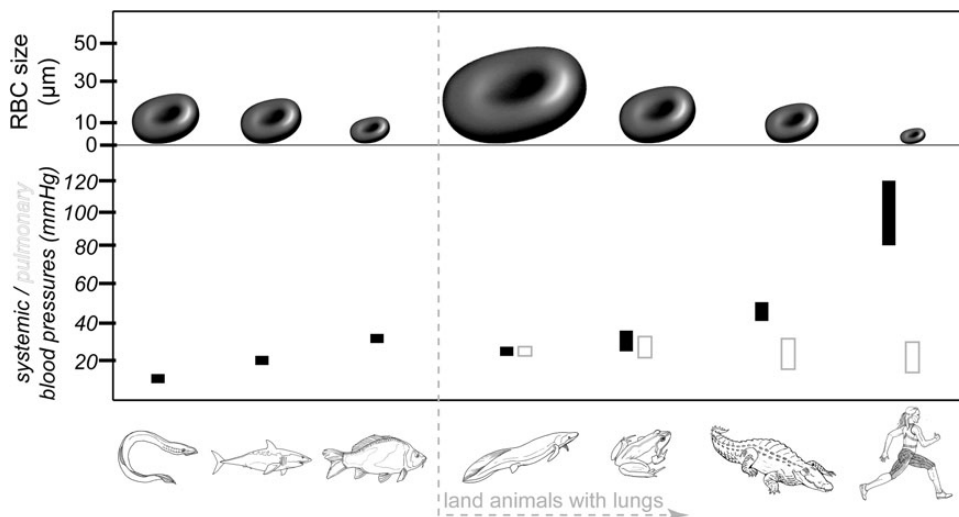
A low systemic blood pressure is the reason why early land animals are unable to deliver a sustained high physical performance. The adaptive changes in the microcirculation of low-pressure animals explain why these animals are not good runners.

Early air-breathing animals, i.e. lungfish and some amphibians, have the largest erythrocytes of all vertebrates. With a diameter of ~40–50 µm, their erythrocytes are much larger than those of humans (7 µm). Several studies have analysed the size of the red blood cells of vertebrates and found two trends in which the lungfish/amphibians instituted a major evolutionary transition (Figure 3). From the earliest fish, the agnathans (jaw-less), to the most recent bony fish (osteichthyes), the erythrocyte diameter has decreased from ~20–12 µm. The terrestrial vertebrates show the same tendency. From the earliest terrestrial vertebrates, the amphibians, to mammals, the size has declined from a diameter of 50 µm to a diameter of ~5–7 µm [21, 22]. As a side note, on this evolutionary path, the erythrocyte nucleus was removed in mammals but not in birds.

What was the evolutionary advantage driving this formidable reduction in erythrocyte size? A positive correlation exists between erythrocyte size and capillary diameter [23]. On average, red blood cell diameter is ~25% larger than the capillary diameter and erythrocytes are deformed and squeezed during each passage. This minimizes the distance between the erythrocytes and the tissue optimizing gas exchange. However, in addition, this is also a mechanism that defines a constant



**FIGURE 2:** Adaptations of the vertebrate cardiovascular system during phylogenesis on our eternal strive towards personal bliss. From left to right: The fish’s cardiovascular system is a relatively simple loop, where the heart (H) drives the blood first across the capillary bed of the gills (G) and then into the peripheral tissues (T). In ‘early’ lungfish, the lung (L) is perfused just like any other peripheral organ. In the simplified example shown, the lungfish is breathing air only, the gills do not participate in oxygenation of the blood. In a submerged animal blood oxygenation would be different. In amphibians, the gills involute after metamorphosis, and even though the heart still ejects the blood from one single chamber, the partial separation of the heart as well as of the pulmonary circulation is already apparent. The reptile’s heart is nearly, and the mammalian heart completely, divided by a septum. In mammals, the systemic arterial pressure can be increased independent of the pulmonary perfusion pressure.

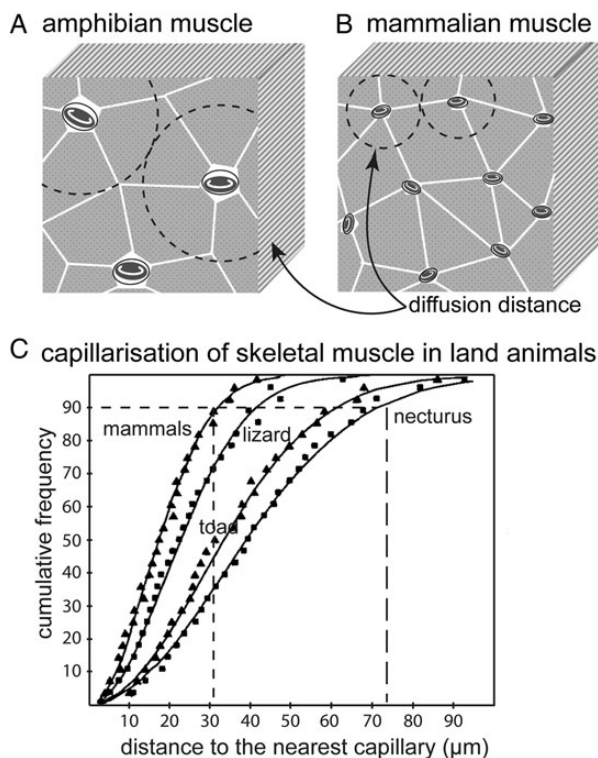


**FIGURE 3:** Relationship of erythrocyte and capillary diameter to systemic and pulmonary blood pressures. From the early fish (agnatha) to the cartilaginous (e.g. shark) and finally modern bony fish, erythrocyte diameter (and therewith the capillary diameter) became progressively smaller, while systemic perfusion pressure doubled. A similar development can be observed in all land animals with lungs. While pulmonary perfusion pressures (empty bars) remained constantly low (to avoid pulmonary oedema), systemic blood pressure (black bars) increased progressively. In the ‘more modern, high-performance’ animals on the right (e.g. humans), the systemic and pulmonary circulation are separated entirely. This allowed formation of a denser peripheral capillary bed with smaller capillary diameters for better gas exchange, which in turn requires an increased systemic blood pressure for adequate perfusion.

diameter of the capillary microvasculature [23]. In short, mean capillary diameter is determined by erythrocyte size.

Why are small erythrocytes and small capillaries evolutionarily advantageous? In general, the number of capillaries per tissue volume increases with the reduction of the capillary diameter [23]. Therefore, mammals have more capillaries in their muscles than an amphibian but they are smaller. As a consequence, the diffusion distance for gas exchange correlates with capillary diameter: it becomes shorter and more efficient with smaller capillaries but there are more of them (Figure 4). In summary, a denser capillarization enabled an increase in sustained aerobic activity level which represented, therefore, an evolutionary benefit.

However, a denser capillarization comes with a price tag. To maintain an adequate blood flow in a vascular system with a high resistance, a higher blood pressure is needed. According to the Hagen–Poiseuille law, a reduction of the vessel radius increases vascular resistance to the 4th power ( $r^4$ )! In fact, the resistance at the tissue level was estimated to be ~10-fold higher in mammals than in some amphibians [23].



**FIGURE 4:** Erythrocyte diameter and capillarization in low- and high-performance land animals. Schematic cross sections through amphibian (A) and mammal (B) skeletal muscle (same magnification). Mammalian skeletal muscle has a higher density of capillaries with a smaller diameter. As illustrated by the dashed circles, this leads to shorter diffusion distances across muscle fibres. (C) Within a mammalian muscle, in 90% of the cases, the nearest capillary can be found in less than 32  $\mu\text{m}$  from a randomly chosen point (dashed circles in B). In the amphibian *Necturus*, the animal with the largest erythrocytes, the distance is >2-fold longer (72  $\mu\text{m}$ , dashed circles in A). The capillarization of toads (amphibian) and lizards (reptile) lies between these extremes (adapted from [23]).

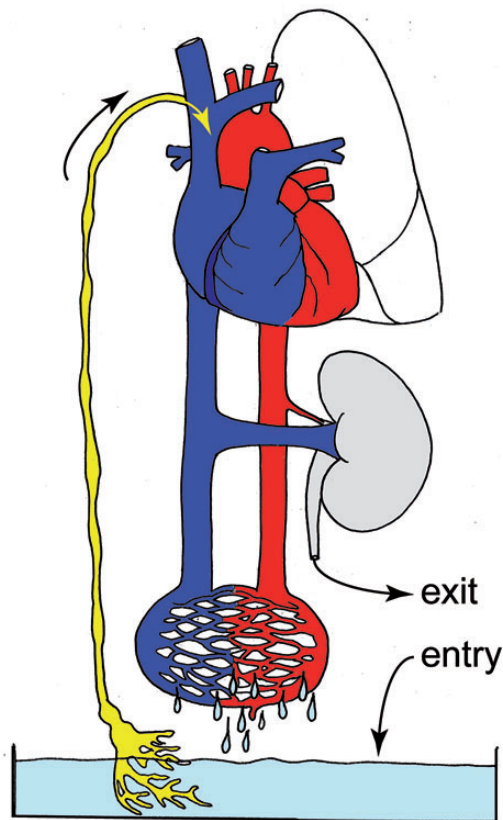
Consistent with this hypothesis, blood pressures as well as physical performance have increased from the earliest fish (jaw-less agnathans) to the more modern bony fish and from lungfish/amphibians to mammals [24–26] (Figures 2 and 3). Lungfish and amphibians first conquered terrestrial life. But because the systemic and pulmonary circulation was not yet separated, a low systemic blood pressure and a low systemic resistance was required to protect the lungs from pulmonary oedema.

## EVOLUTION OF A WATER-RETAINING KIDNEY AND WHY AN ELEVATED BLOOD PRESSURE FEELS GOOD

Although somewhat controversial, we embrace the opinion that the kidney is one of the major determinants for regulating long-term blood pressure [27]. Due to space limitations, just one exemplary argument will be mentioned. In clinical practice, it is a generally accepted observation that, in patients without renal function (i.e. chronic dialysis patients), blood pressure can be adequately controlled by achieving an euvoletic status alone. How does extracellular fluid status determine long-term systemic blood pressure? The circulatory system of vertebrates is designed as a ‘fluid collection apparatus’ (Figure 5). Interstitial fluid is constantly filtered from the capillary microvasculature. All interstitial fluid is constantly collected by the lymphatic system and returned to the venous system. From there, it reaches the left ventricle increasing its output by the Frank–Starling mechanism (i.e. cardiac output is proportional to diastolic pre-filling). Therefore, our circulatory system will return all extracellular fluid to the blood where it increases systemic blood pressure. In healthy vertebrates, the kidneys regulate extracellular fluid homeostasis. The ‘modern’ lifestyle of contemporary humans may likely interfere with fluid homeostasis by increased salt intake and meat and alcohol consumption, obesity etc., and this could explain in part an increased incidence of arterial hypertension. Nephrologists are well aware of this. For example they advise a low-protein diet because an increased uptake of amino acids has been shown to increase extracellular volume and renal plasma flow [28, 29]. Considering the above-described necessity of a higher blood pressure in order to perfuse a dense but narrow capillary bed, it is not surprising that sub-clinical hypertension feels good to the patient and that lowering an elevated blood pressure will reduce the well-being and performance of the patient significantly—at least during the first 6–12 months. By then, the patient usually will have forgotten how good it felt to have a moderately elevated blood pressure ...

## ADAPTING TO LIVING ON DRY LAND: THE WATER-RETAINING KIDNEY WAS INVENTED TWICE

Since our days as amphibians, several adaptations have taken place that allowed us to become independent of water. For



**FIGURE 5:** The vertebrate circulatory system is designed to return all interstitial fluid to the circulatory system. All interstitial fluid (light blue) is collected constantly by the lymphatic system (yellow) and returned to the venous blood (blue) where it modifies cardiac filling and blood pressure. There is a linear relationship between venous return and cardiac output across a wide range (Frank–Starling law). The kidneys (grey) regulate fluid homeostasis and thus systemic blood pressure.

example we have encapsulated the primordial sea within us by the development of thick skin. The thin mucosal skin of amphibians, which also participated in gas exchange, became impermeable to water and gas in reptilian-like animals.

In addition, a water-retaining kidney developed twice in evolution, in a ‘convergent’, independent fashion. The first version of a water-retaining kidney was the mammalian metanephric kidney [30]. Its novel feature was the loop of Henle including a medulla with extraordinary high osmolarity (Figure 6B). The mammalian metanephric kidney consists almost exclusively of tightly packed but highly ordered tubules. In contrast to earlier kidneys (pro- and mesonephros), nephrogenesis (i.e. formation of new additional nephrons) was no longer possible in the metanephric kidney. The loop of Henle represents the most efficient water retrieval system on Planet Earth. This also explains why loop diuretics induce predominantly a loss of water rather than salt (water diuresis rather than saluresis). However, importantly, the loop of Henle requires urea to function.

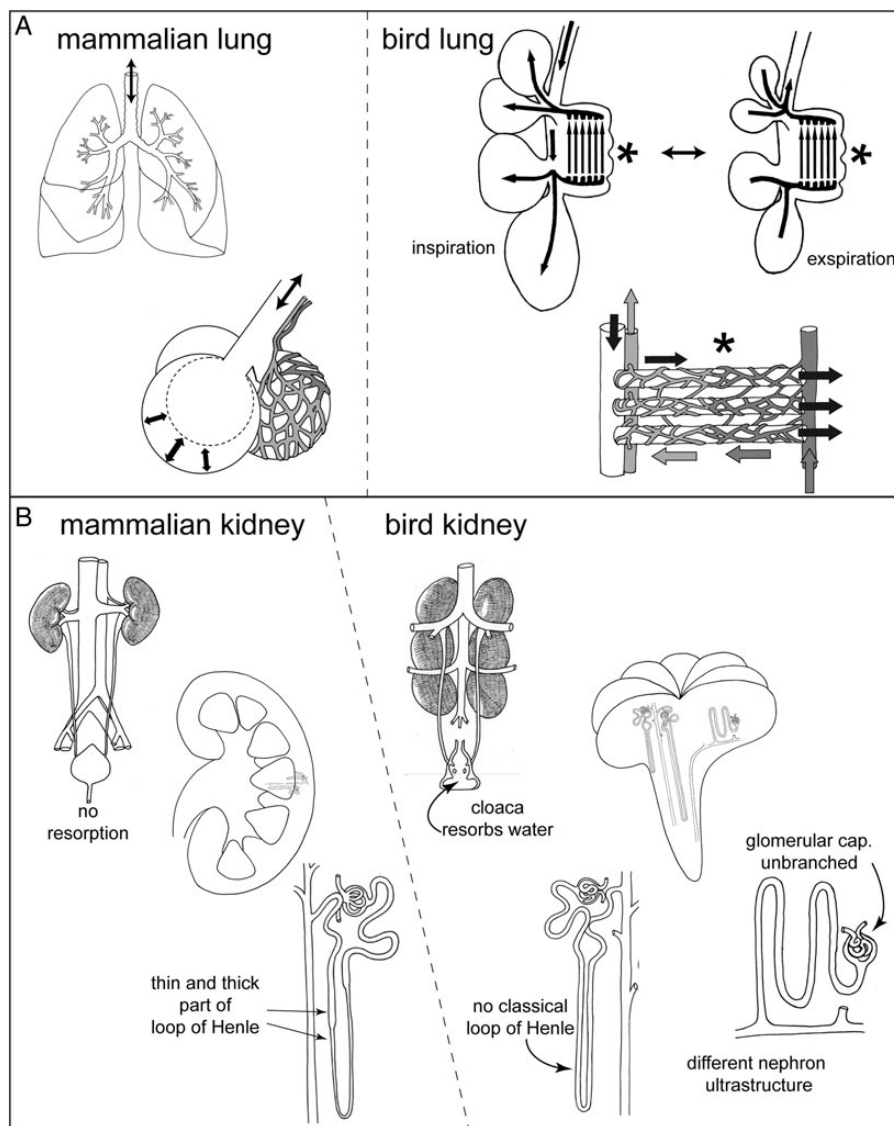
Most fishes excrete the nitrogenous end products of protein metabolism as simple ammonium via the gills (ammonotelism) [31] (Figure 7). Ammonium is very soluble in water

and it can directly diffuse into the ocean. Bacteria then metabolize and detoxify the ammonium (for this purpose, aquarium owners cycle the water through a filter with a large surface, which is colonized by bacteria). In some fishes (including elasmobranchii, e.g. sharks) and monotremes to mammals, ammonium is converted to non-toxic urea (ureotelism). Here again, this is accomplished by (former) bacteria: the mitochondria (urea cycle) (Figure 7). In liver failure, ammonium accumulates in mammals and exerts toxic effects (e.g. encephalopathy). In the mammalian branch of evolution (Figure 1), urea could be utilized by the kidney to create a high osmolarity within the medulla to concentrate urine. Mammalian kidneys can increase the osmolarity on average by  $\sim 4\times$  ( $300 > 1200$  mOsmol). But the best mammalian concentrators can do much more, for example the Australian hopping mouse, which can create urine with up to 10 000 mOsm/L (i.e.  $30\times$  plasma to urine concentration) [32]. This is accomplished by extending the length of the loop of Henle. Urea is the perfect osmotic agent because it passes the cellular membranes so that no osmotic gradients across the cellular walls occur (in contrast to NaCl, see below) and because it has relatively little toxicity.

Although the mammalian kidney is the best concentrator of urine on earth, the solution is not perfect. To excrete the urea and other small-molecule metabolic waste products, humans still have to excrete at least 0.5 L of urine per day. For this reason, mammals and in particular humans, are relatively thirsty animals. In clinical practice, the nephrologists experience the consequences of the mammalian thirst in anuric dialysis patients, who have to remove the ingested fluid (often as much as 2.5 L/day) within only a few hours of haemodialysis treatment.

Birds (and most other hard shell egg-laying animals) found a potentially better solution. Birds convert their nitrogenous waste into uric acid (uricotelism) (Figure 7). In humans, uric acid is the metabolic end product of only purine nucleotides (present in DNA/RNA). Uric acid is virtually insoluble in water. For this reason, most mammals convert uric acid to the less problematic allantoin, but for unknown reasons, humans lost the necessary enzyme (uricase) relatively recently in the course of evolution. Therefore, humans suffer from precipitations of uric acid, which manifest as kidney stones and/or gout. In birds, the synthesis of uric acid is a relatively energy-consuming process but it has a major advantage: within the urine, the uric acid precipitates in a very orderly fashion into small white crystals which can be excreted as a white paste next to their faeces. This white paste of uric acid is the reason why car drivers dislike bird droppings, which dissolve car paint.

The bird ‘metanephric’ kidney evolved totally independent of the mammalian metanephros (in a process called ‘convergent evolution’), and several observations provide evidence for this. Firstly, in contrast to the mammalian-type kidneys, the bird glomeruli consist of only a short and unbranched single capillary. Secondly, the avian kidney has an additional blood supply (portal venous system) [33]—while all blood passes first through the glomeruli in the mammalian kidney. This explains why mammals suffer from acute ischaemic tubular necrosis in states of hypovolaemia or hypotension, while birds (and also amphibians, reptiles and likely also dinosaurs) can

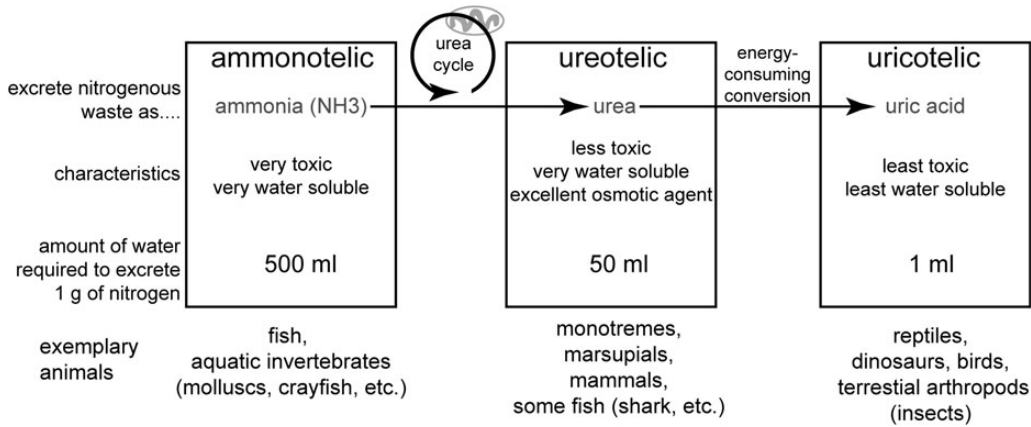


**FIGURE 6:** Separate evolution of the lung and kidneys in mammals and birds. (A) Simplified schematic of the anatomy of the mammalian and the avian lung. Arrows illustrate the airflow during in- and expiration. The mammalian alveoli are dead ends, and oxygen-rich air only enters during inspiration. In birds, reptiles and sauropods, gas exchange takes place in the parabronchi (asterisc). A complex system of air sacs ensures that the parabronchi are constantly perfused with fresh air only in one direction during in- and expiration. Blood flow (grey arrows) is directed into the opposite direction of the airflow (white arrows). (B) Schematic of the mammalian and avian urinary system. Unlike the mammalian kidney, the avian kidney is macroscopically sub-divided into divisions each consisting of several lobes, which are in turn made up of a group of lobules. Each lobule has a cortex and a medulla. In mammals, fluid reabsorption occurs exclusively in the loop of Henle but with great efficiency (using urea as an osmotic agent). In contrast, the bird kidney cannot concentrate as well, but additional water can be reabsorbed within their cloaca. In birds, the glomerular capillary has no branches and is relatively short. Because the metanephric kidneys evolved after the lungs, the different anatomy of the lungs is evidence for the independent evolution of the mammalian and bird metanephric kidneys.

vary their GFR across a wide range (~5 to 10-fold) [34]. However, the most obvious proof for the independent development of the bird kidney is actually the lung (Figure 6A). The ‘avian-type lung’ has a totally different (and more efficient) anatomy in birds, crocodiles (a surviving ‘cousin’ of the bird-line of evolution) and almost certainly also in dinosaurs (Figure 6A). This is why it can be assumed that the evolutionary lines of mammals and birds diverged at the level of the lungfish at the latest—which is long before a water-retaining kidney was required. The fundamentally different anatomy of the lung provides the evidence that the development of a

water-retaining kidney occurred independently in mammals in contrast to birds and dinosaurs. For the same reason, the formation of a heart septum, isolated pulmonary circulation, high blood pressure and warm-bloodedness (see below) occurred at least twice and independently over the course of evolution (see Figure 1, where these evolutionary accomplishments occurred after lung development), also emphasizing its strong evolutionary advantages.

Although some bird kidneys form a similar but less developed structure than the loop of Henle, they could not use urea to concentrate urine [35]. Instead, bird kidneys use salt (NaCl)



**FIGURE 7:** Schematic for the nitrogen metabolism in different animal species. Early aquatic animals excrete their nitrogenous waste as ammonia which is toxic but can be easily disposed into the unlimited water surroundings. Some fish and our mammalian branch of evolution convert ammonia to the less toxic urea using the ‘urea cycle’ (which partly takes place in mitochondria). Ureotelic animals use urea as an osmotic agent to concentrate urine but still have to excrete a minimal amount of water to dispose of the urea (in humans 0.5 L/day). Sharks also use urea as an inert osmotic agent increasing their internal osmolarity to that of ocean saltwater (using a urea-retaining kidney). In a relatively energy-consuming chemical process, uricotelic animals convert their nitrogenous waste to uric acid, which is hardly soluble in water. It precipitates in the urine forming a white paste. Although the kidney of uricotelic animals cannot concentrate well (because it lacks urea as an osmotic agent), these animals still have the most efficient water retrieval system because water can be reabsorbed within the cloacae.

as an osmotic agent which does not penetrate into the cells and therefore cannot be used to build up very high interstitial osmolarities. The osmotic gradient across the cellular membrane would become too big and renal tubular cells would shrink and be unhappy. On average, bird kidneys can accomplish  $\sim 1.4\text{--}2.8\times$  plasma-to-urine-concentrations [36, 37]. Nevertheless, birds are able to shut down glomerular filtration intermittently in states of dehydration (similar to mesonephric kidneys from fish to reptiles) [38] and birds reabsorb the water in the urine from the cloacae (the common final opening for faeces, urine and eggs) and the distal intestine. Thus, birds (and also reptiles/dinosaurs) can excrete their nitrogenous waste virtually without substantial loss of precious water. The ability to recycle water from urine and to deposit nitrogenous waste in a concentrated form is a solution for embryonic development in an egg with a hard shell, where hatchlings have to cope with a limited amount of water and limited amount of space to deposit metabolic waste products. The fact that birds have to drink so little also facilitated evolution of the capability to fly.

Interestingly, some animals switch from uricotelism to ureotelism after hatching, such as the freshwater turtle, because the synthesis of uric acid is quite energy expensive and the freshwater turtle obviously has sufficient access to water.

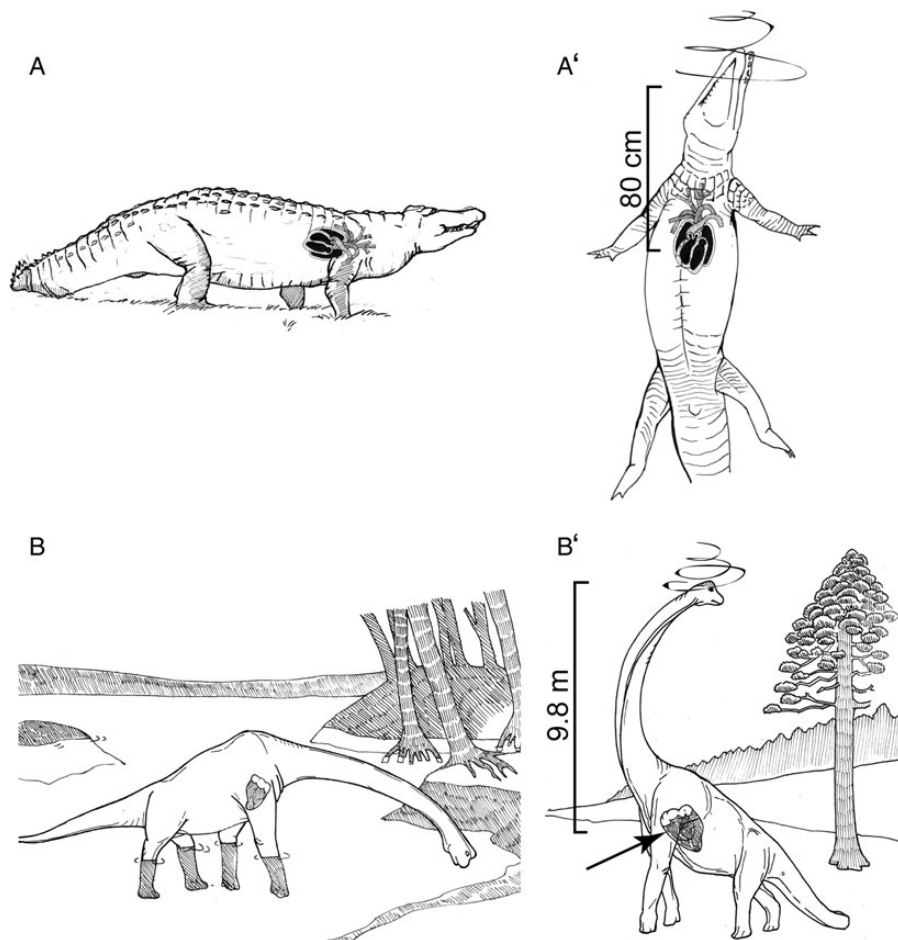
## HEROES SHOULD BE MEDIUM-SIZED AND BIPEDAL

Water animals have no problem with gravity. The external hydrostatic pressure of the water compensates for any gravitational effects [24]. The cardiac output pressure in fish is  $\sim 25\text{--}50$  mmHg; nevertheless, they do not experience orthostatic problems [24, 39]. For terrestrial animals, gravity does pose a problem. A water column of 1 m translates to a

hydrostatic pressure difference of 73 mmHg! A human of 1.70 m in size and a systolic blood pressure of 120 mmHg at the level of the heart will have a systolic blood pressure of approximately only 70 mmHg in the brain (that is why we get dizzy so easily) and 190 mmHg within the toes. This simple calculation also explains why the heart is usually located in the middle of the body (with the kidneys as pressure regulators in close vicinity). As outlined above, early terrestrial animals generated a systolic blood pressure of only less than 30–40 mmHg to avoid pulmonary oedema. For this reason, amphibians and reptiles always have a horizontal body posture (Figure 8A and A’). You will never meet a crocodile standing on its hind legs—as it is often depicted in comics. The crocodile would feel dizzy rather quickly.

At the other extreme is probably the famous dinosaur *Brachiosaurus*, which was considered to be the largest terrestrial animal for a long time. With a length of 30 m and an estimated body weight of 80 tons, it had the dimensions similar to the blue whale. In virtually all children and adult textbooks, the *Brachiosaurus* is shown with his head lifted high up into the air (‘to feed on trees’) (Figure 8B and B’) [40]. The distance from the heart to the head would be  $\sim 9.8$  m. To lift its head, the *Brachiosaurus* required a systolic blood pressure of at least 800 mmHg to guarantee a brain perfusion pressure of 60 mmHg [41]. Such an erect *Brachiosaurus* also violates the law of Laplace [42]. In vertebrates, the cardiac muscle adapts to high cross-sectional stress with hypertrophy. If the mean arterial blood pressure was 700 mmHg, the heart of the *Brachiosaurus* would have to weigh 2 tons (i.e. 5% of the total body mass) and the left ventricular wall had an end diastolic diameter of 52 cm. This would be 15 times larger and 5 times thicker than the heart of a blue whale [42]. The *Brachiosaurus*’ heart muscle would have accounted for 60% of the resting metabolic rate (in humans  $\sim 5\%$ ) [42]. Therefore, it can be assumed that the *Brachiosaurus* was more likely romping about in the water of





**FIGURE 8:** Posture and blood pressure. (A) The main body axis of low-pressure reptiles is always orientated horizontally. Thus, most critical organs (kidneys, brain) are located close to the hydrostatic indifference line and brain perfusion pressure is similar to central blood pressure. (A') An upright crocodile (as shown in numerous comics) should feel dizzy, because brain perfusion pressure would be predicted to drop below 15 mmHg. (B) Physiology requires that the *Brachiosaurus* moved its long neck only sideways. (B') Had *Brachiosaurus* lifted its head, a blood pressure of ~800 mmHg would have been necessary to allow this posture. An enormous heart, weighing ~2 tons (arrow), would have been required to generate this pressure.

swamps, and only rarely lifting its head—in which case it would run the risk of fainting. Indirect confirmation for this conclusion comes from a recent analysis of the anatomy of the neck bones of the sauropod, which was incompatible with an erect posture [43]. However, the body size of the *Brachiosaurus* strongly suggests that it was already a high-pressure animal (i.e. a systolic blood pressure of ~140 mmHg, similar to birds).

Humans have the ideal body size to perform heroic acts: a higher blood pressure is a pre-requisite for larger body size—which is necessary to be stronger than other animals. On the other hand, we are just large enough not to run into significant orthostatic problems. Out of all the mammals, humans are the only ones to evolve an erect body posture and to walk on two legs (bipedalism), which has two advantages: bipedal locomotion may not allow rapid sprints but is rather efficient in endurance running [44]; and second, our hands could now be used for other things. Dinosaurs and birds were also bipedal, but ultimately they used their arms to fly.

#### HIGH-PRESSURE ANIMALS: WHY HIGHER BLOOD PRESSURE MAY NOT BE BETTER

The average systolic blood pressure is highest in birds (~140 mmHg) and mammals (~120 mmHg), while it is much lower in reptiles (~40–60 mmHg). In the 1960s, the heart, aorta and central arteries were analysed in 816 animals which had died from natural causes in the London Zoological Garden [45]. Among those animals, there were 485 birds, 233 mammals and 98 reptiles. In 1% of the reptiles, 3% of the mammals and 18% of the birds analysed, arteriosclerosis was present. There was no correlation between the cholesterol levels and the incidence of arteriosclerosis. A sub-analysis revealed that the Falconiformes (eagles, hawks etc.), the top performers of all birds with a resting blood pressure of 200 mmHg [46], were the front runners in developing arteriosclerosis (i.e. ~54% of the analysed specimens). No arteriosclerosis was seen in penguins (Sphenisciformes), which have a resting blood pressure of only

92 mmHg [46]. Obviously, a high arterial pressure is needed to meet the metabolic demands of flying. The downside of this ability is the natural affinity to develop arteriosclerosis. In captivity, parrots with a high blood pressure live with a generous supply of food and the best medical care. In these animals, arteriosclerosis reaches an incidence of up to 70–90% and is, together with heart failure, a major cause of death [47].

## WHY ONLY HUMAN BEINGS CAN RUN A MARATHON

Warm-bloodedness evolved from reptilian-like animals to monotremes/mammals and independently also to birds (which have an even higher body temperature of 38–39°C). At least ‘sauropods’ (gigantic dinosaurs) were already warm-blooded (‘endothermic’ versus ‘ectothermic’ earlier animals) [48]. To facilitate this, dinosaurs and birds developed feathers, while all mammals have fur. All mammals? Humans are the only exception in that they are naked. In addition, humans have by far the highest density of eccrine sweat glands [49] and can regulate their body temperature much better than any other living animal on earth. When engaged in ‘persistence hunting’, the Aboriginal hunters will simply throw off their clothes allowing them to run for hours in mid-day heat in the Sub-Saharan African bushland, where humans likely evolved. Their mammalian prey cannot throw off its fur. In addition, panting as a way of additional cooling (e.g. in dogs) is not possible when cantering or galloping. When landing on all fours in the cycle of a gallop (i.e. from suspension to the first beat on the ground), the abdominal organs need to be stabilized by contraction of the abdominal muscular wall, which also requires holding your breath and closing the vocal chords or glottis. So the mammalian prey will gallop intermittently until it overheats and then will eventually be caught [4].

Using the furry skin of other animals (by processing it and stitching it together to make a coat) to regulate body temperature is a remarkable accomplishment of the human brain. In addition, humans discovered how to make a fire. Very likely, stone-age women preferred well-dressed men who knew how to hunt and handle fire.

Our ridiculously hypertrophied brains introduced two novel aspects: humans may choose to do crazy (i.e. heroic) things, such as deciding to run a marathon or to build a pyramid (usually driven by the urge to impress females or to become ‘immortal’), and humans are inherently curious. Nowadays, humans have managed to speed up the evolutionary process by several orders of magnitude and ‘scientific methodology’ is probably the most significant recent human accomplishment. Of course, the eternal human journey towards personal bliss is never meant to end.

## ACKNOWLEDGEMENTS

The majority of the facts described here had to be simplified to some extent for the purpose of this review. Evolution never runs in a straight line but much rather has many parallel

branches much like a bush. This review was written with the purpose of highlighting some of the unexpected roles of high blood pressure, the kidney and how many things are intertwined. If the reader finds this review not only enlightening but also entertaining and fun, we will have come one step closer to personal bliss. Financial support for this work was received by TP17, SFB/Transregio 57 “Mechanisms of organ fibrosis” of the German Research Foundation (DFG), and the eRARE consortium “Rare-G” (01 GM 1208A, to M.J.M.).

## CONFLICTS OF INTEREST STATEMENT

None of the authors declare an intellectual or financial conflict of interest. The results presented in this paper have not been published previously in whole or part, except in abstract format.

## REFERENCES

1. Kenyans chase down and catch goat-killing cheetahs. BBC News, 2013
2. Berlowitz V. Programme 10 Food for thought. [http://www.bbc.co.uk/pressoffice/pressreleases/stories/2002/10\\_october/31/progs6-10\\_mammalspack.pdf](http://www.bbc.co.uk/pressoffice/pressreleases/stories/2002/10_october/31/progs6-10_mammalspack.pdf) (1 January 2014, date last accessed)
3. McDaugall C. Born to Run: a Hidden Tribe, Superathletes, and the Greatest Race the World Has Never Seen. New York: Knopf Doubleday Publishing Group, 2011
4. Carrier DR, Kapoor AK, Kimura T *et al.* The energetic paradox of human running and hominid evolution. *Curr Anthropol* 1984; 25: 483–495
5. Mathews SC, Narotsky DL, Bernholt DL *et al.* Mortality among marathon runners in the United States, 2000–2009. *Am J Sports Med* 2012; 40: 1495–1500
6. Vize PD, Smith HW. A Homeric view of kidney evolution: a reprint of H. W. Smith’s classic essay with a new introduction. *Evolution of the kidney*. 1943. *Anat Rec A Discov Mol Cell Evol Biol* 2004; 277: 344–354
7. Epstein FH. The sea within us. *J Exp Zool* 1999; 284: 50–54
8. Dawkins R. *The Ancestor’s Tale, a Pilgrimage to the Dawn of Evolution*. London: The Orion Publishing Group, 2005
9. Skadhauge E. Drinking rate and oxygen consumption in the euryhaline teleost *Aphanius dispar* in waters of high salinity. *J Exp Biol* 1974; 60: 547–556
10. Tetsuya H. Some factors regulating water intake by the eel, *Anguilla japonica*. *J Exp Biol* 1974; 61: 737–747
11. Evans DH. Cell signaling and ion transport across the fish gill epithelium. *J Exp Zool* 2002; 293: 336–347
12. Wilson JM, Whiteley NM, Randall DJ. Ionoregulatory changes in the gill epithelia of coho salmon during seawater acclimation. *Physiol Biochem Zool* 2002; 75: 237–249
13. Hickman CPJ, Trump BF. The kidney. In: Hoar WS, Randall DJ, eds. *Fish Physiology*. New York: Academic Press, 1969, pp. 91–239
14. Ali MA. *Environmental Physiology of Fish*. New York and London: Plenum Press, 1980
15. Nebel C, Romestand B, Negre-Sadargues G *et al.* Differential freshwater adaptation in juvenile sea-bass *Dicentrarchus labrax*: involvement of gills and urinary system. *J Exp Biol* 2005; 208(Pt 20): 3859–3871
16. Brown JA, Oliver JA, Henderson IW *et al.* Angiotensin and single nephron glomerular function in the trout *Salmo gairdneri*. *Am J Physiol* 1980; 239: R509–R514
17. Graham JB. Circulatory adaptations for air-breathing fishes. In: Farrell AP (ed). *Encyclopedia of Fish Physiology*. London: Academic Press, 2011, pp. 1875
18. Johansen K, Lenfant C, Schmidt-Nielsen K *et al.* Gas exchange and control of breathing in the electrical eel, *Electrophorus electricus*. *J Comp Physiol* 1968; 61: 137–163

19. Brauner CJ, Ballantyne CL, Randall DJ *et al.* Air breathing in the armoured catfish (*Haplosternum litorale*) as an adaptation to hypoxic, acidic, and hydrogen sulphide rich waters. *Can J Zool* 1995; 73: 739–744
20. von Euler US, Liljestrand G. Observations on the pulmonary arterial blood pressure in the cat. *Acta Physiol Scand* 1946; 12: 301–320
21. Hartmann FA, Lessler MA. Erythrocyte measurements in fishes, amphibia and reptiles. *Biol Bull* 1964; 126: 83–88
22. Snyder GK, Weathers WW. Hematology, viscosity, and respiratory functions of whole blood of the lesser mouse deer, *Tragulus javanicus*. *J Appl Physiol Respir Environ Exerc Physiol* 1977; 42: 673–678
23. Snyder GK, Sheafor BA. Red blood cells: centerpiece in the evolution of the vertebrate circulatory system. *Amer Zool* 1999; 39: 189–198
24. Satchell GH. *Physiology and Form of Fish Circulation*. Cambridge: Cambridge University Press, 1991
25. Bennett AF. Exercise performance of reptiles. *Adv Vet Sci Comp Med* 1994; 38B: 113–138
26. Bennett AF, Ruben JA. Endothermy and activity in vertebrates. *Science* 1979; 206: 649–654
27. Wade HM, Textor SC. The role of the kidney in regulating arterial blood pressure. *Nat Rev Nephrol* 2012; 8: 602–609
28. Weening JJ, Van Guldener C, Daha MR *et al.* The pathophysiology of protein-overload proteinuria. *Am J Pathol* 1987; 129: 64–73
29. Wilson KH, McIndoe RA, Eckenrode S *et al.* Alterations of renal phenotype and gene expression profiles due to protein overload in NOD-related mouse strains. *BMC Nephrol* 2005; 6: 17
30. Natchin YV. Evolutionary aspects of renal function. *Kidney Int* 1996; 49: 1539–1542
31. Kardong K. *The Urogenital System. Vertebrates Comparative Anatomy, Function, Evolution*. New York: McGraw-Hill Higher Education, 2009
32. Gorge L, Roberts JR. Kidney function in the Spinifex hopping mouse, *Notomys alexis*. *Comp Biochem Physiol A Mol Integr Physiol* 2008; 150: 90–101
33. Carretero A, Ditrich H, Navarro M *et al.* Afferent portal venous system in the mesonephros and metanephros of chick embryos: development and degeneration. *Anat Rec* 1997; 247: 63–70
34. Dantzler WH. Significance of comparative studies for renal physiology. *Am J Physiol* 1980; 238: F437–F444
35. Braun EJ, Reimer PR. Structure of avian loop of Henle as related to counter-current multiplier system. *Am J Physiol* 1988; 255(3 Pt 2): F500–F512
36. Nishimura H, Fan Z. Regulation of water movement across vertebrate renal tubules. *Comp Biochem Physiol A Mol Integr Physiol* 2003; 136: 479–498
37. Lavery G, Skadhauge E. Adaptive strategies for post-renal handling of urine in birds. *Comp Biochem Physiol A Mol Integr Physiol* 2008; 149: 246–254
38. Dantzler WH, Braun EJ. Comparative nephron function in reptiles, birds, and mammals. *Am J Physiol* 1980; 239: R197–R213
39. Sandblom E, Axelsson M. Venous hemodynamic responses to acute temperature increase in the rainbow trout (*Oncorhynchus mykiss*). *Am J Physiol Regul Integr Comp Physiol* 2007; 292: R2292–R2298
40. Joyce W. *Dinosaur Bob and his Adventure with the Family Lizardo*. New York: Harper Collins, 1995
41. Hohnke LA. Haemodynamics in the *Sauropoda*. *Nature* 1973; 244: 309–310
42. Seymour RS, Blaylock AJ. The principle of laplace and scaling of ventricular wall stress and blood pressure in mammals and birds. *Physiol Biochem Zool* 2000; 73: 389–405
43. Cogley MJ, Rayfield EJ, Barrett PM. Inter-vertebral flexibility of the ostrich neck: implications for estimating sauropod neck flexibility. *PLoS One* 2013; 8: e72187
44. Bramble DM, Lieberman DE. Endurance running and the evolution of Homo. *Nature* 2004; 432: 345–352
45. Finlayson R, Symons C. Arteriosclerosis in wild animals in captivity [Abstract]. *Proc R Soc Med* 1961; 54: 973
46. Millard RW, Johansen K, Milsom WK. Radiotelemetry of cardiovascular responses to exercise and diving in penguins. *Comp Biochem Physiol A Comp Physiol* 1973; 46: 227–240
47. Bavelaar FJ, Beynen AC. Atherosclerosis in parrots. A review. *Vet Q* 2004; 26: 50–60
48. Eagle RA, Tutken T, Martin TS *et al.* Dinosaur body temperatures determined from isotopic ((1)(3)C-(1)(8)O) ordering in fossil biominerals. *Science* 2011; 333: 443–445
49. Folk GE, Jr, Semken HA, Jr. The evolution of sweat glands. *Int J Biometeorol* 1991; 35: 180–186

Received for publication: 3.7.2014; Accepted in revised form: 23.7.2014