Reiner Bartl
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Bone Disorders

Biology, Diagnosis, Prevention, Therapy

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With a contribution by
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Preface

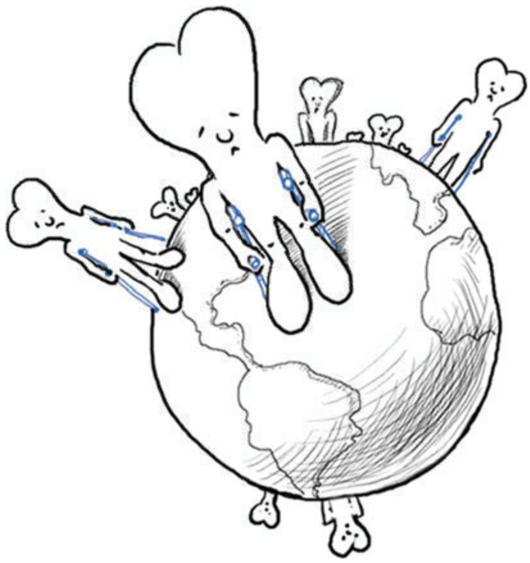


Fig. 1 Bone disorders: a worldwide challenge!

With the dawn of the twenty-first century has come the realisation that bone and joint diseases are the major cause of pain and physical disability worldwide. Moreover, according to the WHO Scientific Group, there are more than 150 diseases and syndromes of musculoskeletal conditions, usually associated with pain and loss of function. It is undoubtedly these insights that prompted the WHO to declare the first 10 years of the new century as "The Bone and Joint Decade 2000–2010". This declaration obviously made a highly significant impact on international, national and medical authorities, as well as on physicians, scientists and citizens worldwide as evidenced by an overwhelming flood (a regular tsunami) of articles, studies and books on the subject in the last few years alone! Not to mention the coverage in newspapers and journals, on the radio and television, and of course all the up-to-date information freely available on the Internet. The number of people suffering from these diseases – already many millions in the developed and underdeveloped countries in the world – is expected to double within the next 20 years. In many countries, this increase will be even greater due to the longer survival and consequently larger numbers of older people in the population. It is therefore inevitable that the

Fig. 2 Osteoporosis: a silent thief!

already astronomical costs of health care will rise proportionally. According to the International Osteoporosis Foundation (NOF), the worldwide incidence of hip fracture is projected to increase by 240 % in women and 310 % in men by 2050, unless appropriate preventive measures will be taken on sufficiently large national and international scales, for which, hopefully, this book will provide a stimulus!

On the positive side, the enormous amount of work, research and study of disorders of bone over the past 10–20 years or so has contributed greatly to our understanding of the causes, treatment and prevention of osteoporosis and other disorders. Most importantly, perhaps, the skeleton is now regarded in a new light, as a dynamic organ undergoing constant renewal throughout life from start to finish, from the cradle to the grave. And what is more: it is now abundantly clear that the skeleton participates, usually not to its advantage, in almost every condition that may affect the organs and tissues in the body! This applies especially to *osteoporosis*, which is now under control!

How did this come about?

- Because of the elucidation of many of the factors involved in osseous remodelling.
- Because of the development of simple, fast, reliable and non-invasive methods for measurement of bone density, and for testing other factors such as mineralisation, trabecular architecture, cortical thickness, and the bone cells themselves.
- Because of the identification of general and individual risk factors, so that appropriate measures can be taken to prevent development of osteoporosis and/or its progression, if and when fractures have already occurred.
- And finally, because effective medication for prevention and therapy is now readily available worldwide.

The efficacy of the classes of compounds known as "bisphosphonates" as well as of the "selective oestrogen receptor modulators" (SERMs) and more

Fig. 3 Be active and be happy!

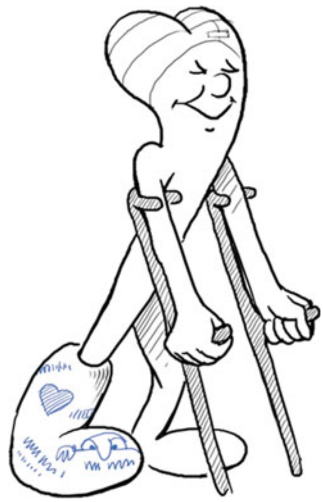
recently of the anabolic parathyroid hormones and denosumab has now been unequivocally established by numerous large multicentre trials involving literally millions of patients. In addition, simple methods such as a healthy lifestyle, adequate nutrition, sufficient physical activity, vitamin D and calcium supplements, as required, can be recommended and adopted on a large scale, beginning with the responsible authorities and reaching to the individual citizens.

Introduction and acceptance of these methods require public awareness and support and the realisation that every individual is the guardian and caretaker of his/her own bones and responsible for their structural and functional integrity. Fortunately, some progress has been made, as shown by the numerous articles recently published from the "four corners of the globe" which unequivocally establish the epidemic proportions of the problem. Well-founded diagnostic techniques and effective therapies – both antiresorptive and osteoanabolic – are now available for prevention, diagnosis and treatment of bone disorders. It should be emphasised that the treatments recommended in this text are all founded on "evidence-based medicine" (unless otherwise stated) for which the appropriate references are given at the end of the text.

The aim of this book is to demonstrate that "Bone is EveryBody's Business" and especially every patient's and doctor's, and to provide guidelines for the diagnosis, therapy and prevention of bone disorders – from paediatrics to geriatrics. It is hoped and anticipated that this book will raise awareness and provide information to anyone seeking it, and especially to doctors across all disciplines concerned with various "bone problems". Clinical osteology is now an independent specialty which nevertheless encompasses all branches of medicine and affects each and every one of us.

Consequently we have adhered stringently to simplicity, comprehensiveness, and to practicality of approach to examinations, methods and implementation of up-to-date testing, to strategies for prevention, to criteria for

Fig. 4 Fragility fractures: focussing not only on prevention and treatment but also on ways to deal with the personal and social consequences of the disease such as pain, depression, loss of self-esteem and social isolation!



diagnosis, and to presentation of therapeutic possibilities, as well as to our own particular goal which is to keep this text as "user-friendly" as possible, so that any doctor seeking information on a particular topic in bone disorders has uncomplicated and time-saving access to it.

We wish all our readers success in their endeavours to help patients and to reduce suffering in this strife-ridden, beautiful planet of ours!

Munich, Germany

Reiner Bartl
Christoph Bartl

Contents

Part I

Evolution and Biology of Bone

1 Evolution of the Skeleton

1.1 From the Primeval Sea to the Precambrian Period

The earth had existed for about 4500 million years. This corresponds to about a third of the time since the creation. The oldest animal fossils (multicelled) come from the time 500–1000 million years before the evolution of mankind. A dive through the primeval sea about 600 million years ago would be very colourless and unspectacular. Ten million years earlier, the earth had emerged from an ice age which had lasted for many million years with glaciers at the equator. The earth had over many million years the same appearance of the Jupiter moon Europa today, whose whole surface is covered by a very thick layer of ice. Sunlight and therefore photosynthesis was blocked and totally absent. Living organisms had a difficult time, so only the simplest organisms could exist in the oceans. The seafloor was covered by a solid mat of bacteria and along the coasts grew, by the photosynthesis of blue algae, huge chalk towers, "stromatolites". There was no trace of higher, differentiated animals.

On the floor of the ocean along the tectonic plates between the smoking chimneys of the "black smokers" swarmed bizarre life forms. Experts estimate the biomass in these deep sea oases to be many kilogrammes per square metre. The photosynthesis of the vegetation in the coastal areas could not be the basis of the ecosystem in this underworld but was a chemical synthesis of microbes: sulphur-containing bacteria oxidised there in the chimneys giving rise to hydrogen sulphide.

Multicelled organisms first developed in the closing Precambrian period: sponges and Cnidarians, primitive precursors of all modern animal stems. Considerably more complex, mirror invert constructed life forms (bilateralia) developed slowly: these animals had for the first time different tissues, a nervous system, a blood circulation, internal organs, as well as mouth and intestinal openings. In stone, which is more than 550 million years old, hardly any traces of the existence of these animal species can be found. The animals were apparently too small and too soft and did not have a skeleton and thus did not leave any recognisable fossils behind in the rock.

1.2 The "Cambrian Explosion"

Fifty million years later, the picture basically changed: the whole sea swarmed with life forms of many types. At the beginning of the earth epoch Cambrian, 550 million years ago, an unexpected sediment was deposited full of small shells, small teeth and spines. Considering the sheer endless period of more than 3 billion years, in which only the primitive single-cell organisms populated the oceans, an event must now have occurred which was the decisive ignition of this

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"origin of life". This "Cambrian explosion" probably had both internal and external causes:

- *Warming and circulation of the ocean and an increasing oxygen concentration in the atmosphere:* Nourishment-rich deep water flowing to the top and flooding the continental shelf areas with nourishment.
- *Enrichment of the ocean with calcium:* Following the erosion of the primeval continents, huge amounts of calcium and other minerals were spewed into the sea. Calcium in too high concentration is in fact a cell poison; however, the life forms made a virtue out of a danger: they process the calcium into shells and armour – the birth of the outer skeleton (exoskeleton) (Fig. 1.1). At the beginning, the hard shell served as protection against high waves and the movement of currents and marked the start of the "Cambrian radiation (family tree)" with the development of ever more refined skeletons, which guaranteed survival.
- *Development of meat eaters:* The occurrence of the first predators was a considerable catalyst for evolution and it began a continuous armament race between the hunter and the hunted with manifold possibilities through new genealogy: tentacles, spines, fins and eyes. With that came a new order in the evolution of the world: eat or be eaten. Naturally under these conditions, those which could protect themselves with armour had an advantage.
- *Development of armours and shells:* The great amount of calcium and other minerals in the water accelerated the development of a variety of hard parts for protection from the "hunters". Skeletons proved to be the breakthrough in the point of evolution. The storage of calcium carbonate in organic tissue matrix created protective armour: shells and thorns for the "hunted" (Fig. 1.2a, b), but also new types of hunting tools like teeth and claws for the "hunters" (Fig. 1.3). The hard parts of the animals from the time of the "Cambrian explosion", a geological short period of only 10–20 million years, are found in the basins of the former seas as metre-thick sediment layers.

The Cambrian ocean proved to be the "playground of evolution" with the development of remarkable creatures. The earliest life form, which used the high concentration of minerals in the ocean, is *Cloudina*, a 1.5 cm small, elongated creature, which successfully protected itself against enemies by the production of tubes in which it lived. The predominant part of these creatures died out, but some of them which could win through, were the predecessors of all animals which populate the earth today. Biologically successful models of them like the *Monoplacophora*, a primitive predecessor of the snail have survived almost unchanged for 450 million years. For example, *Neopilina* can be found as a living fossil at a depth of 3000 m in the Pacific. Also today there are still creatures with a suitable outer skeleton, which are encased with a shell or armour, for instance, mussels, insects or spiders.

1.3 Development of the External Skeleton

Only a few creatures like the jelly fish (Cnidarians) exist completely without body support; however, with the deployment of strong poisons, they have developed other strategies for defence. A great disadvantage for animals with armour or shells lies in the lesser movement and in the lesser

Fig. 1.1 Fossilisation of a huge ammonite, a cuttlefish fossil which died out at the end of the chalk age with 4–12 turns of rolled chalk housing. Ammonites had a diameter from 2 to 200 cm with many separating walls and gas-filled chambers

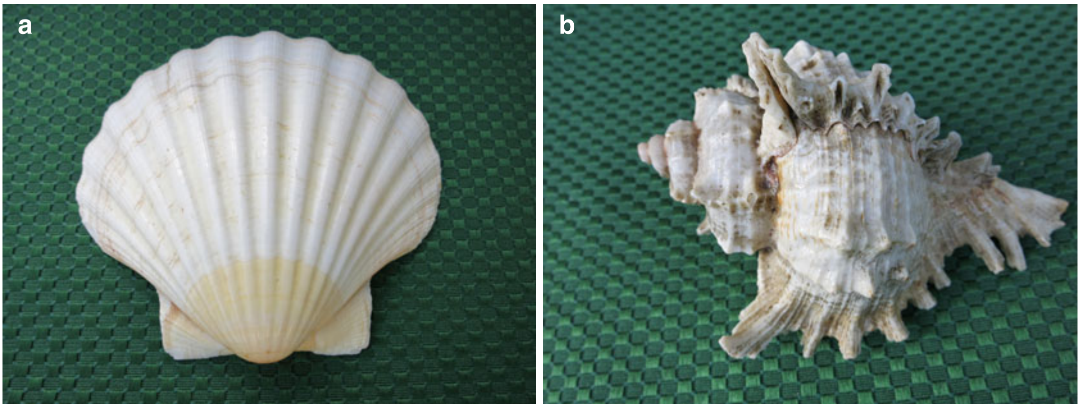


Fig. 1.2 (**a**, **b**) Two variants of exoskeletons: examples of effective shells, beautiful in their shapes

Fig. 1.3 Variant of a hunting tool, with numerous teeth

potential for escape against the increasingly faster emergent hunters. An important development produced powerful muscles, which joined the body of snails with the shells. At time of danger, they were able to retreat into the protective chamber. The hinged connection between shell and muscle enabled a rearward movement and further mobility. One animal group surpassed all others on diversity with the help of an ingenious muscular-skeletal system and its segmentation: the arthropod. All insects, crustaceans, spiders and millipedes descend from them. The ingenious mixture of calcium, protein and carbohydrate, known as chitin, allowed the construction of different organs such as tentacles, claws, pincers and masticatory organs. But the exterior skeleton of the arthropod had one great disadvantage: it constricted the animal in a stiff corset and did not allow any further growth. The act of "skinning" meant a deadly failure in development in the dangerous underwater world.

1.4 Development of the Internal Skeleton

Animals with an inner skeleton, a structure of cartilage, bones or a combination of both, are fishes, amphibians, birds and mammals. The successor of the chordate, today's vertebrates, moved the supporting exterior skeleton (*exoskeleton*) to inside (*endoskeleton*), developed an ingenious muscle system and gained thereby a considerably higher movement capability. The act of switching from an external to an internal skeleton brought a decisive advantage for the development of the movement apparatus and enlarged the radius of action. The speed of movement was decisive for survival and thereby the driver for further evolution. The growth of the life forms was also no longer limited.

1.5 Calcium Phosphate: The New Building Material

A further step in the development of a stable but light internal skeleton (Endoskeleton) and for movement lies in the chemical situation: the hard parts built of calcium carbonate were replaced by crystalline calcium phosphate. In the seawater and on the land, huge quantities of the mineral calcium complex with pyrophosphate were deposited. Pyrophosphates were split by enzymes into phosphates. This highly insoluble calcium phosphate, in the form of *hydroxylapatite* $Ca_{10}(PO_4)_6\ (OH)_2$, was stored in the newly developed bone matrix (Fig. 1.4). This building material consisted of collagen and, a few nanometres larger, calcium phosphate crystals. In comparison to the nonelastic, brittle and readily soluble calcium carbonate of the shelled creatures, it was firmer, more elastic and more acid resistant – the ideal building material for the demands of lightweight construction.

1.6 Development of the Backbone

About 500 million years ago, a small, inconspicuous and primeval fish appeared, which in the survival struggle no longer had an armour, but had built a simple pliable support rod out of connective tissue in the interior of the body. This made it an especially fast and nimble swimmer. From this rod gradually developed the jointed backbone, at the start out of cartilage, later of bone (*Chondrichthyes* and *Osteichthyes*). On the vertebrae followed bones, e.g. ribs, which protected the body and offered further muscle support. Alongside the optimisation of movement, a bony jaw emerged in the area of gill, with which the fish could grip and crush their prey. A few species became the largest predators of the oceans: the great sharks weighing several tons.

1.7 Invasion of the Dry Land

After the divide of the Silurian/Devonian periods, the plants increasingly inhabited the dry land, and in their wake, animal organisms also followed. Towards the end of the Devonian period

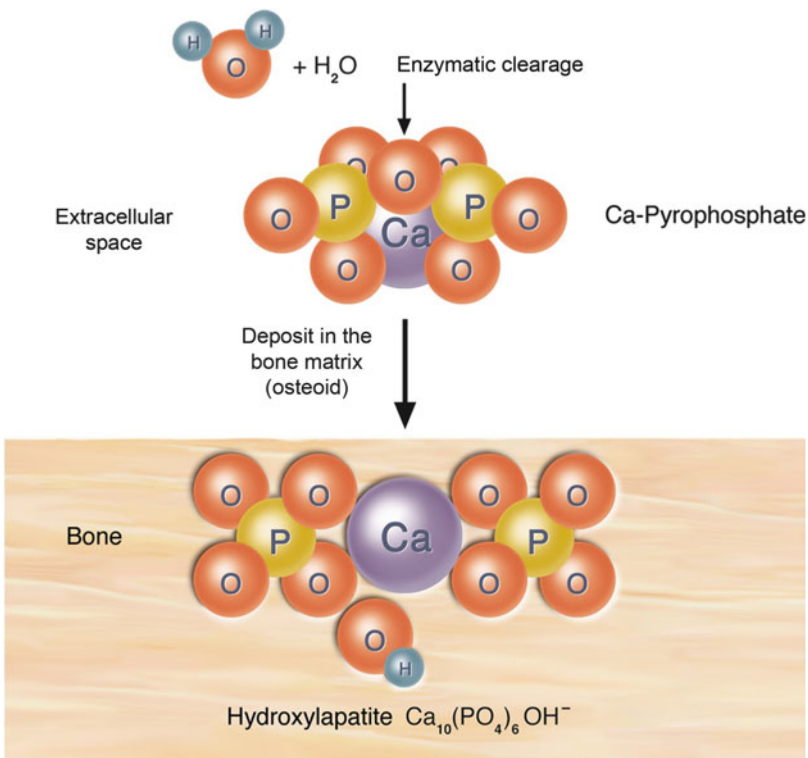


Fig. 1.4 Enzymatic splitting of calcium pyrophosphate in the extracellular space and formation of crystalline calcium phosphate in the form of hydroxylapatite in the bone matrix

(about 350 million years ago), the amphibians separated from the bony fish group and began to move to the dry land (Fig. 1.5). The reptiles which developed from them became the main type of vertebrate from the carboniferous period. The loading on the bones, caused by the gravity on land, placed particular demands on their capacity, but was overcome by diverse innovations relating to lightweight construction: the "spongification and lamination" of the bone construction. Additionally the development of core cavities provided space for blood formation, for the marrow.

The next development period, the dinosaurs were the lords of the earth, until the end of the chalk age (about 60 million years ago). The *Ankylosaurus* protected itself with thick bone plates on its skin (the principle of the impregnable castle against meat eaters). This armament developed in the first year of life and utilised enormous quantities of calcium and phosphate. Palaeontologists from Bonn (Germany) could recently show that the armoured dinosaurs used their long skeletal bones as a mineral source and probably in their youth suffered periodically from strong bone shrinkage. As soon as the armour was complete, the bones at the extremities were again strengthened.

Before the abrupt extinction of the dinosaurs, a bird developed on the model of especially lightweight bones (the principle of elastic, load-bearing spongy bones). The triumphant march of the predatory animals, which remains to today, began with the extinction of the dinosaur about 60 million year ago.

1.8 Bone and Blood Formation

Further progress in the evolution of the skeleton produced the combination of blood formation and bones. The bone marrow finds protection in

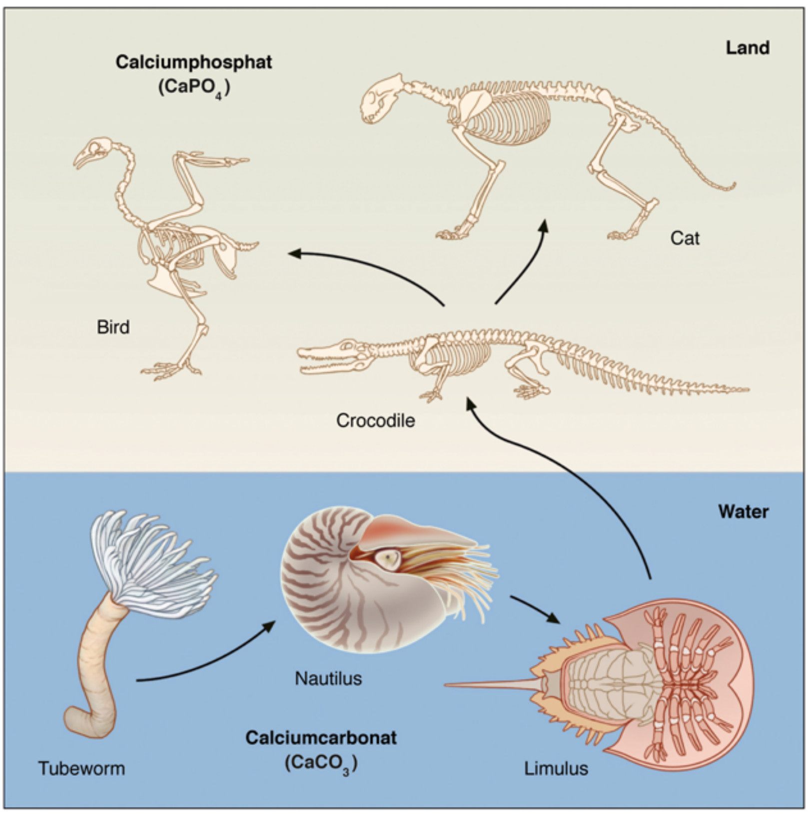
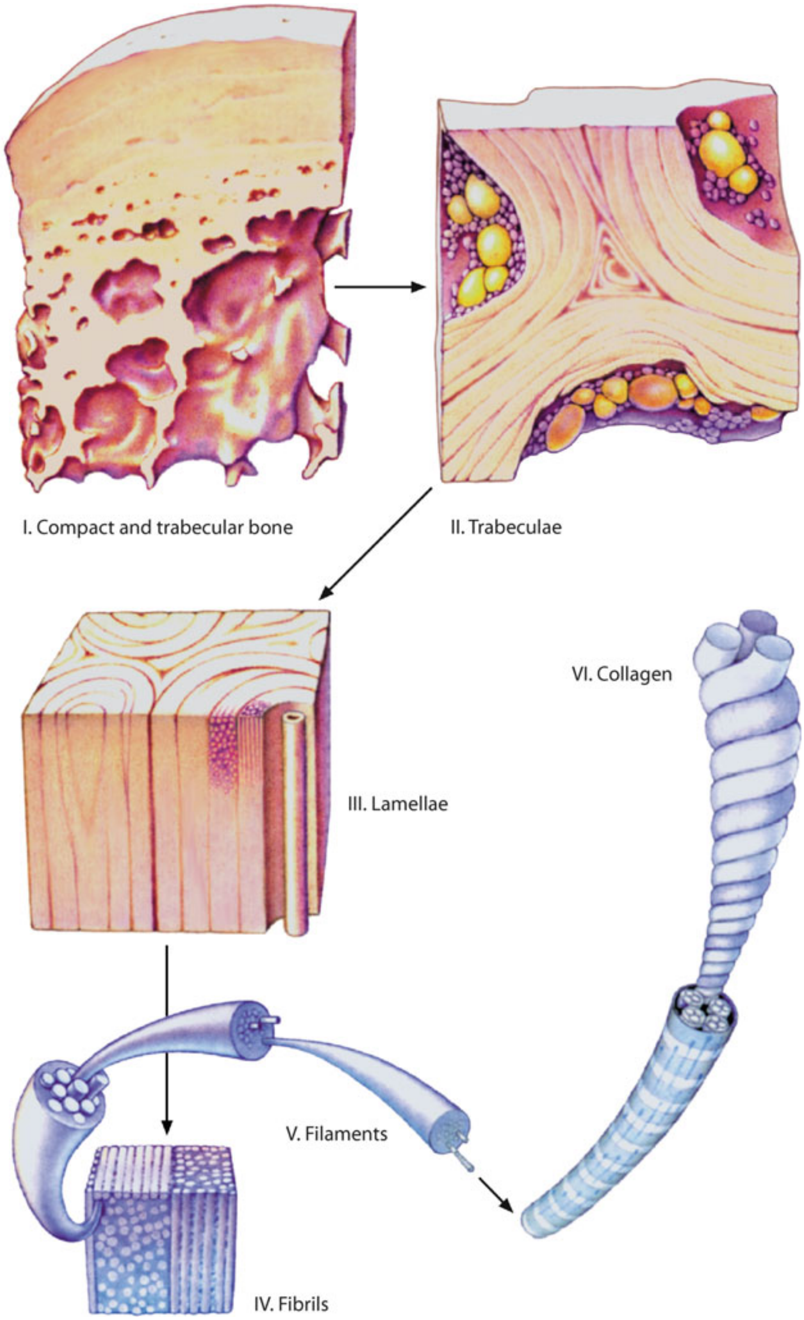


Fig. 1.5 Evolution of the skeleton, from tubeworms to mammals

Fig. 1.6 Organisational levels of bone structure, which ensure both flexibility and rigidity of the skeleton: from macroscopic via microscopic to molecular levels



many spongy cavities of the skeleton; on the other hand, important bone cells are recruited direct from the bone marrow (osteoclasts from the haematopoietic stem cells and osteoblasts from the stroma cells), so that one correctly speaks about a functional anatomical unit, the "bone-bone marrow system". The continually running bone rebuilding ("modelling and remodelling") and the fracture healing would not be thinkable without recruitment of haematopoietic cells and without blood supply from the neighbouring bone marrow.

1.9 The Human Skeleton

These stages of the development of life in water and on the earth are substantiated by fossil finds. Thereby the impressive chronology of the development of the intelligent inner skeleton from simple exterior shells and armour can be understood in the fossilisation. The current modern skeleton of the predatory animals combines on one side through its strength and flexibility (resistance against the omnipresent gravity), on the other side through its low weight (advantage for movement and fast locomotion). This occurs in particular in the skeleton of a bird, through the refinement of its light construction, which first enabled flight.

The current modern human skeleton, in all structure orders – from molecular via microscopic and to the macroscopic levels – which took place over more than 500 million years of continual development, is a masterpiece of bioarchitecture (Figs. 1.6 and 1.7).

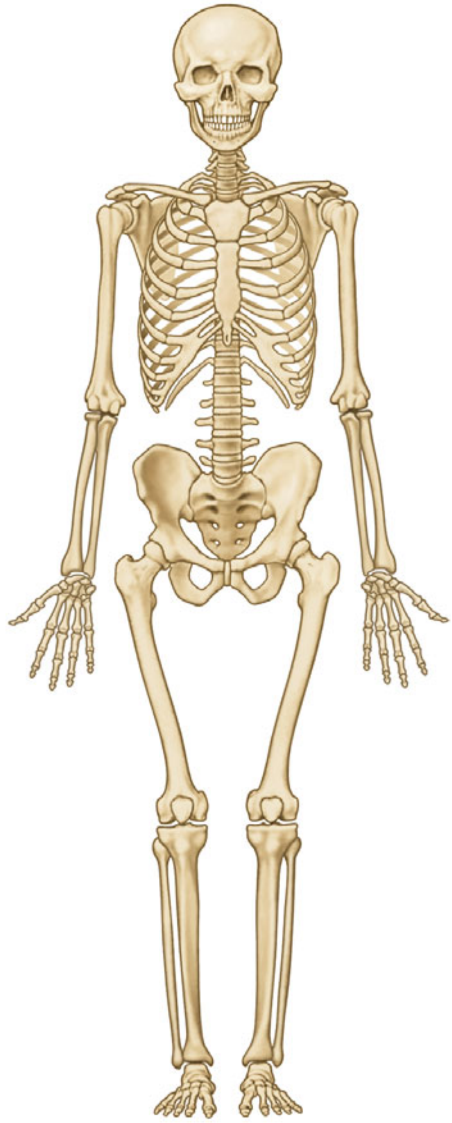


Fig. 1.7 The adult human skeleton – a masterpiece of architecture. It comprises about 210 individual bones, each of which is sculpted by the process of "modelling" and constantly renewed by the process of "remodelling". It has a total weight of about 10 kg (minerals 50–70 %, organic matrix 20–40 %, water 5–10 % and fats 3 %) and contains 15 % of the body weight