# Preface

IT'S HARD TO RECALL A TALK ON THE ENDOCRINE FUNCTION OF bone that did not prompt the question, "But why bone?" This question came with the regularity of a clock as if the notion that bone could be an endocrine organ was not only novel but plain anathema—one reason this may be is that bone in any culture is a symbol of death or danger of death. Similarly, any scientist outside the field of bone biology asked to comment on a new hormone found in bone typically responds "The authors will now have to answer the question: But why bone?" Why is this question so common in the case of bone but never asked, for instance, in the case of fat, another tissue that was recently elevated from the status of biological neutrality to the that of endocrine organ? This interrogation prompts numerous thoughts and queries, some more positive, some negative, all defensive. Yet, from the perspective of bone biology what is more important is that this debate has been so intellectually stimulating and fertile. Indeed, this blunt question has pushed, and continues to push, us to conceptualize in broader terms why this is the case and what kinds of functions bone should regulate in this capacity. In doing so, it has forced us to revisit bone physiology as a whole. The regular posing of the question has thus been a blessing for the field; at least this is how we see it. The demonstration that bone is an endocrine organ did not occur by serendipity but was in fact predicted by a relatively restrictive working hypothesis we have been using to revisit bone physiology. Therefore, a more in-depth analysis of this working hypothesis inferring that bone must be an endocrine organ eventually provided an answer to the elusive "But why bone?" question.

So how did the hypothesis that bone is an endocrine organ emerge? The premise was the suspicion that the cell biological processes underpinning each arm of bone modeling and remodeling, bone resorption and bone formation, had to be energetically expensive. Furthermore, if one assumed that the energetic cost of the physiological function of any given organ is in part proportional to the surface area of the organ, then undoubtedly bone (re)modeling should be an expensive process given the area that bones occupy. The hypothesis was supported by frequent clinical observations. Any situation that reduces food (i.e., energy) intake in children results in an arrest of longitudinal growth; in other words, in the absence of energy intake, bone modeling is stalled. Likewise, any long-term decrease in food intake in adults results in low bone mass. Moreover, and independently of a possible link between bone mass and energy metabolism, any arrest of gonadal functions in either sex results in a severe loss of bone mass. Together, these two separate ideas suggest the general hypothesis that *bone growth, energy metabolism, and reproduction should be coordinately regulated*. Given the distance between the organs involved, such coordinated regulation has to be of endocrine nature. Therefore, one tenet of this hypothesis is that bone should be an endocrine organ that regulates aspects of both energy metabolism and reproduction. We now know that this is indeed the case. Through the hormones osteocalcin and lipocalin 2, and possibly others, bone regulates multiple aspects of energy metabolism in mice and humans. Likewise, working via osteocalcin, it is necessary for optimal testosterone secretion by Leydig cells of the testes in mice and men. These observations were critically important as they provided much needed genetic and molecular experimental validation of the original hypothesis.

These findings did not even begin to address the "why" question. One approach to this question is to examine first the implicit surprise it entails. Why is it surprising that bone is an endocrine organ? The implication is that this is a departure from the traditional functions that this tissue is known to fulfill. Such an inference is grounded in the contemporary view of bone. However, if we consider an

evolutionary perspective, and accept as a fundamental principle of biology that every organ of the body exists to favor reproduction or survival, or both, then this view misses the mark. There is no reason bone should not obey this fundamental rule. As a matter of fact, bone abides by this rule. When animals left the sea to live on land, having a rigid tissue such as bone that could protect internal organs from trauma and conferred the ability to walk and run yielded a significant survival advantage. This has remained true throughout evolution for all bony vertebrates. If the classical functions of the bony skeleton serve in part a survival purpose, is this also the case for its endocrine functions? If we consider one physiological function enhanced by bone in its endocrine capacity, reproduction, the argument can be made that it also has survival function. Under this light, the ambulatory or "classical" and the endocrine or "novel" functions of bone share a common goal: to make of a bony skeleton a survival tool for animals living in the wild, i.e., in frequently hostile conditions.

Can a similar point be made about the other endocrine functions of bone? Do they also help us to put the "but why bone" question to rest? One of the most severe phenotypes observed in *Osteocalcin* knockout mice is a major increase in anxiety and a severe decrease, if not a complete absence, of spatial learning ability and memory. In an evolutionary context, memory was likely necessary to remember where food and/or predators were for the animal to survive. By the same token, the ability to take up glucose in peripheral tissues and increase the catabolism of glucose and fatty acids in muscle to increase exercise capacity was undoubtedly needed for the same animals to escape the same predators. This reminds us that we need not restrict the field of bone biology to what bone does (or does not do in older individuals) in humans in modern times. Rather, we need to consider the fact that the roles of the two endocrine functions of bone mentioned above have not changed for all other bony vertebrates. If our interpretation of the endocrine functions fulfilled by osteocalcin and now lipocalin 2 is correct, then it becomes clear: There is not and there has never been any discontinuity between the ambulatory and endocrine functions of bone.

The ambulatory and endocrine functions of bone thus appear to be two distinct, complementary means to the same end: to provide a survival tool that allows animals to reproduce and escape danger. This evolutionary perspective not only removes the defensive significance of the question "but why bone?" but also finds its answer. More importantly, this unifying view of bone biology pushes the envelope further as it points to a wealth of still unknown physiology to be found. Indeed, it is likely that, through osteocalcin, lipocalin 2, and/or other hormones yet to be discovered, bone regulates other processes that might be loosely defined as "emergency physiology." The aim of this volume is to provide a state of the art at a given time and therefore it cannot possibly address this latter question. Yet we believe it is important to state it now as it is undoubtedly one direction the field is taking.

What this volume tries to demonstrate is that such discussion has forced an entire field to rethink the logic behind apparently unrelated functions that are fulfilled by the same organ and often the same hormone. Looking for a common thread between these functions reveals a single conceptual framework encompassing all endocrine functions of bone in which the ambulatory and endocrine functions of bone serve the same purpose: to make bone a survival tool.

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