Thomas C.G. Bosch · David J. Miller

The Holobiont Imperative

Perspectives from Early Emerging Animals

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Contents

Introduction: The Holobiont Imperative

1

This book is being written at a time when fundamental shifts in thinking are occurring in the life sciences, but when the metaphorical ground has not yet settled under our feet. There are no germ-free animals in nature. Epithelia in contact with the environment are colonized by microbial communities, and all multicellular organisms must be considered an association of the macroscopic host in synergistic interdependence with bacteria, archaea, fungi, and numerous other microbial and eukaryotic species. We refer to these associations that can be analyzed, measured, and sequenced, as "holobionts" or "metaorganisms" (Fig. 1.1).

Half a century ago, Lynn Margulis (1993) popularized the idea that symbiosis has been an important factor in evolution, but much of the immediate interest was on the most obvious and significant eukaryote–eukaryote symbioses such as corals and giant clams, the only symbioses involving prokaryotes to receive significant attention being lichens and rhizobia. By contrast, there is now a growing realization of the importance and ubiquity of associations involving prokaryotes and archaea to every aspect of animal life—bacteria not only enable animals to metabolize otherwise indigestible polysaccharides such as lignin and cellulose, but also shape animal development and behavior.

This scenario is also playing out within the field of "traditional" symbioses, so that whereas 20 years ago, the coral symbiosis was viewed simply as a cnidarian–dinoflagellate association, current thinking has the coral "holobiont" beside the photosynthetic algae *Symbiodinium* also including bacteria and also viruses.

Interactions between the members of the holobiont, i.e., bacteria, eukaryotic symbionts, and host cells, have probably been critical to enabling the key transitions in animal evolution. However, the reciprocal is also true—animals have dramatically transformed the physical environment that is available for bacterial colonization. Animals also provide niches that simply do not exist elsewhere—for example, the rumen and the vertebrate gut, the light organ of the bobtail squid, or the intracellular environment of an ascidian. Animals also exercise enormous selective forces on bacterial populations—think only of the spread of multidrug-resistant (MDR)

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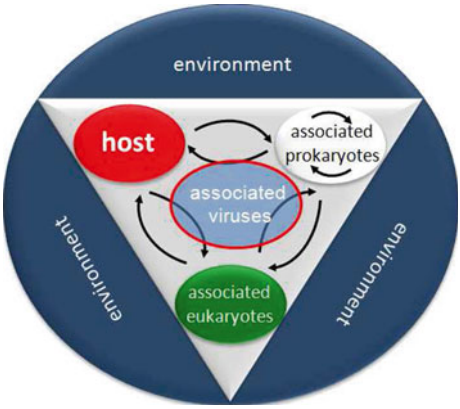

Fig. 1.1 Any multicellular organism must be considered a holobiont or metaorganism, a complex community of many species which have been, and are being, evolved

strains of *Staphylococcus aureus*, or the evolution of bacteria capable of degrading completely novel chlorinated hydrocarbons.

Since their Precambrian origins, the Metazoa have transformed the physical environment, but always in collaboration with bacteria. Along the way, some animals have also formed close relationships with other eukaryotes, but these macrosymbiotic bonds have been forged in the context of preexisting host–bacteria interactions. As discussed in Chap. 5, the partnerships that animals have forged with bacteria have been powerful agents of change. This becomes particularly apparent by the transformation of vegetation as a consequence of the evolution of the ruminants.

The increasing realization that animals cannot be considered in isolation but only as a partnership of animals and symbionts has lead to two important realizations. First, it is becoming increasingly clear that to understand the evolution and biology of a given species, we cannot study the species in isolation. Second, the health of animals, including humans, appears to be fundamentally multiorganismal. Any disturbance within the complex community has drastic consequences for the well-being of the members.

1.1 Of Complex Diseases and Animals as Complex Systems: Why Bacteria Matter

The last 50 years have seen fantastic progress in combating and eradicating terrible diseases. Deaths from infectious diseases have declined markedly in the last 50 years. In 2002, Jean-Francois Bach published a study in the New England Journal of Medicine showing an inverse relationship between the prevalence of infectious diseases (decreasing) and the prevalence of immune disorders (increasing) (Fig. 1.2a). The development of antibiotics and other antimicrobial medicines together with strategic vaccination campaigns has virtually eliminated diseases that previously were common in the United States and Europe, including diphtheria, tetanus, poliomyelitis, smallpox, measles, mumps, rubella, and *Haemophilus*

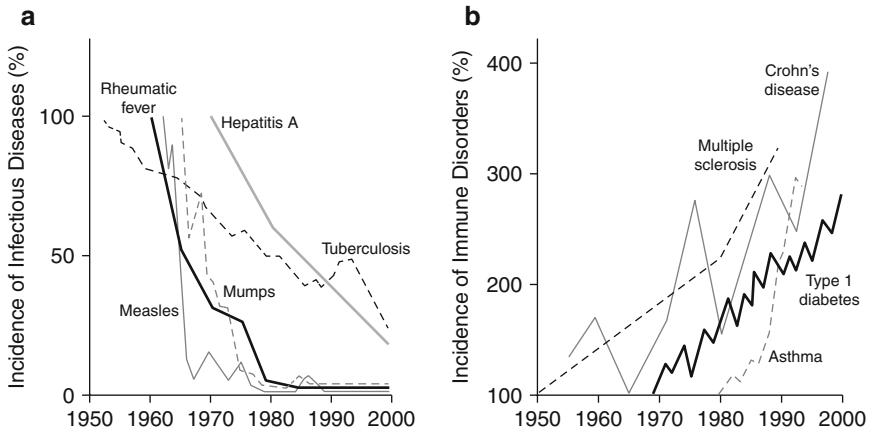

Fig. 1.2 Inverse relationship between the incidence of infectious disease (*left*) and immune disease (*right*) from 1950 to 2000 (Bach 2002)

influenzae type b meningitis. As reported by the National Center for Infectious Diseases, CDC, of the United States in 1999, this decline contributed to a sharp drop in infant and child mortality and also to a significant increase in life expectancy.

However, this success story has a second face (Fig. 1.2b). As pointed out first by Jean-François Bach (2002) from the INSERM Research Institute and Hôpital Necker in Paris, epidemiologic data provide strong evidence of a steady rise in the incidence of allergic and autoimmune diseases in developed countries over the last 50 years. The incidence of many diseases of these two general types has increased: asthma, rhinitis, and atopic dermatitis, representing allergic diseases, multiple sclerosis, and insulin-dependent diabetes mellitus (type 1 diabetes)—particularly in young children—and Crohn's disease, representing autoimmune diseases. The prevalence of asthma, hay fever, and atopic dermatitis doubled in Swedish schoolchildren between 1979 and 1991, and in Lower Saxony, Germany, the incidence of multiple sclerosis also doubled from 1969 to 1986. The incidence of Crohn's disease more than tripled in northern Europe from the 1950s to the 1990s. The incidence of these disorders apparently began to increase in the 1950s and continues to do so today, although the incidence of some of these diseases may have plateaued.

Thus, success in reducing morbidity and mortality from infectious diseases during the first three quarters of the twentieth century, however, came at a cost and was accompanied by the appearance of diseases which were unknown before in humans and animals. Allergies used to be rare condition, but now as many as 1 in 50 persons has the condition. Although most cases are mild, and overdiagnosis is likely, allergic reactions can be severe, sometimes leading to sudden death. The prevalence of both hay fever and eczema has been rising dramatically in recent years, paralleling the increase in asthma and type 1 diabetes. Another condition to consider is what is called inflammatory bowel disease (IBD), a group of chronic, relapsing disorders of the intestine. IBD manifests in two main types, ulcerative colitis and Crohn's disease, which partially overlap but have different pathology.

The etiology of IBD is complex, multifactorial, and incompletely understood. Throughout the past century, many theories have proposed and/or implicated the role of different bacteria. In particular, microbial dysbiosis has been hypothesized as a key player in disease development (Dasgupta and Kasper 2013).

Studies that have examined the role of altered microbiota in IBD demonstrate reduced gut microbiome richness and biodiversity, such as a decrease in *Faecalibacteria* with *Faecalibacterium prausnitzii* in mucosa-associated microbiota or feces. A definite causal relationship between bacteria and the pathogenesis of IBD has not yet been identified. Two recent observations and developments point to causal relationships rather than simple associations between the microbiome and IBD. First, nearly every mouse model of the disease requires the presence of microbes for colitis to develop. And second, in humans, fecal microbiota transplantation (FMT) turns out as a safe, but variably efficacious novel treatment option for inflammatory bowel diseases (IBD) (Colman and Rubin 2014). Although we may not know yet which is cause and which is effect—are the microbes causing the disease or not and is there a proof of Koch's postulates for IBD or is it elusive—these studies show that microbes are somehow involved. And then there is autism. When the disorder was first described in 1943 by Dr. Kanner, it was uncommon. Today, about one in 88 children has autism or autism spectrum disorder (ASD). Although overdiagnosis certainly contributes to the rise in cases, it is not enough to explain the enormous increase. Multiple theories try to explain the increase in autism cases, including toxins in water, food, and air and exposures to chemicals and pesticides during pregnancy. But no one knows for sure. Correlation does not equal causation. Evidence, however, is mounting that intestinal microbes exacerbate or perhaps even cause some of autism's symptoms. Recent observations in animal models show not only that gut microbes are involved in brain development but also that autism-like syndromes are not developing in germ-free animals, and that syndromes can be cured by addition of certain bacterial compounds. Again, it is not clear whether these microbial differences drive the development of the condition or are instead a consequence of it. A study published in December 2013 in cell (Hsiao et al. 2013) supports the former idea. When researchers at the California Institute of Technology incited autism-like symptoms in mice using an established paradigm that involved infecting their mothers with a viruslike molecule during pregnancy, they found that after birth, the mice had altered gut bacteria compared with healthy mice. By treating the sick rodents with a health-promoting bacterium called *Bacteroides fragilis*, the researchers were able to attenuate some, but not all, of their behavioral symptoms. The treated mice had less anxious and stereotyped behaviors and became more vocally communicative. Taken together, the composition of the gut microbes and their metabolic activity seems to be an important factor to keep in mind when attempting to understand why the incidence of autism is increasing so dramatically in the last few years.

It seems, therefore, that we have traded the eradication of infectious diseases with the appearances of immune deficiencies, allergies, asthma, and inflammatory bowel disease (Fig. 1.2). The reason for that is not fully understood. However, since any animal and any human individual appears to be in very close interaction with a stable microbiota, there must be an enormous crosstalk going on between the

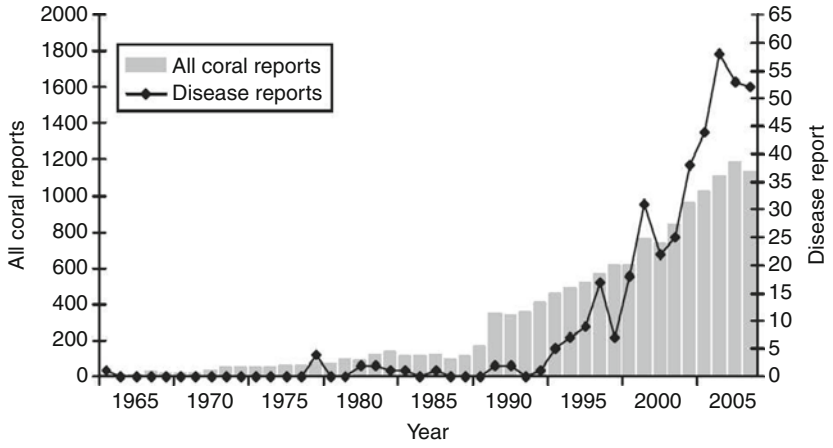

Fig. 1.3 Number of coral disease reports (excluding noninfectious bleaching) compared with all other coral reports over time (Source: Sokolov (2009))

symbionts and the host cells. Any disturbance of this crosstalk may result in severe disturbances. This phenomenon is not limited to the human population, but a worldwide phenomenon and a characteristic feature which can be traced back even to one of the most simple forms of multicellular animal life, the coral polyps.

Susanne Sokolow, a researcher working at the University of California, Santa Barbara, with interest in infectious disease ecology in marine and aquatic ecosystems, compiled a list of all articles about coral disease, published up to December 2008, since the first coral disease report in 1965 (excluding those pertaining only to stress-induced bleaching) (Sokolov 2009). This list was compared to all reports from the same time period retrieved in the ISI Web of Science using the search word "coral." Both disease and non-disease reports exponentially increased over the observation period. As shown in Fig. 1.3, Sokolow's findings indicate that coral diseases (not just bleaching) are emerging and also that coral disease research is rapidly expanding. Thus, these simple creatures also suffer from complex diseases that have increased in the last 50 years (Fig. 1.3).

Most dramatically and visible to any tourist snorkeling in a reef is a disease termed "coral bleaching" (Fig. 1.4). Coral bleaching is the loss of intracellular endosymbionts (*Symbiodinium*, also known as zooxanthellae) through either expulsion or loss of algal pigmentation. Bleaching occurs when the crosstalk between the symbionts and the coral cells is disturbed and the conditions necessary to sustain the coral's zooxanthellae cannot be maintained.

The fact that we and obviously all multicellular organisms coexist with bacteria (for reference see, e.g. Knowlton and Rohwer (2003)) tells us that our microbial "companions" may be there for a reason. Everything that changes the symbiotic partners appears to have a potential cost to us. That is obviously how we have evolved. This raises a profound set of questions. Why do we tolerate them? How do we achieve a stable partnership with our microbes? And how do the microbes manage to live with us for such a long time?