THE HUMAN MICROBIOTA AND CHRONIC DISEASE
Dysbiosis as a Cause of Human Pathology

Edited by Luigi Nibali and Brian Henderson

WILEY Blackwell
The Human Microbiota and Chronic Disease
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Preface

The human organism comprises $10^{13}$ eukaryotic cells divided into a large number of distinct organs and tissues, with unimaginable requirements for inter- and intra-cellular communication. Malfunction in such communication inevitably results in the state we define as human disease. The emergent properties of the eukaryotic cellular complexity in *Homo sapiens* were beginning to be suspected in the 1950s and 1960s, when it was becoming clear that the bacteria that actually existed within the healthy human could have a major influence on many of its cellular and tissue systems, including innate and adaptive immunity. The development of antibiotic resistance in the 1970s produced a renaissance in microbiology that revealed just how heavily colonised healthy vertebrates were with bacteria. The human appears to be the acme of this colonisation process and it is now a familiar expression that ‘for every human cell in our bodies there are ten bacteria’. Not only are we colonised by around $10^{14}$ bacteria, but the human population carries round with it a diversity of bacterial phylotypes that swamps the diversity of all the species in the aggregate of the world’s zoological collections. Thus we can no longer think of bacteria in terms of ‘us’ and ‘them’. *Homo sapiens*, like most vertebrates, must be viewed as a supra-organism colonised, on its mucosal surfaces and on the skin (and who knows where else) with complex populations of bacteria; each individual has a unique mixture of these bacteria, presumably a result of genetic (and/or epigenetic) factors controlling commensal bacterial colonisation and the stability of such colonisation.

Not only are we colonised by a large and diverse collection of bacteria (this volume will ignore colonisation by single-celled eukaryotes and by Archaea), but these bacteria generally take the form of dynamic multi-species biofilms that, like the comparison of human tissues to the disaggregated cells of these tissues, have emergent properties. Thus the collection of microbes in our bodies, which we call the microbiota, is a dynamically complex collection of multi-species biofilms. The formation of these biofilms requires an inordinate amount of intercellular signalling and this signalling must reciprocate with the cellular surfaces on which these biofilms co-exist. These cellular surfaces are ‘us’.

In the 21st century, the concept of human health and disease has to take into account our intimate relationship with our microbiota. The regional complexity of the human microbiota is only now being revealed with the application of bacterial phylogenetic analyses and next-generation sequencing (NGS) methodologies. This overcomes the problem that only around 50% of the bacteria colonising the human can be cultivated and studied. Each of us is colonised with hundreds of bacterial phylotypes, each phylotype itself being composed of a varied range of strains, each containing different populations of genes. This generates the concept of the pan-genome in which each bacterial pan-genome perhaps has as many protein-coding genes as its host. This means that the individual bacterial population colonising each human has 10–100 (or more) times the number of genes utilised
by the host. Every human host is colonised by a different combination of microbes, making him/her more or less susceptible to disease. Host genetic variants are largely responsible for determining the composition of human microbial biofilms. This creates a level of complexity that is difficult to comprehend but must be fully explored if we are to understand the healthy human and the diseases s/he is susceptible to.

Modern medicine, as a successful practice, can largely be dated from the late-19th-century discovery of the role of the bacterium in human infectious disease. At this stage it was assumed that humans were largely sterile and that infection was an aberrant state. For several decades after this monumental discovery, the paradigm of human disease was founded on bacterial or other infections as the causation of all disease, and it was only in the 1940s onwards that other mechanisms began to be sought for human disease pathology. The identification of monogenic diseases generated a successful paradigm for a proportion of human ailments, and this has morphed into our current belief that all idiopathic, and even infectious, disease has a genetic component. This paradigm has further developed with the identification of the effects of chemical modifications of our DNA on DNA function and has introduced the role of epigenetics in human diseases. However, the determination, starting in the 1980s, of how enormously colonised we are by bacteria, and the potential that these bacteria have for interfering with all aspects of our cellular homeostasis, has brought the bacterium to centre stage as a causative factor in maintaining human health and disease and even playing a role in our ageing processes.

Readers of this book live in a time when a major paradigm shift is in the offing about the causation of all human disease. There is a growing realisation that, in addition to directly causing ‘infectious’ disease, the bacteria that colonise us may generate other forms of pathology and that these will be dependent on our genetic/epigenetic constitution and on the composition of the bacteria colonising us. Microbiota-associated pathology can be a direct result of changes in general bacterial composition, such as might be found in periodontitis and bacterial vaginosis, and/or as the result of colonisation and/or overgrowth of so-called keystone species, such as the oral organism Porphyromonas gingivalis or the gastrointestinal bacterium Helicobacter hepaticus. This introduces the concept of dysbiosis, defined as a disruption in the composition of the normal microbiota.

This volume discusses the role of the microbiota in maintaining human health and introduces the reader to the biology of bacterial dysbiosis and its potential role in both bacterial disease and idiopathic chronic disease states. The current book is divided into five sections, starting from the concept of the human bacterial microbiota (chapter 1) with particular attention paid to the microbiota of the gut, oral cavity and skin. A key methodology for exploring the microbiota, metagenomics, is also described. The second section attempts to show the reader the cellular, molecular and genetic complexities of the bacterial microbiota, its myriad connections with the host and how these can maintain tissue homeostasis. Section 3 begins to consider the role of dysbioes in human disease states, dealing with two of humanity’s commonest bacterial diseases, periodontitis and bacterial vaginosis. In section 4 the discussion moves to the major chronic diseases of Homo sapiens and the potential role of dysbiosis in their induction and chronicity. This is a rapidly growing area where major discoveries are expected. The composition of
some if not all microbiotas can be controlled by the diet and this is will be discussed in the final section, section 5. This last section will also take the reader to the therapeutic potential of manipulating the microbiota, introducing the concepts of probiotics, prebiotics and the administration of healthy human faeces (faecal microbiota transplantation), then to gaze into the crystal ball and imagine the future of medical treatment viewed from a microbiota-centric position.

This book should be of interest to a very wide audience ranging from clinicians interested in infectious and idiopathic diseases to pathologists interested in pathomechanisms of disease and on to immunologists, molecular biologists, microbiologists, cell biologists, biochemists, systems biologists, and so forth, who are attempting to understand the cellular and molecular bases of human diseases.

Luigi Nibali
Brian Henderson
SECTION 1
An introduction to the human tissue microbiome
CHAPTER 1
The human microbiota: an historical perspective

Michael Wilson
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1.1 Introduction: the discovery of the human microbiota: why do we care?

The discovery by Antony van Leeuwenhoek in 1683 that we have a microbiota was very surprising and undoubtedly of great interest to 17th-century scientists. However, as modern-day researchers know only too well, this alone is not sufficient to ensure continued investigation of a subject. Further research into the microbes that inhabit humans proceeded at a very slow pace until it was realized that these microbes were able to cause disease and, much later, that they contribute to human health (i.e., in modern-day research parlance the research would be recognized as having “impact”). Our knowledge of those microbes with which we coexist has increased enormously during the last few years. An indication of the effort that has been devoted to determining the nature and function of the microbial communities inhabiting the various body sites of humans can be gleaned from the number of publications in this field listed in PubMed: in 2013 more than 2500 papers were published, nearly four times as many as in 2000.

What accounts for this recent huge growth of interest in the human microbiota? There appear to be two main driving forces: (a) increasing awareness of its importance in human disease, development, nutrition, behavior and wellbeing; (b) the development of technologies that enable us not only to identify which microbes are present but also to determine what these microbes are up to. In this chapter these two driving forces are described from a historical perspective.

1.2 The importance of the indigenous microbiota in health and disease

It has long been known that members of the indigenous microbiota of humans are responsible for a variety of infections, but only relatively recently has it been recognized that these microbes play an important role in maintaining human health and wellbeing.
1.2.1 The indigenous microbiota and human disease

In the late 19th and early 20th centuries many members of what we now recognize as the indigenous microbiota of humans were found to be the causative agents of a number of human infections (Table 1). However, at that time there was little understanding of what constituted the indigenous microbiota and therefore it was not realized that these newly recognized, disease-causing microbes were in fact regularly present on some, if not all, healthy humans and that, for the most part, they lived in harmony with their host (Table 1).

Subsequently, as knowledge of the indigenous microbiota improved, the involvement of members of these communities in disease processes became of great interest and was the subject of more intense research. Other members of the indigenous microbiota now known to cause human disease are shown in Table 2.

More recently, it has become apparent not only that individual members of the microbiota are able to cause disease, but that shifts in the overall composition of the microbiota at a site can result in disease (Table 3). Such “dysbioses” are discussed in greater detail in subsequent chapters of this book. Recognition of the disease-inducing potential of the indigenous microbiota became an important stimulus to research into the characterization of the microbial communities associated with humans.

1.2.2 The indigenous microbiota and human health

Towards the end of the 19th century it became evident to many researchers that the intestinal microbiota was important in intestinal physiology, and Pasteur in 1885 went even further by suggesting that animal life would not be possible in the absence of the indigenous microbiota19. In the second half of the 20th century it became evident that the indigenous microbiota not only contributed to mammalian health and wellbeing in a number of ways but that it also played an important

Table 1 Early discoveries of the involvement of members of the indigenous microbiota in human infections.

<table>
<thead>
<tr>
<th>Year</th>
<th>Researcher</th>
<th>Organism</th>
<th>Disease</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1881</td>
<td>Alexander Ogston</td>
<td>staphylococci</td>
<td>abscesses</td>
<td>1</td>
</tr>
<tr>
<td>1884</td>
<td>Friedrich Rosenbach</td>
<td><em>Strep. pyogenes</em></td>
<td>Wound infections</td>
<td>2</td>
</tr>
<tr>
<td>1884</td>
<td>Friedrich Rosenbach</td>
<td><em>Staphylococcus aureus</em></td>
<td>Wound infections</td>
<td>2</td>
</tr>
<tr>
<td>1884</td>
<td>Friedrich Rosenbach</td>
<td><em>Staphylococcus albus</em> (i.e. <em>Staph. epidermidis</em>)</td>
<td>Wound infections</td>
<td>2</td>
</tr>
<tr>
<td>1884</td>
<td>Albert Fraenkel</td>
<td><em>Diplococcus pneumoniae</em> (i.e. <em>Strep. pneumoniae</em>)</td>
<td>Lobar pneumonia</td>
<td>3</td>
</tr>
<tr>
<td>1890s</td>
<td>Theodor Escherich</td>
<td><em>Bacterium coli commune</em> (i.e. <em>Escherichia coli</em>)</td>
<td>Colicystitis (i.e. urinary tract infection)</td>
<td>—</td>
</tr>
<tr>
<td>1892</td>
<td>George Nuttall and William Welch</td>
<td><em>Bacillus aerogenes capsulatus</em> (i.e. <em>Clostridium perfringens</em>)</td>
<td>gangrene</td>
<td>4</td>
</tr>
<tr>
<td>1898</td>
<td>Veillon and Zuber</td>
<td>A variety of anaerobic species including <em>Bacteroides fragilis</em>, <em>Fusobacterium nucleatum</em></td>
<td>gangrene</td>
<td>5</td>
</tr>
<tr>
<td>1906</td>
<td>Thomas Horder</td>
<td><em>Strep. salivarius</em></td>
<td>Infective endocarditis</td>
<td>6</td>
</tr>
<tr>
<td>1891</td>
<td>Albert Fraenkel</td>
<td><em>Bacillus coli communis</em> (i.e. <em>Escherichia coli</em>)</td>
<td>Peritonitis</td>
<td>7</td>
</tr>
</tbody>
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