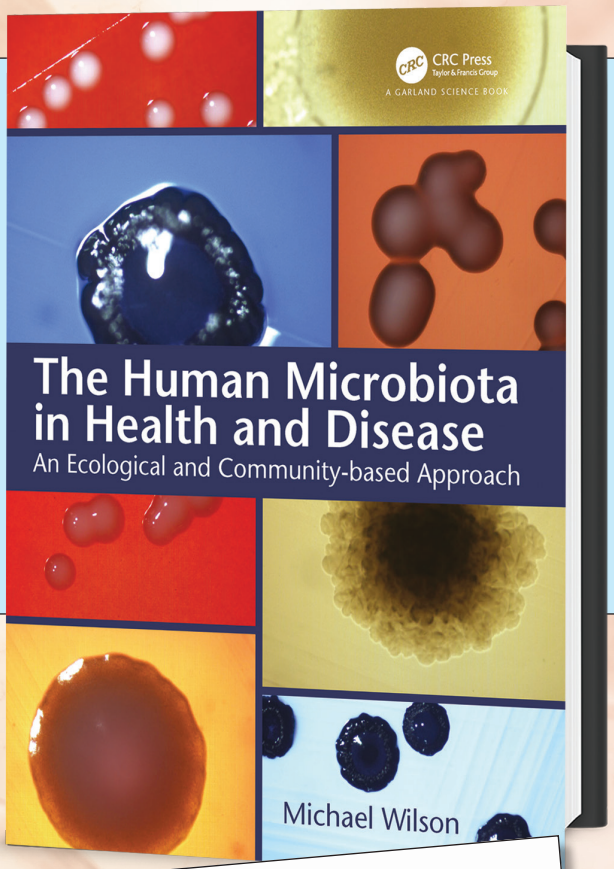
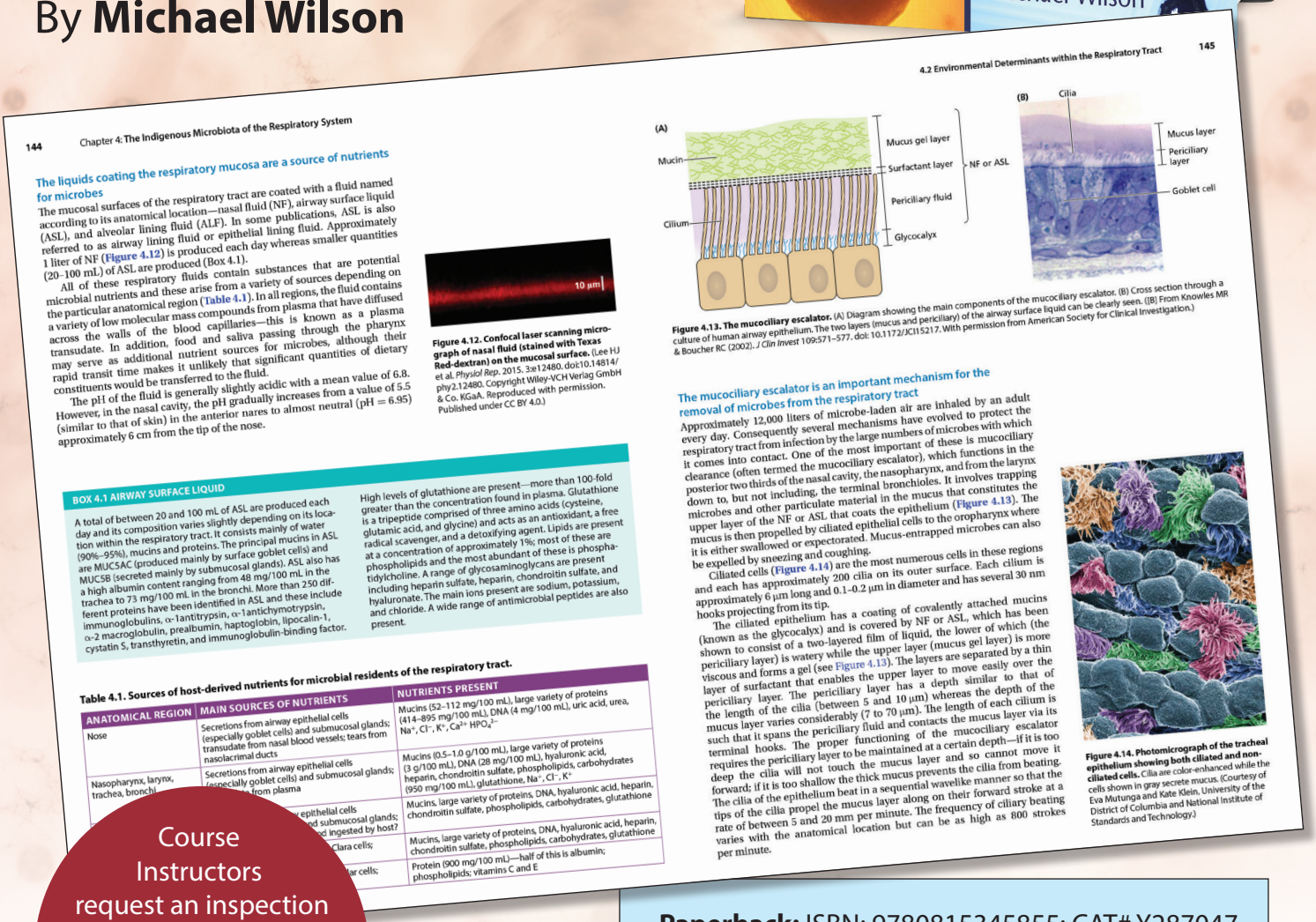
The Human Microbiota in Health and Disease

An Ecological and Community-based Approach

By **Michael Wilson**





144 Chapter 4: The Indigenous Microbiota of the Respiratory System

The liquids coating the respiratory mucosa are a source of nutrients for microbes

The mucosal surfaces of the respiratory tract are coated with a fluid named according to its anatomical location—nasal fluid (NF), airway surface liquid (ASL), and alveolar lining fluid (ALF). In some publications, ASL is also referred to as airway lining fluid or epithelial lining fluid. Approximately 1 liter of NF (Figure 4.12) is produced each day whereas smaller quantities (20–100 mL) of ASL are produced (Box 4.1).

All of these respiratory fluids contain substances that are potential microbial nutrients and these arise from a variety of sources depending on the particular anatomical region (Table 4.1). In all regions, the fluid contains a variety of low molecular mass compounds from plasma that have diffused across the walls of the blood capillaries—this is known as a plasma transudate. In addition, food and saliva passing through the pharynx may serve as additional nutrient sources for microbes, although their rapid transit time makes it unlikely that significant quantities of dietary constituents would be transferred to the fluid.

The pH of the fluid is generally slightly acidic with a mean value of 6.8. However, in the nasal cavity, the pH gradually increases from a value of 5.5 (similar to that of skin) in the anterior nares to almost neutral (pH = 6.95) approximately 6 cm from the tip of the nose.

Figure 4.12. Confocal laser scanning micrograph of nasal fluid (stained with Texas Red-dextran) on the mucosal surface. (Lee HJ et al. *Physiol Rep*. 2015. 3:e12480. doi:10.14814/phy2.12480. Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission. Published under CC BY 4.0.)

BOX 4.1 AIRWAY SURFACE LIQUID

A total of between 20 and 100 mL of ASL are produced each day and its composition varies slightly depending on its location within the respiratory tract. It consists mainly of water (90%–95%), mucins and proteins. The principal mucins in ASL are MUC5AC (produced mainly by submucosal glands). ASL also has MUC5B (secreted mainly by submucosal glands). ASL also has a high albumin content ranging from 48 mg/100 mL in the trachea to 73 mg/100 mL in the bronchi. More than 250 different proteins have been identified in ASL and these include immunoglobulins, α-1antitrypsin, α-1antichymotrypsin, α-2 macroglobulin, prealbumin, haptoglobin, lipocalin-1, cystatin S, transthyretin, and immunoglobulin-binding factor. High levels of glutathione are present—more than 100-fold greater than the concentration found in plasma. Glutathione is a tripeptide comprised of three amino acids (cysteine, glutamic acid, and glycine) and acts as an antioxidant, a free radical scavenger, and a detoxifying agent. Lipids are present at a concentration of approximately 1%; most of these are phospholipids and the most abundant of these is phosphatidylcholine. A range of glycosaminoglycans are present including heparin sulfate, heparin, chondroitin sulfate, and hyaluronate. The main ions present are sodium, potassium, and chloride. A wide range of antimicrobial peptides are also present.

Table 4.1. Sources of host-derived nutrients for microbial residents of the respiratory tract.

ANATOMICAL REGION	MAIN SOURCES OF NUTRIENTS	NUTRIENTS PRESENT
Nose	Secretions from airway epithelial cells (especially goblet cells) and submucosal glands; transudate from nasal blood vessels; tears from nasolacrimal ducts	Mucins (52–112 mg/100 mL), large variety of proteins (414–895 mg/100 mL), DNA (4 mg/100 mL), uric acid, urea, Na^+, Cl^-, K^+, Ca^{2+} HPO_4^{2-}
Nasopharynx, larynx, trachea, bronchi	Secretions from airway epithelial cells (especially goblet cells) and submucosal glands; [illegible] from plasma	Mucins (0.5–1.0 g/100 mL), large variety of proteins (3 g/100 mL), DNA (28 mg/100 mL), hyaluronic acid, heparin, chondroitin sulfate, phospholipids, carbohydrates (950 mg/100 mL), glutathione, Na^+, Cl^-, K^+
[illegible]	[illegible] epithelial cells [illegible] submucosal glands; [illegible] ingested by host?	Mucins, large variety of proteins, DNA, hyaluronic acid, heparin, chondroitin sulfate, phospholipids, carbohydrates, glutathione
[illegible]	[illegible] Clara cells;	Mucins, large variety of proteins, DNA, hyaluronic acid, heparin, chondroitin sulfate, phospholipids, carbohydrates, glutathione
[illegible]	[illegible] cells;	Protein (900 mg/100 mL)—half of this is albumin; phospholipids; vitamins C and E

4.2 Environmental Determinants within the Respiratory Tract 145

Figure 4.13. The mucociliary escalator. (A) Diagram showing the main components of the mucociliary escalator. (B) Cross section through a culture of human airway epithelium. The two layers (mucus and periciliary) of the airway surface liquid can be clearly seen. ((B) From Knowles MR & Boucher RC (2002). *J Clin Invest* 109:571–577. doi: 10.1172/JCI15217. With permission from American Society for Clinical Investigation.)

The mucociliary escalator is an important mechanism for the removal of microbes from the respiratory tract

Approximately 12,000 liters of microbe-laden air are inhaled by an adult every day. Consequently several mechanisms have evolved to protect the respiratory tract from infection by the large numbers of microbes with which it comes into contact. One of the most important of these is mucociliary clearance (often termed the mucociliary escalator), which functions in the posterior two thirds of the nasal cavity, the nasopharynx, and from the larynx down to, but not including, the terminal bronchioles. It involves trapping microbes and other particulate material in the mucus that constitutes the upper layer of the NF or ASL that coats the epithelium (Figure 4.13). The mucus is then propelled by ciliated epithelial cells to the oropharynx where it is either swallowed or expectorated. Mucus-entrapped microbes can also be expelled by sneezing and coughing.

Ciliated cells (Figure 4.14) are the most numerous cells in these regions and each has approximately 200 cilia on its outer surface. Each cilium is approximately 6 μm long and 0.1–0.2 μm in diameter and has several 30 nm hooks projecting from its tip.

The ciliated epithelium has a coating of covalently attached mucins (known as the glycocalyx) and is covered by NF or ASL, which has been shown to consist of a two-layered film of liquid, the lower of which (the periciliary layer) is watery while the upper layer (mucus gel layer) is more viscous and forms a gel (see Figure 4.13). The layers are separated by a thin layer of surfactant that enables the upper layer to move easily over the periciliary layer. The periciliary layer has a depth similar to that of the length of the cilia (between 5 and 10 μm) whereas the depth of the mucus layer varies considerably (7 to 70 μm). The length of each cilium is such that it spans the periciliary fluid and contacts the mucus layer via its terminal hooks. The proper functioning of the mucociliary escalator requires the periciliary layer to be maintained at a certain depth—if it is too deep the cilia will not touch the mucus layer and so cannot move it forward; if it is too shallow the thick mucus prevents the cilia from beating. The cilia of the epithelium beat in a sequential wavelike manner so that the tips of the cilia propel the mucus layer along on their forward stroke at a rate of between 5 and 20 mm per minute. The frequency of ciliary beating varies with the anatomical location but can be as high as 800 strokes per minute.

Figure 4.14. Photomicrograph of the tracheal epithelium showing both ciliated and non-ciliated cells. Cilia are color-enhanced while the cells shown in gray secrete mucus. (Courtesy of Eva Mutunga and Kate Klein, University of the District of Columbia and National Institute of Standards and Technology.)

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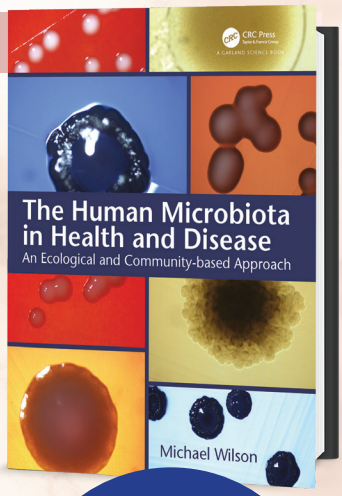
SUMMARY



A human being consists of a mammalian component and a multiplicity of microbes, collectively referred to as the "microbiota" or "microbiome," with which it has a symbiotic relationship. The microbiota is comprised of a variety of communities, the composition of each being dependent on the body site it inhabits. This community variation arises because the numerous locations on a human being provide very different environments, each of which favors the establishment of a distinct microbial community. Each community consists of bacteria, fungi and viruses with, in some cases, archaea and/or protozoa.

It is increasingly being recognized that the indigenous microbiota plays an important role in maintaining the health of its human host. However, changes in the overall composition of a microbial community at a body site, or an increase in the proportion of a particular species in that community, can result in disease or other adverse consequences for the host.

The Human Microbiota in Health and Disease: An Ecological and Community-Based Approach describes the nature of the various communities inhabiting humans as well as the important roles they play in human health and disease. It discusses techniques used to determine microbial community composition and features a chapter devoted to the many factors that underlie this mammalian–microbe symbiosis. Uniquely, the book adopts an ecological approach to examining the microbial community's composition at a particular body site and why certain factors can shift a community from a eubiotic to a dysbiotic state.

The book is for undergraduates and postgraduates on courses with a module on the indigenous microbiota of humans. It will also be useful to scientists, clinicians, and others seeking information on the human microbiota and its role in health and disease.

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Professor Michael Wilson is emeritus Professor of Microbiology at University College London (UCL), where he has worked since 1983. He has taught students on Bachelor and Master's courses in microbiology covering many aspects of the subject including the human microbiota, infectious diseases, bacterial pathogenesis, microbial biofilms, infection control, and antimicrobial chemotherapy. He has published 334 peer-reviewed scientific papers, 238 conference abstracts and 11 books, one of which, *Bacteriology of Humans: An Ecological Perspective* was awarded the first prize in the Royal Society of Medicine and Society of Authors Medical Book Awards in 2008. He has supervised the research projects of 35 PhD students and 46 MSc students.

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