

Contents

Preface	xix
---------	-----

CHAPTER 1	The Ancient Origin of Microbes	1
1.1	IN THE BEGINNING	2
	Origin of Life	3
	The Very First Cell	5
	BOX 1.1 RESEARCH IN ACTION Building Life from Scratch—The Quest for a Protocell	6
	Competition Drives Diversification	7
	Anaerobic versus Aerobic Respiration	7
	Photosynthesis Evolves	8
	Endosymbiosis and the Origin of Eukaryotes	10
1.2	THE GREAT TREE OF LIFE	12
	A Molecular Tree of Life	13
	The Three Domains of Life	14
	The Tiniest Microbes	16
1.3	MAKING THE INVISIBLE VISIBLE	17
	The First Sightings of Bacteria	17
	Culturing the Invisible	18
	Extremophiles, Life on the Edge	18
1.4	THE MICROBES WITHIN US	19
	A Universe of Microbes within Us	19
	How Much of You Is Human?	20
1.5	OUR MICROBIOMES, OUR HEALTH	21
	Microbiomes and Human Nutrition	22
	Microbial Metabolites, Key to Human Health	22
	Reflections on Your Microbiome	22
CHAPTER 2	A Brief History of Microbiome Research	27
2.1	OUR FIRST VIEW OF MICROBES	27
	Spontaneous Generation, or Not?	29
	BOX 2.1 Redi's Exemplary Experimental Design	30

Modern Experimental Design	30
The Germ Theory of Disease	31
Koch's Postulates	32
The Discovery of Antibiotics	34
BOX 2.2 Discovery of Penicillin	34
2.2 THE GOLDEN AGE OF MICROBIOLOGY	35
Discovering Colonization Resistance	36
Not Just Germs	37
Anaerobic Culturing Methods	37
2.3 GENOMICS AND BIOINFORMATICS	38
Environmental Metagenomics	38
Fecal Microbiota Transplantation	39
Germ-Free Mice	40
2.4 BRINGING IT ALL TOGETHER	41
Fluorescing Microbes	42
The Father of Microbiome Research	43
Human Microbiome Project	45
No One Else Has Your Exact Microbiome	45
The Normal Human Microbiome	45
CHAPTER 3 The Human Holobiont	51
3.1 THE HUMAN HOLOBIONT	51
3.2 THE MANY HUMAN MICROBIOMES	52
A Healthy versus Normal Microbiome	52
Microbiome in Names and Numbers	52
Microbial Taxonomy	53
The Core Microbiome	54
Primary Functions of the Core	55
Hallmarks of a Healthy Microbiome	56
3.3 THE MICROBES IN OUR GI TRACT	58
Crowdsourcing for Carbs	59
Cooperation and Conflict in the Large Intestine	61
The Friendly Gut Phageome	63
BOX 3.1 Communication between the Large Intestine Microbiome and Immune System	64
Dysbiosis of the Large Intestine Microbiome	64
BOX 3.2 Bacteriophages Protect Epithelial Cells in the Large Intestine	65
Inflammatory Bowel Disease	66
BOX 3.3 RESEARCH IN ACTION Fecal Amino Acids and Dysbiosis—Unlocking Crohn's Disease Therapies	68
3.4 THE MICROBES IN OUR MOUTH	69
Archaeal Syntrophy	69
Fungal Diversity of Unknown Function	69
Creation of Dental Plaque	70
The Diverse Roles of the Oral Microbiome	70

Our Evolving Oral Microbiota	70
Oral Microbiome Dysbiosis	71
BOX 3.4 The Gum Microbiome and Gum Disease	72
3.5 THE MICROBES ON OUR SKIN	73
A Nutritional Desert	73
Primary Functions of the Skin Microbiome	74
Skin Microbiome Dysbiosis	75
Acne and Your Skin Microbes	75
3.6 SAMPLING YOUR OWN MICROBIOME	76
Identifying a Testable Hypothesis	76
BOX 3.5 Bacterial Growth Media Protocol	77
Preparing Nutrient Media	77
Experimental Controls Are Key	77
Sampling Your Skin	78
BOX 3.6 Culturing Your Skin Microbiome	79
CHAPTER 4 Generating Microbiome Data	85
4.1 AN OPPORTUNITY AND MANY CHALLENGES	86
Training to Become a Microbiome Scientist	86
Designing a Microbiome Study	86
Using Model Organisms When Practical	87
A Testable Hypothesis Is Key	87
Experimental Variables	89
Exploring the Primary Literature	89
Performing a Literature Search	90
4.2 DESIGNING OUR STUDY	90
Choosing Our Subjects	91
Statistical Power Is Key	91
Testing for Statistical Significance	91
The Power of Our Sample Size	94
Taking Control of Our Experiment	95
Cross-Sectional versus Longitudinal Study Design	96
Experimental Data versus Metadata	96
4.3 ENTERING THE EXPERIMENTAL PHASE	97
Obtaining Our Samples	97
DNA Chemistry	98
Extracting Metagenomic DNA	99
Amplifying Metagenomic DNA	101
Billions of Amplification Products	102
High-Throughput DNA Sequencing	104
4.4 THE “OMICS”	106
Metatranscriptomics	106
Metaproteomics	107
Metabolomics	109
Spatial Omics	109

CHAPTER 5	Analyzing Microbiome Data	115
5.1	THE DATA ANALYSIS PIPELINE	115
	The Raw Data	117
	Garbage In, Garbage Out	118
5.2	RECONSTRUCTION OF GENES AND GENOMES	118
	Locating Open Reading Frames	119
	Predicting Sequence Functions	120
5.3	MICROBIOME DATA ANALYSIS	121
	Online Data Analysis Package Programs	121
	Operational Taxonomic Units (OTUs)	121
	Assigning Taxonomic Identities	121
	Species Accumulation Curves	124
5.4	SPECIES DIVERSITY MEASURES	126
	Alpha Diversity	126
	Alpha Diversity Indices	129
	Faith's Phylogenetic Diversity Metric	132
	Beta Diversity	135
	Bray-Curtis Dissimilarity Metric	135
	Unique Fraction Metric	137
5.5	VISUALIZING DIVERSITY ESTIMATES	139
	Principal Component Analysis	139
CHAPTER 6	Applying Microbiome Analysis	145
6.1	THE SCIENTIFIC PRIMARY LITERATURE	146
6.2	DISSECTING A RESEARCH ARTICLE	148
	Abstract	150
	Introduction	152
	Results	153
	Methods	154
	Data Analysis	154
	Discussion	157
6.3	INTRODUCTION TO QIITA	158
	The Basics	158
	Diving Deeper into Qiita	163
	Qiita-Based Taxonomic Distribution Analysis	164
	Qiita-Based Alpha Diversity Analysis	166
	Qiita-Based PCA Analysis	169
6.4	BEYOND QIITA	170
CHAPTER 7	Mother's First Gift	175
7.1	THE MICROBIOME OF THE FEMALE REPRODUCTIVE TRACT	176
	Vaginal Community State Types	177
	Primary Functions of the Vaginal Microbiome Types	178
	Dysbiosis of the Vaginal Microbiome Types	179

7.2	THE MOTHER'S MICROBIOME DURING PREGNANCY	179
	What We Can Learn from the Mouse about a Mother's Microbiome during Pregnancy	180
	Immune Interactions between the Developing Fetus and the Maternal Microbiome	180
	The Maternal Impact on Development of the Fetal Immune System	182
7.3	THE BIRTHING PROCESS AND THE NEWBORN MICROBIOME	186
	Vaginal Delivery	186
	Cesarean Section	186
7.4	THE INFANT'S CORE MICROBIOME	187
	Structuring the Infant's Core Microbiome	187
	Wave after Wave of Microbial Colonization	189
7.5	BEYOND THE GUT MICROBIOME	190
	The Newborn's Skin Microbiome	190
7.6	THE WONDER OF MOTHER'S MILK	191
	The Composition of Breast Milk	191
7.7	TRANSITIONING TO SOLID FOODS	194
7.8	ENVIRONMENTAL IMPACTS ON THE INFANT'S MICROBIOME	194
7.9	HEALTH IMPACTS OF A NEWBORN'S DYSBIOTIC MICROBIOME	196
	Antibiotics	196
	BOX 7.1 RESEARCH IN ACTION Antibiotics and the Newborn Gut—Long-Term Impacts on Microbiome Development	197
	Malnutrition	197
	Allergic Diseases	198
	Obesity	199
	Diabetes	200
7.10	MICROBIOME-BASED THERAPIES	201
	Probiotics	201
	Vaginal Microbiome Transplant	202
	Fecal Microbiota Transplant	202
	Oral Probiotics	203
	Oral Prebiotics	203
CHAPTER 8	The Microbiome and the Brain	209
8.1	THE NERVOUS SYSTEM	210
8.2	THE MATERNAL MICROBIOME AND NEURAL DEVELOPMENT	212
	BOX 8.1 RESEARCH IN ACTION Maternal Microbiota—Shaping the Fetal Brain's Biochemistry	215
	Formation of the Blood-Brain Barrier	216
8.3	THE MICROBIOTA-GUT-BRAIN AXIS	217
	MGBA Communication via the Endocrine Pathway	218
	MGBA Communication via the Neural Pathway	220
	MGBA Communication via the Immune Pathway	221
	MGBA Communication via Autophagy	222
8.4	GUT MICROBIOTA AND NEUROPSYCHIATRIC DISORDERS	222
	Depression	223
	Autism Spectrum Disorder	226
	Parkinson's Disease	227

8.5	GUT MICROBIOME-BASED THERAPIES	228
	Probiotic Therapies	229
	Prebiotic Therapies	229
8.6	THE EVOLVED DEPENDENCE OF OUR MICROBIOTA	229
CHAPTER 9	The Microbiome and Immunity	235
9.1	COMPONENTS AND ACTIVATION OF THE IMMUNE SYSTEM	236
	Primary Components of the Immune System	236
	Activating the Immune System	237
	BOX 9.1 Components of the Innate and Adaptive Immune Systems	238
9.2	THE GUT MICROBIOME AND IMMUNE RESPONSE	239
9.3	THE MUCOSAL FIREWALL INFLUENCES IMMUNE FUNCTION	239
9.4	IMMUNE SYSTEM AND EXTRA-INTESTINAL MICROBIOME CROSS TALK	239
	Skin	240
	Lung	240
	Liver	241
9.5	INFLUENCE OF THE MATERNAL MICROBIOTA DURING FETAL DEVELOPMENT	242
	Immune Cells in Fetal Development	242
	Distinguishing Self from Non-Self	243
	Maternal Inflammation and Infection and the Fetus	243
9.6	INFLUENCE OF THE MATERNAL AND FETAL MICROBIOTA DURING THE INFANT YEARS	244
	Breast Milk	244
	Immunoglobulin A	245
9.7	IMMUNE DISEASES AND DYSBIOSIS OF THE GUT MICROBIOME	245
	Rheumatoid Arthritis	246
	Cardiometabolic Disease	247
	Cancer	248
CHAPTER 10	Microbiome Dysbiosis	253
10.1	DEFINING EUBIOSIS AND DYSBIOSIS	254
	The Eubiotic Microbiome	254
	The Dysbiotic Microbiome	254
	More Is Not Necessarily Better	255
10.2	AN ECOLOGICAL PERSPECTIVE ON THE MICROBIOME-HOST RELATIONSHIPS	255
	Ecological Interactions between the Gut and Its Microbiome	255
	The Microbial Leash Metaphor	256
	Host Control of Microbiomes in Small versus Large Intestines	257
	Host Control of a Microbiome-Based Disease	258
	Microbial Control of the Gut Microbiota	259
	Dysbiosis, the Cause or Consequence of Disease?	260
10.3	A FRAMEWORK FOR ASSESSING MICROBIOTA-DISEASE ASSOCIATIONS	260
	Polymicrobial Synergy and Dysbiosis	261
	Polymicrobial Synergy in Gum Disease	262
	BOX 10.1 A Microbiome-Based Model of Periodontal Disease	263

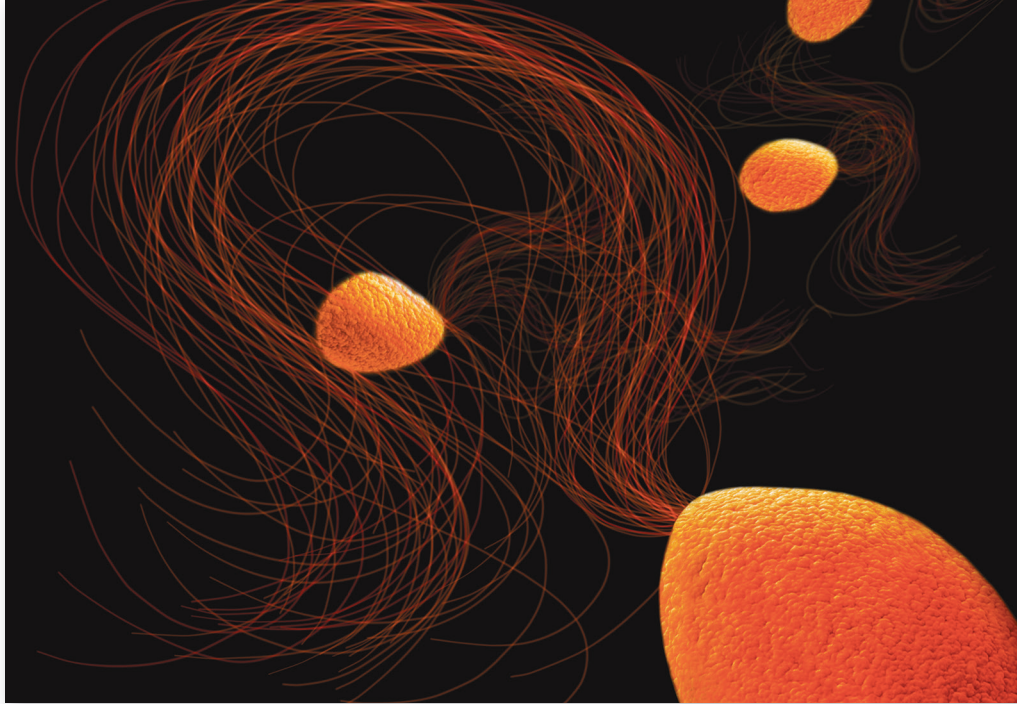
	BOX 10.2 RESEARCH IN ACTION Breaking the Single-Species Myth in Periodontal Disease	264
	Shared Dysbiosis	265
	Is the Term <i>Dysbiosis</i> Still Useful?	266
	Koch's Postulates Applied to Microbiome-Health Associations	267
	BOX 10.3 A Comparison of the Original and Ecological Koch's Postulates	268
CHAPTER 11	The Microbiome and Obesity	273
	11.1 THE OBESITY EPIDEMIC	274
	Losing Weight Is Hard to Do	275
	11.2 THE MICROBIOME OF OBESITY	276
	Obese versus Lean Gut Microbiomes	277
	Microbial Guilds at Work in Obesity	279
	Not Just Your Gut Microbes	281
	11.3 METABOLIC MARKERS OF WEIGHT LOSS	281
	Rendering Bile Acids Impotent	283
	Triggers of Fat Storage	283
	Mediating Low-Grade Inflammation	284
	11.4 THE GUT MICROBIOME AND WEIGHT LOSS	285
	BOX 11.1 RESEARCH IN ACTION Microbiome Predictors—Biomarkers for Weight Loss Success	286
	11.5 DIET-BASED APPROACHES	287
	Phytochemicals	287
	Fermented Foods	288
	Probiotics	288
	Prebiotics	289
	Fecal Microbiota Transplantation	290
CHAPTER 12	Allergic Diseases and the Microbiome	295
	12.1 THE ALLERGIC RESPONSE	295
	The Allergic Cascade	296
	12.2 A CRITICAL WINDOW OF IMMUNE TRAINING TO PREVENT ALLERGIC DISEASE	297
	12.3 EPIGENETIC CHANGES AND ALLERGIC DISEASE	298
	12.4 IMPACT OF THE MATERNAL MICROBIOME ON ALLERGIC REACTIONS	299
	12.5 THE IMPACT OF THE ENVIRONMENT IN ALLERGIC DISEASE	300
	The Response of Gut Microbes to Environmental Triggers of Allergic Disease	301
	The Farm Effect	302
	The Atopic March	303
	12.6 THE OLD FRIENDS AND BIODIVERSITY HYPOTHESES	303
	12.7 THE ROLE OF ANTIBIOTICS IN ALLERGIC DISEASE	304
	12.8 THE IMPACT OF THE MICROBIOME ON ALLERGIC DISEASE	305
	Asthma	306
	Atopic Dermatitis	309
	Food Allergy	311
	12.9 MICROBIOME-BASED THERAPEUTICS FOR ALLERGIC DISEASES	313
	Oral Immunotherapy	313
	Synbiotics	314

Fecal Microbiota Transplantation	314
<i>Faecalibacterium</i> , <i>Lachnospira</i> , <i>Veillonella</i> , and <i>Rothia</i>	314
Inulin	315
12.10 A CIRCLE OF CAUSALITY	315
CHAPTER 13 Our Evolving Microbiome	321
13.1 WHERE DID OUR MICROBIOME COME FROM?	322
Our Closest Living Relatives	324
Looking to Our Evolutionary Siblings	326
Coprolites	326
Dental Plaque	327
Oral Microbiome	328
BOX 13.1 Expansion of the Human Brain May Have Been Triggered by a Starch-Rich Diet	329
Microbes from the Middle Ages	330
Bacteriophages	330
13.2 THE INDUSTRIALIZATION OF OUR MICROBIOME	331
The Hygiene Hypothesis	333
The Disappearing-Microbiota Hypothesis	334
Antibiotics	335
Diet	335
The Consequences of the Missing Microbiota	336
Recolonizing a Vacated Niche	337
13.3 THE MICROBIOME AND THE MISSING-HERITABILITY PROBLEM	339
13.4 REACQUIRING OUR ANCIENT MICROBIOTA	339
BOX 13.2 RESEARCH IN ACTION Lactose Digestion and the Microbiome—An Evolutionary Link	340
CHAPTER 14 The Microbiome of the Built Environment	345
14.1 WHAT IS THE BUILT ENVIRONMENT?	346
The Earliest Human-Built Environments	346
The Earliest Homes Appear	346
14.2 WHAT IS THE MICROBIOME OF THE BUILT ENVIRONMENT?	347
Health Impacts of the MoBE	348
Controlling the MoBE	348
Physical Factors Influence the MoBE	349
Early Studies of the MoBE	349
Human Microbial Clouds	350
14.3 MICROBIOLOGY OF THE BUILT ENVIRONMENT	350
Constituents of the MoBE	351
The Skin and Oral Microbiomes Contribute Most to the MoBE	351
The Virome	352
Plant Microbiomes	352

14.4	BE FACTORS THAT INFLUENCE THE MoBE	353
	Humidity and Mold	355
	Ventilation and Microbial Spread	355
	Light Influences Which Microbes Survive	355
	Indoor Plumbing	355
	Cleaning Practices Impact the MoBE	356
14.5	THE IMPACT OF THE MoBE ON HEALTH	356
	Sick Building Syndrome	356
	The Farm Effect	357
	BOX 14.1 RESEARCH IN ACTION The Amish Advantage—How Dust Exposure Reduces Asthma Risk	358
14.6	TRACKING MICROBES IN THE BUILT ENVIRONMENT	358
	Tracking Hospital Pathogens	359
	The Neonatal Intensive Care Unit	360
	The Hospital MoBE	361
	The Hospital Resistome	362
14.7	MICROBIAL METABOLOMICS AND THE BE	362
	Metabolites in the BE	363
	Volatile Organic Compounds and the BE	364
14.8	THE FUTURE MoBE	365
	COVID-19 and the MoBE	365
	Build Back Better	365
	The Rewilding Hypothesis	366
	Nature-Based Solutions	366
CHAPTER 15	Taking Charge of Your Microbiome	373
15.1	IS YOUR GUT MICROBIOME HEALTHY?	374
15.2	SEEKING PROFESSIONAL ADVICE	375
	Consulting a Medical Professional	375
	Gut Microbiome Index	376
	BOX 15.1 RESEARCH IN ACTION Gut Microbiome Health Index—A Predictor of Disease Probability	377
	Consulting a Naturopath	377
15.3	THE DIY APPROACH	378
	Assessing Stool Quality	378
	Assessing Gut Transit Time	379
	Assessing Gut Microbiome Composition	380
15.4	DEFINING A HEALTHY MICROBIOME	384
	Fiber-Fermenting Bacteria	385
15.5	THE HEALTHY PLATE	387
15.6	MICROBIOME-BASED THERAPEUTICS	388
	Probiotics	389
	Prebiotics	392
	Synbiotics	393

15.7	MICROBIOME RECOVERY FOLLOWING ANTIBIOTIC USE	394
15.8	LET FOOD BE THY MEDICINE	396
Glossary	401	
References	417	
Index	435	

The Ancient Origin of Microbes



Hi there! My name is *Pyrococcus furiosus*. No fears, I am not a furious microbial monster. I am simply an extremophilic, hyperthermophilic archaeon that thrives in extremely hot environments. Maybe now you would prefer me to simply be furious! It isn't that hard to figure me out. I love hot! I mean I really, really love hot. My optimal growth temperature is a mere 100°C (or 212°F). I am also “allergic to oxygen,” meaning I need to live in anaerobic environments, such as near hydrothermal vents. In fact, I was first found in waters near Italy, hanging out in a vent. Why should you care about little ‘ole me? Well, I am a chemoorganotroph, meaning I break down sulfur to obtain energy. In the process I produce hydrogenases and amylases that are extremely heat-stable and efficient, which makes them valuable for some of your human industrial applications. So, a little kudos to me, please! (Photo from Power and Syred / Science Source)

Before we begin our exploration of the human microbiome, we must first develop an understanding of microorganisms, also called microbes—those minute creatures, far too small to be seen by the naked eye, that are both the creators and constituents of a breathtaking spectrum of microbiomes found on Earth. As you will learn, microorganisms emerged on our planet shortly after its origin and have spent over 4 billion years adapting to every conceivable environment our planet has to offer, including us! This first chapter provides an overview of the origins and diversification of microbes on Earth, with a special emphasis on what makes microbes so unique among life on our planet.

1

CHAPTER CONTENTS

- 1.1 In the Beginning
- 1.2 The Great Tree of Life
- 1.3 Making the Invisible Visible
- 1.4 The Microbes within Us
- 1.5 Our Microbiomes, Our Health

“If you don’t like bacteria, you’re on the wrong planet.”

—Stewart Brand (Brand, 2014)

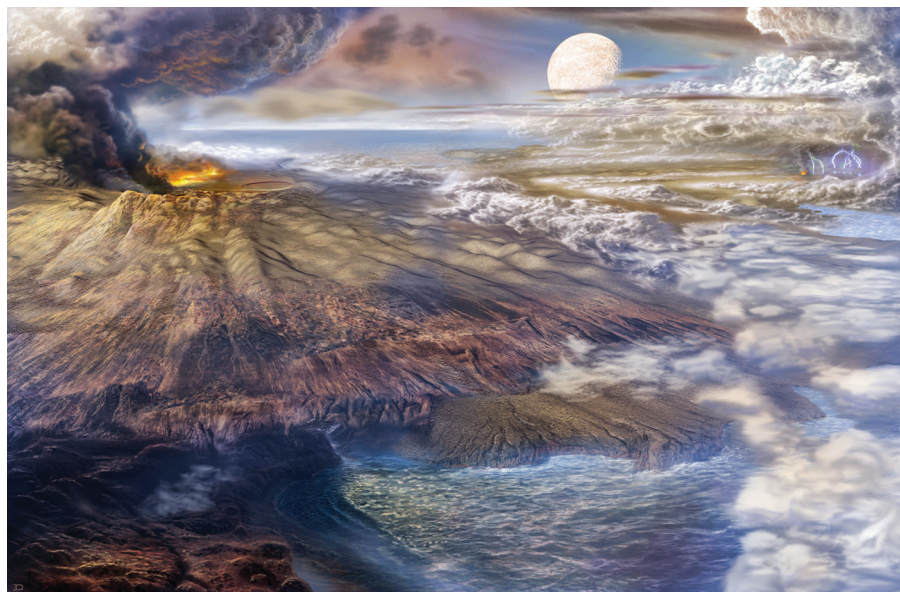
1.1 IN THE BEGINNING

If you could peer back in time to the birth of our planet, some 4.5 billion years ago (bya), what might you find? Certainly nothing even remotely resembling the Earth of today. Our young planet had no oceans, although there were plenty of volcanoes spewing out magma, water vapor, and gasses. It had no free oxygen in its atmosphere and no protective **ozone layer**, which is the thin layer of the Earth's atmosphere that absorbs most of the sun's harmful ultraviolet light. It would have been an exceedingly hot place—imagine a surface temperature upwards of 2,000° Celsius (3,632° Fahrenheit). An artist's rendition of early Earth shows a planet that does not appear even remotely hospitable to life (**Figure 1.1**).

Or was it? In fact, some of the earliest signs of life appear in 3.7 bya rock, formed when our planet was just beginning to cool from its volcanic origin (Dodd et al., 2017). Some of this ancient rock has survived the ages and paints a fascinating picture of early life. The dark gray peaks in the cross section of sedimentary rock shown in **Figure 1.2A** have tentatively been identified as fossilized microbial mats, also known as **stromatolites**, which are mounds of layers of lime-secreting bacteria and trapped sediment. Stromatolites were the only biological structures on Earth until about 540 million years ago (mya), and they can still be found in certain lagoons in Australasia (**Figure 1.2B**). In other words, regardless of how inhospitable early Earth might look to us, by 3.7 bya Earth was already teeming with life!

The word **microbe** literally means “small life,” from the Greek words *mikros* and *bios*. Microbes are small life forms that are usually too small to be seen without magnification. As we shall learn, they represent the greatest diversity of life on our planet. Although most of us are aware microbes exist, we may be unaware that they appeared very early in Earth's history and have remained the dominant life forms ever since. Exploring present-day **hydrothermal vents** in the seafloor provides valuable clues about how these earliest life forms flourished in the extreme environments of our young planet. Heated, mineral-rich water flows out of these seafloor vents, and it supports untold numbers of **chemolithotrophs**, which are bacteria that harvest energy from the minerals and chemicals that spew from the vents and release compounds that other microorganisms then use for food. Fossils of hydrothermal vents have been discovered in rock as old as 3.8 bya (Cavalazzi et al., 2021).

Figure 1.1 Early Earth This artist's rendition provides a glimpse of what early Earth may have looked like. Our planet coalesced just over 4.5 billion years ago from cosmic debris. Transient oceans and lakes existed from the start, although they had been repeatedly vaporized by the massive meteorites that showered our planet back then. The environment of the planet had settled down by about 3.8 million years ago, when the earliest rocks appear in the fossil record in what is now southeast Greenland, and the planet might have looked as this artist portrays it. (Photo © Don Dixon)



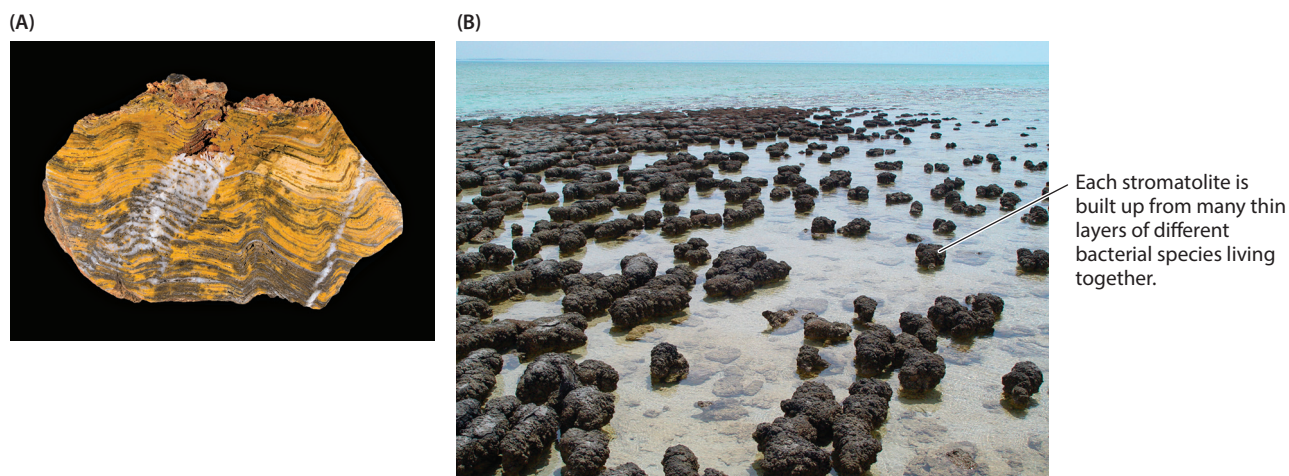


Figure 1.2 Ancient Microbial Fossils (A) The earliest fossil evidence of microbial communities. The layering in this rock is very likely due to biological activity. Cyanobacteria form mats of cells that secrete sticky substances that trap sediments in the surrounding water. Over time, these sediments form a mat and then new layers of Cyanobacteria attach. Layers of volcanic ash compacted against these structures, preserving them in the Greenland fossil record for the past ~3.7 billion years. Small fossils like these, buried under billions of years of collected rock, allow us to learn more about life in the distant past. (B) A cluster of living stromatolites from Shark Bay, Australia. There are very few such structures remaining on Earth. (A photo from Muséum de Toulouse, CC BY-SA 4.0, via Wikimedia Commons; B photo from Paul Harrison, CC BY-SA 3.0, via Wikimedia Commons)

One microbial species commonly found in vents, *Methanopyrus kandleri*, uses hydrogen gas as a food source and releases methane as a waste product. This process is known as **methanogenesis**, and it is one of the most ancient forms of energy production. The name of this microbe describes its fondness for extreme environments; *methanopyrus* literally means “methane fire,” which is highly appropriate as it can grow in temperatures up to 122°C (252°F), the highest temperature known to be compatible with life. Consider that water boils at 100°C; with this in mind, we can begin to imagine how life emerged on what we had previously considered to be an inhospitable early Earth.

Origin of Life

If we can’t rewind the tape of time and return to early Earth, can we ever learn about life’s origins? In 1953, a young scientist, Stanley Miller, and his mentor, Harold Urey, showed us the way by answering the question: Could the complex organic molecules necessary for life be created under the conditions of our planet billions of years ago? Miller and Urey designed a glass chamber in which they could create conditions that were believed to mimic those on early Earth (**Figure 1.3**). Starting with simple ingredients, such as heat, which would have been provided by the Earth’s molten core; an electrical charge to mimic lightning; water (H_2O); and an early atmosphere made of methane (CH_4), hydrogen (H_2), and ammonia (NH_3) gasses, Miller and Urey showed that complex **organic molecules** could be created from what was a predominately inorganic planet. Organic molecules are primarily made of carbon atoms bonded with hydrogen and other elements and are of biological origin. All living things on Earth are composed of organic molecules. In contrast, inorganic compounds are substances that do not contain both carbon and hydrogen. Hydrogen atoms are contained in many inorganic compounds, such as water (H_2O) and the hydrochloric acid (HCl) produced by your stomach. In contrast, only a handful of inorganic compounds contain carbon atoms. Carbon dioxide (CO_2) is one of the few examples. Miller and Urey showed that with heat, electricity, and simple inorganic ingredients, complex organic molecules, such as amino acids, could be produced. Amino acids are

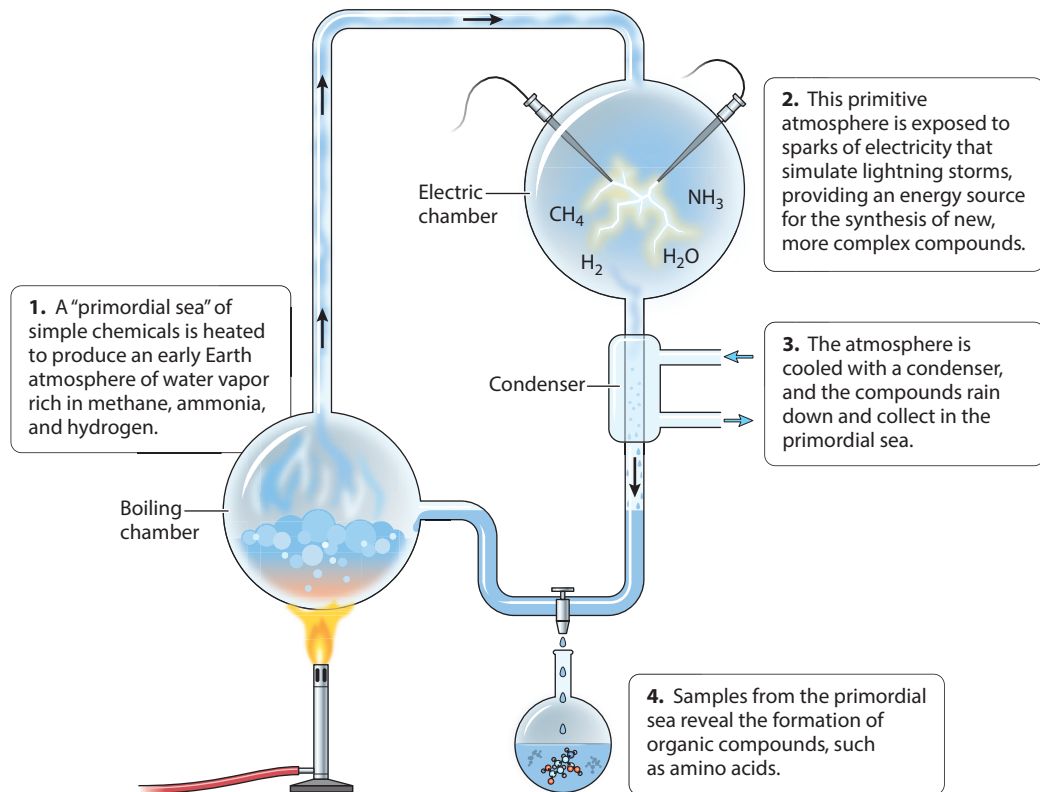


Figure 1.3 The Miller-Urey Origin of Life Experiment This experimental apparatus was designed to simulate the origin of organic compounds on early Earth.

the building blocks of **proteins**, the workhorses of cells that carry out many biological functions.

Miller and Urey's findings were extraordinary for several reasons. First, their data suggested that life could have arisen from the simple ingredients present in the "primordial soup" found on early Earth. We now know that many of the essential building blocks of life, such as amino acids and **nucleotides** (the key ingredients of **deoxy-ribonucleic acid**, or **DNA**), would have rapidly accumulated from simple inorganic constituents. Furthermore, this was the very first experiment in what was to emerge as a rich and exciting field of **abiogenesis**, or the study of the creation of life from nonlife. Their publication helped transform studies of the origin of life into a respectable field of research.

By the 1990s many scientists agreed that at least two functions were required for cellular life to emerge from a nonliving precursor: a means to physically separate the cell's internal functions from the environment (a membrane), and the ability to generate offspring, which involves copying the genetic information and producing daughter cells (replication). **Figure 1.4** provides an overview of how a cell's genetic information, DNA, is transcribed into RNA, which is then used to produce proteins. This theory is known as the **Central Dogma of Molecular Biology**, and there were vigorous debates about which element (DNA, RNA, or protein) came first. One argument emphasized the role of genetics and inheritance (**replication argument**), that is, DNA or RNA was first on the scene. A competing view proposed that creating the cells' structure came first (**membrane argument**), that is, proteins creating the structure of a cell came first. It was at this moment that a particularly innovative thinker entered the field. Jack Szostak, who won a Nobel Prize for his work on **chromosome structure**, which refers to the way DNA is packaged in a cell, decided to retool his lab and to focus on an entirely new research question—the origin of life. Szostak was

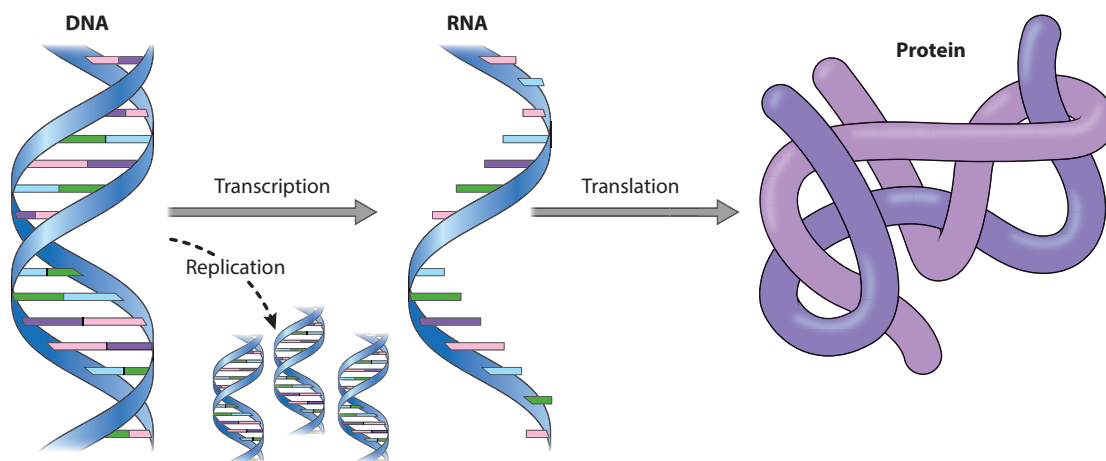


Figure 1.4 Central Dogma The Central Dogma of Molecular Biology describes the fundamental biological process by which proteins are built. In most cells, the genetic information is encoded in the DNA, which can be transcribed into a messenger molecule known as RNA. This RNA is then translated into proteins, using complex cellular machinery to “read” the RNA sequence and build the corresponding protein structure. The Central Dogma is essential to our understanding of early Earth because it illustrates the connection between genetic information and cellular processes.

fascinated with the origins debate, and he set off to create a primitive cell, or **protocell**, that would permit him to experimentally explore how the first cell might have evolved (**Box 1.1**).

The Very First Cell

Szostak knew that fatty acids could transition from small spheres (or **micelles**) into multilayered membranes as the pH of the local environment goes from a basic to a more neutral state, so he decided to simply add more membrane-forming molecules (**fatty acids**) to the mix and see what happened (see Box 1.1 and Figure 1.5B). The team added fatty acids, some of which inserted themselves into the cell’s membrane. This spontaneous growth process transformed the small spheres into long filamentous vesicles, which could be induced to divide when agitated and then to re-form cells when the agitation stopped. This elegantly simple protocell appears to possess one of the key characteristics of life—a cellular structure that could make copies of itself.

Szostak had proven that the earliest cells could have created a protected environment in which metabolism could take place. Next, he tested whether the RNA fragments located in these protocells were able to replicate, or make copies of themselves, which would permit the identical genetic information to be passed on when the protocell divides. Given that RNA is capable of both replicating itself and performing enzymatic activities, it is often considered the likely ancestor to our own DNA-based mode of inheritance. However, RNA requires high concentrations of magnesium, which can destroy the delicate membranes of the cell. Szostak found conditions that protected the membrane but still provided sufficient magnesium to permit RNA replication. These experiments provide us with a membrane-bound genetic system that is capable of self-replication and growth—two of the hallmarks of life. All done in test tubes in a laboratory!

Since this revolutionary experiment, Szostak and many others continue to dive ever deeper into questions about the origin of life (Mann, 2021). One current focus is on planetary habitability, or the potential for planets to develop and sustain life. A second research area examines the environmental conditions required to produce **biomolecules** (such as carbohydrates, lipids, nucleic acids, and proteins) in concentrations that permit metabolism. A third focus is on determining the ways in which the

precursors to DNA and RNA might have assembled and replicated. These studies are just beginning to answer some fundamental questions about the origin of life (Mann, 2021). Szostak himself notes, “Many challenges remain before we will be close to a full understanding of the origin of life, so the future of research in this field is brighter than ever!” (Szostak, 2017).

BOX 1.1. RESEARCH IN ACTION

Building Life from Scratch—The Quest for a Protocell

Researchers in the Szostak lab made their first protocell out of self-replicating genetic material, in this case a fragment of RNA. **Figure 1.5A** shows the organization of this protocell and reveals the inner compartment created by this structure and the fragments of RNA floating within. This internal environment would have permitted the cell to carry out key functions, such as metabolism, which allows the cell to transform food into energy. However, the first cells would have had none of the machinery needed for their own growth and division. The researchers hypothesized that the coupled growth and division of protocells could be achieved using conditions likely to have been present on Earth over 3 billion years ago.

❖ **Experiment.** A protocell is placed in dilute acid, such that the interior of the protocell is slightly

more acidic than the solution. Osmosis will cause water to enter the protocell, resulting in large (~4 mm in diameter) vesicles. Fatty acids are then added to the mixture and modest shear forces are provided (**Figure 1.5B**).

❖ **Results.** The growth of small protocells is achieved by placing them in a solution where liquid permeates the membrane, resulting in the transformation of initially spherical vesicles into long threadlike vesicles that can divide into multiple daughter vesicles.

❖ **Conclusion.** This experiment shows that protocells can be created, enlarged, and replicated in the laboratory, suggesting that similar processes might have occurred under the prebiotic conditions of early Earth.

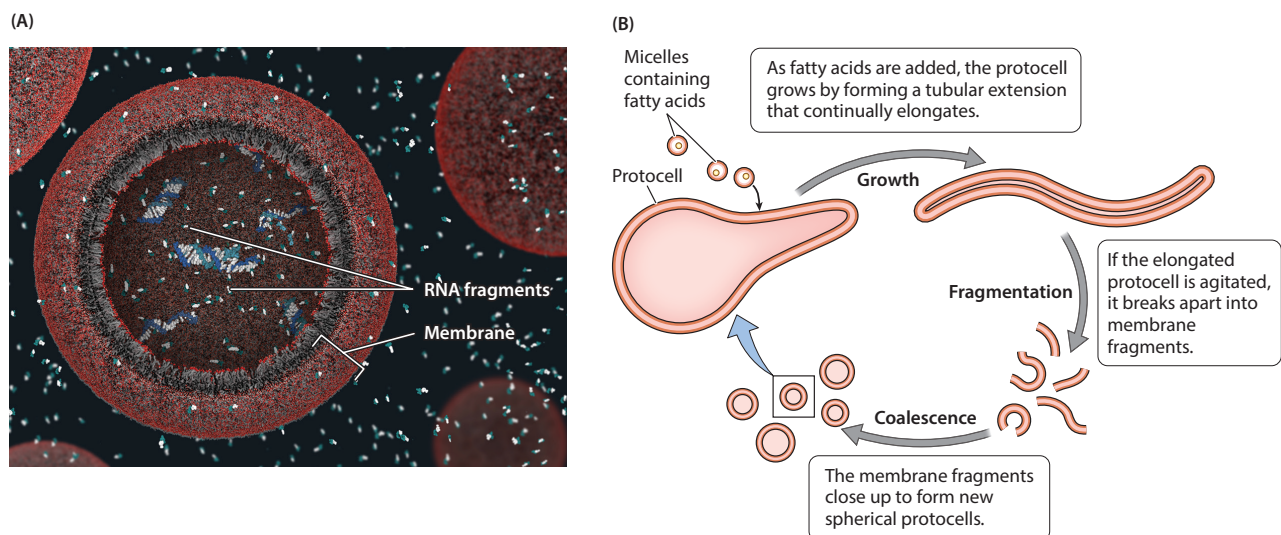


Figure 1.5 The Protocell (A) A computer-generated image of the type of protocell created by the Szostak lab. The protocell is spherical but is shown in cross section here so the inside can be seen. The lipid membrane (red outer circle) provides an internal environment for the protocell to store and replicate its genetic material and undergo metabolic processes to generate energy. Noticeably lacking are more-complex cellular structures that you may already be familiar with, such as a nucleus or mitochondrion. The protocell is surrounded by a “primordial soup” consisting of inorganic and organic molecules. Most of these were small, but some were more complex, such as RNA fragments. (B) The proposed cyclical process of protocell membrane growth and division. The cell incorporates micelles that cause its size to increase until it reaches a point where agitation results in its splitting open. The resulting fragments of the original protocell then reconfigure into new cells. This series of events is a precursor to the modern cell cycle. (A photo courtesy Janet Iwasa, Szostak Laboratory, Harvard Medical School and Massachusetts General Hospital; B after Zhu and Szostak, 2009.)

Competition Drives Diversification

Szostak's research shows us how an ancestral life form could have emerged on early Earth. However, these primitive processes were inefficient. Each time a new protocell was formed, a new RNA fragment would have been captured in the cell, which would have encoded completely different functions, or none at all. We envision the cycle shown in Figure 1.5B repeating itself billions, if not trillions, of times. Some cells captured RNA that encoded novel functions, and those cells might have survived longer and had a greater likelihood of “reproducing,” which at this point means that the protocell divided into two daughter cells that share the same RNA fragment. Imagine a primitive ocean filled with trillions upon trillions of protocells. Those that had features that resulted in the production of more copies would consume more ingredients, which would then not be available for others.

The process just described is known as **natural selection**, and it is one of the most powerful forces affecting life on Earth, through which populations of living organisms adapt to the ever-changing environment. Organisms more adapted to their environment are more likely to survive and pass on the genes that contributed to their success. This process, natural selection, causes species to change and diverge over time. Individuals in a population are naturally variable, meaning that they all differ in some ways. This variation means that some individuals have traits better suited to the present environment than others. Individuals with **adaptive traits**—traits that give them some advantage—are more likely to survive and reproduce. These individuals then pass the adaptive traits on to their offspring. Over time, these advantageous traits become more common in the population. Through this process of natural selection, favorable traits are transmitted through generations, and organisms adapt to their environment.

Overwhelming evidence shows us that all **extant** species (meaning that they are alive today) are related, having descended from a common ancestral protocell. We call this extinct organism the **Last Universal Common Ancestor**, or **LUCA**. LUCA was very likely a single-celled **autotroph**, which means it was able to make its own energy and relied on available inorganic compounds as a food source. It is envisioned that LUCA engaged in **chemolithoautotrophy**, meaning it obtained energy by oxidizing inorganic compounds (like hydrogen or sulfur) and fixing carbon dioxide to produce organic molecules. Its genetic material was almost certainly DNA, and it employed RNA molecules, such as tRNA and mRNA, in translating the information encoded in its DNA into proteins.

Heterotrophs would have emerged next, which are organisms that lack the ability to make their own organic compounds. Instead, heterotrophs obtain their energy by breaking down complex organic molecules, such as carbohydrates, fats, and proteins, which they acquire from other organisms—either by eating plants, animals, or decomposing organic matter. As heterotrophs reproduced and became more numerous, they would have rather quickly consumed the organic compounds being produced by autotrophs, resulting in selection for organisms capable of using alternative foods.

Anaerobic versus Aerobic Respiration

These earliest heterotrophs evolved on a planet with an atmosphere composed of methane, ammonia, and hydrogen cyanide, which derived primarily from the gasses emitted from volcanoes. Free oxygen was present at only trace levels. Therefore, the earliest Earth ecosystems existed in an **anoxic** world, devoid of oxygen, and the microbial communities present were supported by anaerobic respiration. Cellular respiration is the process by which cells break down sugar and turn it into energy, which is then used to perform work at the cellular level. The most primitive form happens in the absence of oxygen and is called anaerobic **respiration** (Figure 1.6A). Early anaerobic microbes used chemicals to derive energy for respiration by mediating the oxidation and reduction of inorganic compounds in their environments. For example, methanogens obtain their energy from hydrogen (H_2) and carbon dioxide (CO_2) and release methane (CH_4) as a waste product, hence their name. Similarly, sulfate-reducing

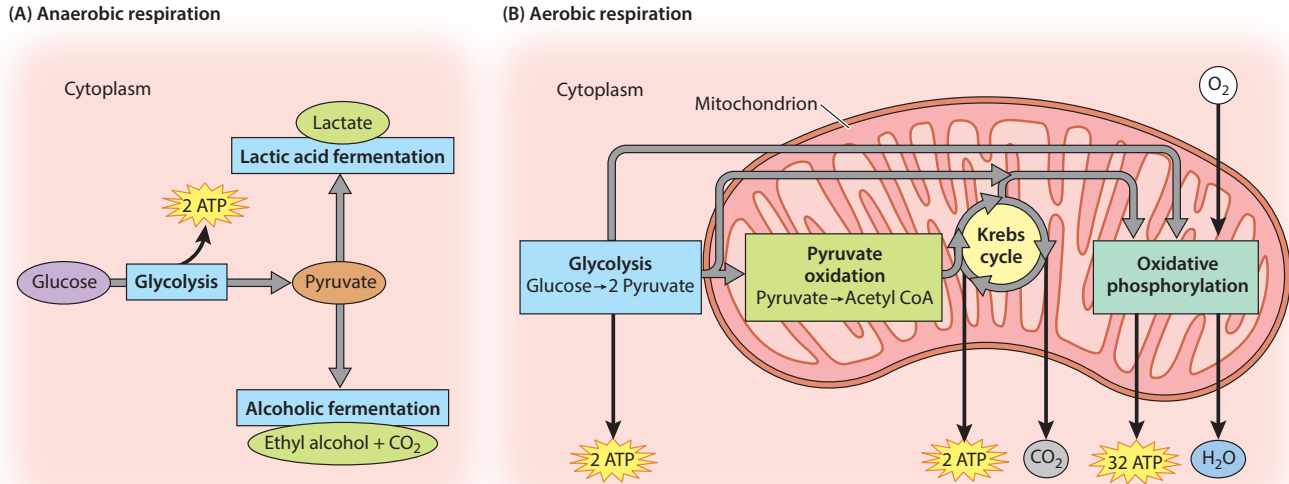


Figure 1.6 Cellular Respiration Cellular respiration is the process by which cells release energy by breaking down sugar molecules, such as glucose. (A) Anaerobic respiration, the most primitive form of respiration on Earth, is how cells convert the stored energy of glucose into adenosine triphosphate (ATP) in the absence of free oxygen. It provides energy to the cells very rapidly. (B) Aerobic respiration is the process through which cells break down the glucose molecule to convert its stored biochemical energy into ATP in the presence of oxygen.

microbes feed on sulfate. These **chemoautotrophs**, which use chemicals for energy, would have had an enormous supply of inorganic chemicals to feed on and are still commonly found in environments rich in inorganic compounds, such as near deep-sea hydrothermal vents.

The anaerobic **biosphere** of early Earth, that is, the regions of the planet occupied by living organisms, was less energetically active than our present-day aerobic biosphere—in other words, energy flow from chemicals into and between microbes was slow, roughly 5% of the rate of energy conversion found in our current biosphere. Life forms would have been engaged in intensive competition for the limited energy sources, which would have driven the process of natural selection, resulting in novel approaches to finding and harvesting energy.

Some microbial lineages evolved the ability to use oxygen as an energy source, which we refer to as aerobic respiration (**Figure 1.6B**). This novel form of respiration converts glucose or other organic molecules into energy in the form of **ATP**, or **adenosine triphosphate**, which is essential for various cellular functions. ATP uses the energy stored in its phosphate bonds to power chemical reactions. It is often referred to as the “currency” of the cell. Although anaerobic respiration also produces ATP, aerobic respiration is much more efficient, and it produces ATP much more quickly. This is because oxygen is an excellent electron acceptor for the chemical reactions involved in generating ATP.

Photosynthesis Evolves

One of the truly great metabolic innovations involved the ability to harness the sun’s energy, a process called **photosynthesis**. The earliest photosynthetic organisms evolved specialized pigments capable of extracting energy directly from sunlight. These pigments captured the sun’s energy and used it to transform carbon dioxide and water into carbohydrates (food) and oxygen (waste product) (**Figure 1.7A**). The first organisms capable of photosynthesis were the ancestors of the modern-day **Cyanobacteria**, a phylum of bacteria also known as blue-green algae. Thanks to photosynthesis, these organisms no longer needed to rely on a limited pool of organic

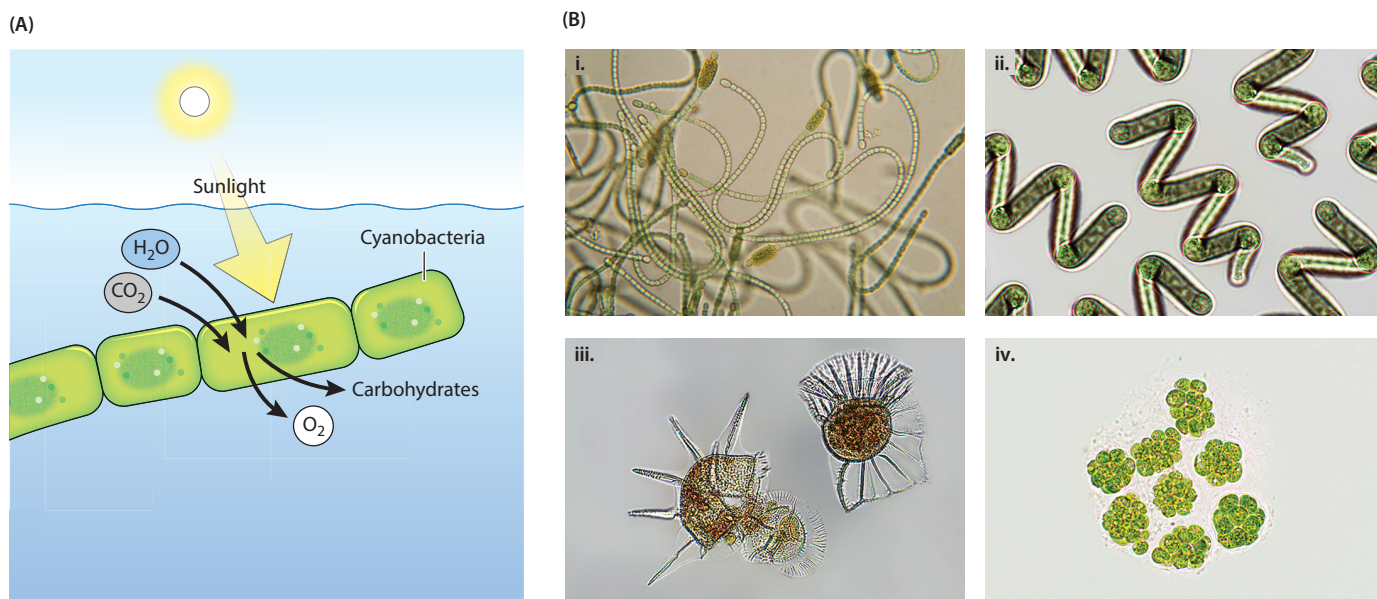


Figure 1.7 Cyanobacterial Photosynthesis and Diversity (A) Cyanobacteria use the energy of sunlight to drive photosynthesis, a process where the energy of light is used to synthesize organic compounds from carbon dioxide and water, resulting in oxygen as a waste product. (B) Some of the diverse types of cyanobacteria. Left column: Blue green algae (top), Dinophysis algae (bottom). Right column: Spirulin (top), Pandorina (bottom). (B photos from [i] istock.com /Nehring; [ii, iii, iv] iStock.com/Elif Bayraktar)

molecules or engage in the far slower process of extracting energy from chemicals and could instead get their energy directly from the sun, which offered them a profound selective advantage. Descendants of these very first photosynthetic cells can be found in almost any water source you examine today. **Figure 1.7B** provides a snapshot of some of the stunning and diverse members of this ancient lineage.

Cyanobacteria played a key role in transforming early Earth's biosphere. Every time a cell broke down a molecule of carbon dioxide, it would release a molecule of oxygen as waste. Imagine trillions upon trillions of cells, each puffing out oxygen over the millennia. At first this free oxygen was captured by minerals, which we see as massive iron oxide (or rust) deposits in the geological record about 2.5 bya (**Figure 1.8**). Once these minerals were saturated with oxygen, the excess began to accumulate in the atmosphere. This period in Earth's history is referred to as the **Great Oxidation Event (GOE)**, in which the atmosphere was transformed into one rich in oxygen, like Earth's atmosphere today, which is 78% nitrogen (N_2), 21% oxygen (O_2), 0.93% argon (Ar), 0.04% carbon dioxide (CO_2), and trace levels of other chemicals. Figure 1.8 shows the dramatic impact of the GOE on levels of atmospheric oxygen on Earth.

The rising levels of oxygen resulted in one of the first mass **extinction** events on our planet. A mass extinction event is identified when species go extinct faster than new species evolve, defined as about 75% of the world's species being lost in less than 3 million years. Oxygen is toxic to anaerobic bacteria, which do not possess mechanisms to protect their enzymes from oxidants, and thus, most did not survive this period of atmospheric transformation. A lucky few found ways to avoid the oxygen. For example, it is likely that the ancestors of modern-day methanotrophs, microorganisms that produce methane (CH_4) as a by-product of their metabolism, would have continued to flourish in the so-called dead zones in the ocean (areas where the levels of oxygen remain low) and deep in the ocean floor. Our fossil record of that time is limited, and given the microscopic size of the organisms, we are forced to infer features of these ancient life forms.

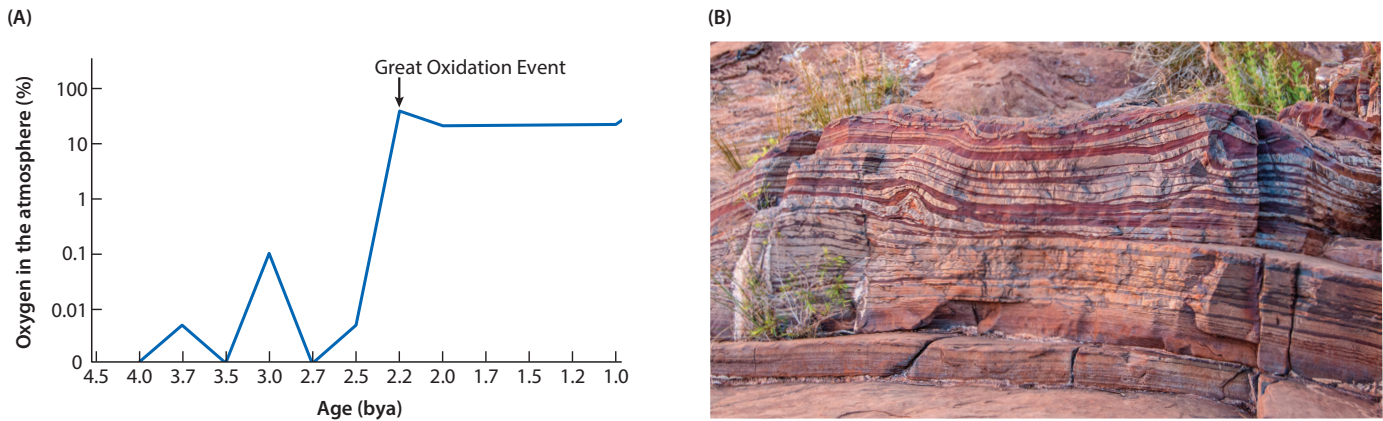


Figure 1.8 The Great Oxidation Event (A) Timeline of atmospheric oxygen levels on early Earth. Note the dramatic increase, labeled Great Oxidation Event, that corresponds with the saturation of minerals with oxygen, resulting in iron oxide sediments. (B) The red inserts of sedimentary rock are rust deposits providing evidence of the Great Oxidation Event. Rust is the common name for the chemicals that result when iron reacts with oxygen and water. Sedimentary rock is built by layering different rocks and soils, where the oldest layers are at the bottom. (A after R.A. White III 2020; oxygen data were provided by Dr. Sean Crowe [University of British Columbia] with permission, D.E. Canfield 2005, C. Dupraz and P. T. Visscher 2005, T. W. Lyons et al. 2014, and S.A. Crowe et al., 2013; B photo from Graeme Churchard from Bristol, UK, CC BY 2.0, via Wikimedia Commons)

Endosymbiosis and the Origin of Eukaryotes

With the rise in atmospheric oxygen and the advent of aerobic respiration, large, complex multicellular organisms first appear in the fossil record. Multicellularity has several obvious advantages over single-celled life forms. One of the earliest selective pressures for it may have been related to the fact that a group of cells presents a great challenge for a predator. As cells group together, their survival rate increases. Further, multicellular organisms can have longer lifespans—the organism survives even when individual cells die. Finally, multicellularity also permits increasing complexity by allowing differentiation of cell types, or tissue specificity (Pentz et al., 2020). These changes paved the way for evolution of circulatory and respiratory systems and intestines that break down food sources and extract nutrients from them.

For the first half of the history of life on Earth, single-celled **prokaryotes**, whose genetic information is found floating in the cell's cytoplasm, were the sole inhabitants. However, sometime around 2 bya, a new type of cellular life form arose: the **eukaryotes**, whose DNA is enclosed in a protective membrane called the **nucleus**. **Figure 1.9** provides a comparison of a simple prokaryote and a more complex eukaryotic cell.

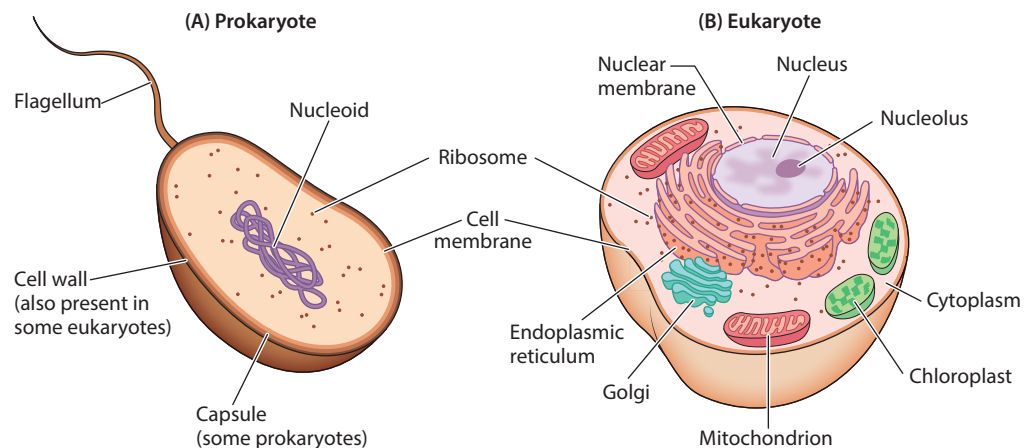


Figure 1.9 Prokaryote versus Eukaryote Cellular Complexity This diagram illustrates the similarities and differences between prokaryotic and eukaryotic cells. Both contain genetic material, a cell membrane, and ribosomes. Eukaryotic cells also contain membrane-bound organelles, such as the nucleus, mitochondria, and Golgi body, whereas prokaryotic cells do not.

In 1967 Lynn Margulis, a microbiologist and evolutionary biologist at the University of Massachusetts, proposed that the eukaryotic cell was the result of a chance fusion between two prokaryotes. An ancestral prokaryotic host cell engulfed, but didn't digest, a second prokaryotic cell, one capable of aerobic metabolism (**Figure 1.10A** shows this with a eukaryotic cell). The engulfed cell, or **endosymbiont**, provided its host with the ability to use oxygen to release energy stored in nutrients. In turn, the host cell protected the endosymbiont from predators. Over time, a **symbiotic** relationship, which refers to a close, long-term interaction between two different species, where at least one of the species benefits from the relationship, developed between the two organisms to the point that neither could survive on its own. This endosymbiotic event is immortalized in eukaryotic cells by the presence of the **mitochondrion**, which is the descendent of that ancient, engulfed aerobic symbiont and now serves as the energy factory in nearly all eukaryotic cells today.

Margulis's idea was largely ridiculed, and some 15 journals rejected her research findings before they were published (Sagan, 1967). She spent much of her career defending the hypothesis until enough experimental evidence was garnered to support its recognition as a valid theory. In fact, it is now clear that a series of symbiotic events (**serial endosymbiosis**) occurred. One endosymbiosis resulted in eukaryotic cells possessing a mitochondrion, which became the cell's energy factory (**Figure 1.10B**). Plant cells went even further, with chloroplasts resulting from a fusion of a heterotrophic bacterium with a photosynthetic cyanobacterium (**Figure 1.10C**). Chloroplasts are the membrane-bound organelles in plants and algae where photosynthesis takes place. Margulis was an extraordinary scientist, one who remained steadfast in her then-revolutionary belief that eukaryotic origins could be found. When questioned about the controversy surrounding her proposal of endosymbiosis, she replied, "I don't consider my ideas controversial. I consider them right" (Teresi, 2011).

With the advent of the eukaryotic cell, the diversification of life took on a whole new dimension. A tidal wave of biological diversification occurred about 540 mya. This period, known as the **Cambrian Explosion**, was literally that, an explosion of macroscopic life forms that appear all at once in the fossil record during the geological period known as the Cambrian. What was previously a planet dominated by microscopic prokaryotes is now rich with complex macroscopic, multicellular life

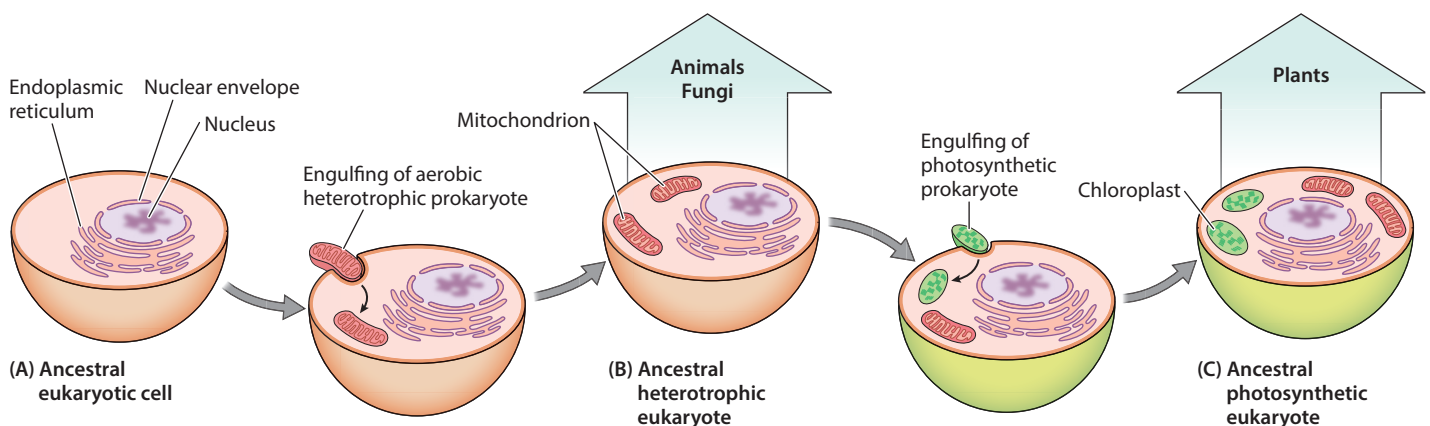


Figure 1.10 The First Endosymbiotic Events Imagine an ancestral eukaryotic cell (A), similar to a present-day amoeba. It engaged in phagocytosis, gaining energy from ingested organic matter, such as prokaryotic cells. The endosymbiotic theory posits that in several instances, the ingested cells survived and developed a symbiotic relationship with the host. Mitochondria (in B) and chloroplasts (in C) were the result of this process and were capable of aerobic respiration or photosynthesis, respectively.

forms that fuel successive waves of ecological and environmental transformations on Earth.

1.2 THE GREAT TREE OF LIFE

Now that our planet is teeming with microscopic and macroscopic life, we need a system to name all this diversity. In 1735, Carolus Linnaeus proposed a hierarchical scheme of classification that started with the most inclusive groupings, **kingdoms**, and descended into smaller and smaller subgroups, ultimately ending with a **species** name. Linnaeus would assign each species a unique two-word Latin name, or **binomial**, such as *Homo sapiens*, the binomial for humans. It consists of the species designation (*sapiens* or “wise man”) preceded by the

genus (*Homo*). Genera were grouped into **families**, families into superfamilies, and so on until the level of kingdom was reached. **Figure 1.11** shows a portion of the hierarchical levels of the Linnaean classification system and provides an example of how the human species is classified. Beyond the level of order, humans are members of the class Mammalia, the phylum Chordata, and the kingdom Animalia.

Although Linnaeus sought to classify organisms based upon similarities, his methods often resulted in clusters that reflected evolutionary relationships, which we can represent in a phylogenetic tree. A **phylogenetic tree** (also **phylogeny** or **evolutionary tree**) is a branching diagram showing the evolutionary relationships among organisms based upon similarities and differences in their physical or genetic characteristics. In 1859, when Charles Darwin published his thesis on the origin of species, he introduced the concept of a great **tree of life (ToL)** connecting all living and extinct life forms to a common ancestor (Darwin, 1859). He envisioned an ever-growing tree whose root is our common ancestor (LUCA), with the branches representing distinct lineages terminating in foliage, which represent the species. **Figure 1.12A** shows Darwin’s illustration of his tree of life. He went so far as to describe the fallen limbs and leaves as those extinct lineages that we know only from the fossil record: “Buds give rise by growth to fresh buds, and these, if vigorous, branch out and overtop on all sides many a feeble branch, so by generation I believe it has been with the great Tree of Life, which fills with its dead and broken branches the crust of the earth, and covers the surface with its ever branching and beautiful ramifications” (Darwin, 1859).

The ToL envisioned by Darwin was transformed over the next hundred years as more and more organisms were discovered, described, and added. **Figure 1.12B** provides a version of the ToL popular in the mid-20th century, called the five-kingdom ToL, with animals, plants, fungi, protists, and monera identified as the five categories, or kingdoms, of life. Animals and plants are obvious; however, you may be less familiar with the other kingdoms. **Fungi** refers to spore-

Classification of *Homo sapiens* within the order Primates

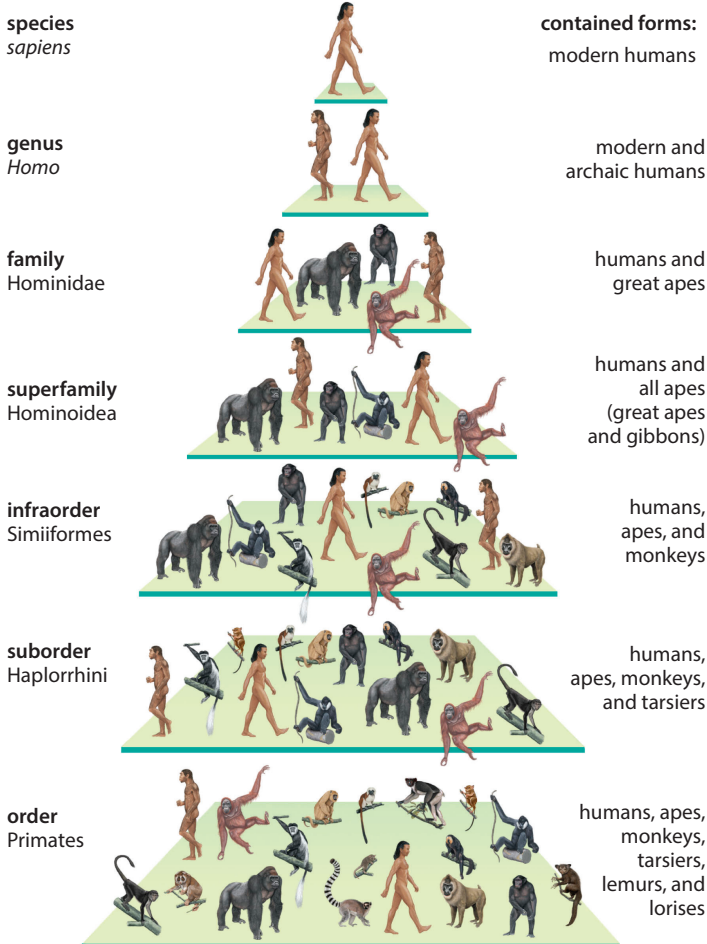


Figure 1.11 Hierarchical Classification This image shows a portion of the Linnaean classification of humans, or *Homo sapiens*. The broadest level of Linnaeus’s classification system is kingdom. The kingdom Animalia includes all animals, including humans. The groups become more specific as classification continues. Humans are in the genus *Homo*, which contains modern humans as well as now-extinct humans, such as Neanderthals. A species’ name consists of its genus name followed by its species name, which is specific to it, so humans are given the name *Homo sapiens*. (Photo from Universal Images Group North America LLC/Alamy Stock Photo)

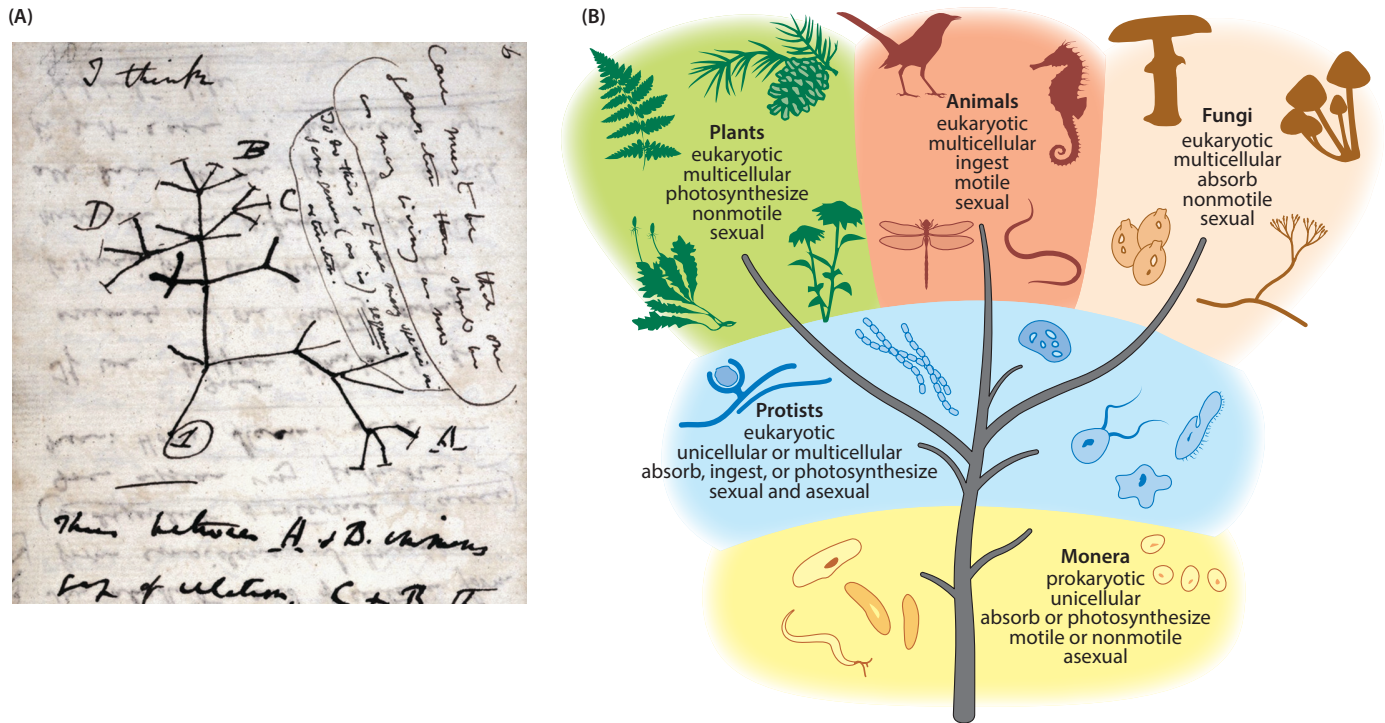


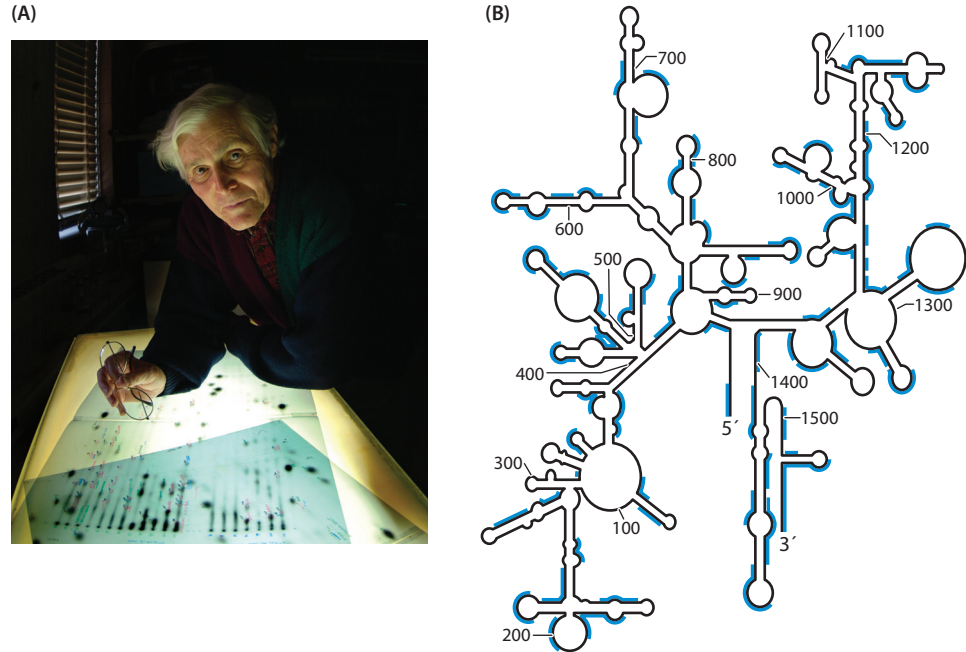
Figure 1.12 Darwin's Tree of Life (A) Darwin's illustration of the tree of life, which was first drawn in one of his notebooks in 1837. The base of the tree, which is labeled by the number 1, represents the cenancestor (or LUCA), and the ends of the branches represent species. A version of this illustration was included in his landmark book on evolution, *On the Origin of Species*, which was published 12 years after Darwin's original tree drawing. (B) The five-kingdom ToL was widely used until molecular technology became advanced enough to permit us a window into the incredible diversity of Protista and Monera, which we now recognize as the prokaryotes. Monera, which includes bacteria and other prokaryotes in this ToL, is at the base. Monera was seen as a more primitive group, from which more-advanced multicellular life evolved. The uppermost branches of the tree represent plants, animals, and fungi. Scientists could easily observe these large, multicellular life forms, so their diversity was better understood and took up most of the branches of the tree. (A illustration reproduced by kind permission of the Syndics of Cambridge University Library.)

producing organisms that feed on organic matter, including molds, yeast, mushrooms, and toadstools. **Protists** are single-celled eukaryotic organisms, such as protozoa or simple algae. **Monera** is the kingdom into which prokaryotes, such as bacteria, are placed. This view of life's diversity focuses your attention first and foremost on the macroscopic organisms and suggests that protists and monera are somewhat more primitive and less diverse. In truth, scientists at that time couldn't make sense of the evolutionary relationships among monera, simply because they didn't have **phenotypes**, or observable characteristics, to compare.

A Molecular Tree of Life

In 1977, Carl Woese tackled this formerly intractable problem, inferring the evolutionary relationships among the monera, or prokaryotes (Woese & Fox, 1977). Lacking visible physical traits with which to classify microorganisms, Woese turned to molecules. He chose the ribosome, which is a complex of RNA and associated proteins that functions to synthesize proteins, and which is one of the most ancient and well-conserved biochemical structures shared by all life. This means that any two species' ribosomes are similar, even if the species are not otherwise closely related. The ribosome is essentially a mini factory that translates genetic information into proteins

Figure 1.13 Carl Woese and a Molecular-Based Tree of Life
(A) Photograph of Carl Woese peering at a radiograph that shows the ribosomal fragments of a microorganism's 16S rRNA separated based upon electrical charge. (B) Two-dimensional structure of the 16S rRNA molecule with regions indicated in blue that are cleaved during the RNA digestion procedure employed by Woese. (A photo courtesy of Jason Lindsey, University of Illinois Urbana-Champaign)



(**Figure 1.13**). All life forms use this same fundamental process for making proteins, so they all share at least some portions of the ribosomal RNA–protein complex.

Woese proposed that by comparing portions of the ribosomal complex among all life forms, it would be possible to group organisms in the same manner that they had been grouped previously using physical traits, or phenotypes. Within the ribosomal complex are subunits made of RNA and protein. The RNA molecules within those subunits are named based upon their weight in Svedberg units, such as 16S and 18S. All organisms, even those from across the three domains of life, have ribosomal subunits. Woese used information obtained by cleaving the RNA sequences of these ribosomal subunits and comparing the resulting fragments to estimate how closely related two organisms are. Pairs of taxa that are more similar in their ribosomal fragments are inferred to be more closely related. The number of differences between the ribosomal RNA fragments then serves as a measure of the amount of evolutionary time that separates a pair of taxa. These evolutionary distances can be used to create a phylogeny.

The Three Domains of Life

Woese first focused on a subunit of the ribosome (the 16S subunit) that is present in all bacteria. He produced fragments of the 16S ribosomal RNA (rRNA) for a diverse sample of what he thought of as bacteria and immediately noticed something striking. There was one cluster of fragments that was quite different from all the others. The organisms represented by that cluster were methanogens, prokaryotic cells that produce methane as a waste product. Woese quickly realized the significance of this finding: methanogens were not bacteria, but something completely different. He then employed an additional subunit of the ribosome (the 18S subunit), which is related to the 16S subunit but is found in eukaryotes, so that he could include eukaryotes in his clustering process. Although methanogens looked superficially like bacteria, their ribosomes reveal a very different ancestry. To his surprise the ribosomal fragments of methanogens were more like those found in eukaryotes than in bacteria. Woese named this new lineage **Archaea**, which is a Latin term meaning “primitive.”

Based upon these results, Woese created a new ToL, which required a higher level of organization than the five kingdoms. He identified and named three groups within a higher level of biological relationships: Eukarya (animals, plants, fungi, and

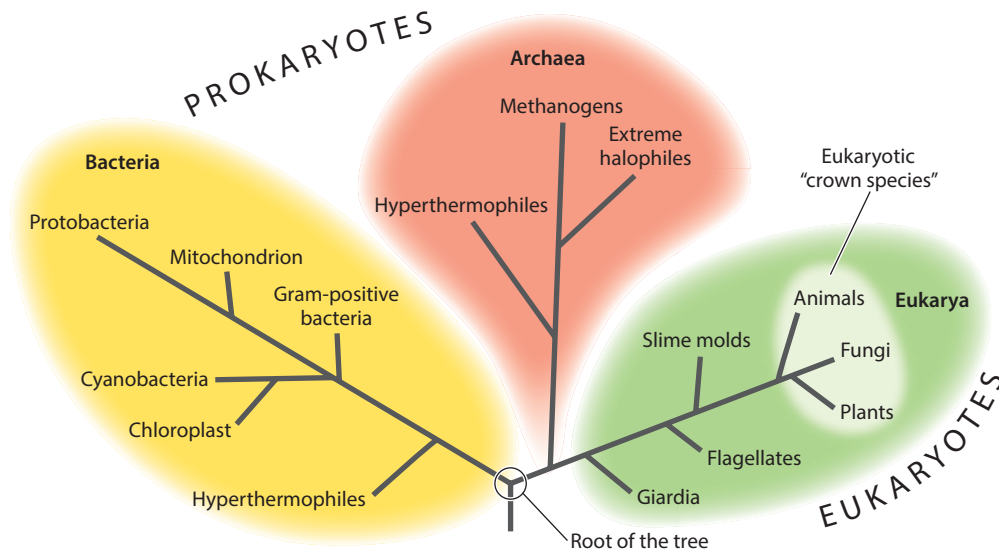


Figure 1.14 The Ribosomal RNA-Based Tree of Life This phylogenetic tree was developed using data from rRNA sequences. While eukaryotes made up most of the five-kingdom-view-based tree, they are only a small portion of the modern tree of life. Monera was found to include two distinct domains: Bacteria and Archaea. Although archaeans are microorganisms like bacteria, they are actually more closely related to eukaryotes, like us, than they are to bacteria! (After M. T. Madigan and M. Martinko, 2006.)

protists), Bacteria, and Archaea (Figure 1.14). The discovery of Archaea stimulated both enormous interest and intense skepticism at first. However, as more lineages of Archaea were identified, it became clear that it did, indeed, represent a novel and ancient branch on the ToL. Table 1.1 summarizes some of the similarities and differences observed between members of the three domains. The prokaryotes, which encompass members of the domains Archaea and Bacteria, share certain characteristics, such as size and a lack of intracellular organelles, while the eukaryotes appear to be chimeras, sharing key characteristics with both archaeans and bacteria. If we think back to the endosymbiotic theory, these patterns of similarities and differences begin to make sense. Eukaryotes, which were created through a series of endosymbiotic events, may very well have been derived from an ancestral archaean host that harbored a bacterial endosymbiont.

Woese's breakthrough was momentous for several reasons. First, by focusing on the ribosome, he had identified a way to compare all cellular life. Second, Woese revealed our ignorance of one of the three main branches of life, the Archaea. Further, he showed us that microbes occupy a dominant place in Earth's biodiversity. If we compare the five-kingdom and three-domain views of biodiversity, we see a fundamental shift from a view of life in which the eukaryotic **crown species** (plants, animals, and fungi) dominate, to one in which these eukaryotes are in the minority (see Figures 1.12B and 1.14). Woese himself described how unsettling this new view of life's diversity truly was: "Imagine walking out in the countryside and not being able to tell a snake from a cow from a mouse from a blade of grass, that's been the level of our ignorance" (Blakeslee, 1996).

Table 1.1 Comparison of Domains

	EUKARYA	BACTERIA	ARCHAEA
Cell type	Eukaryotic	Prokaryotic	Prokaryotic
Chromosomes	Linear	Circular	Circular
Membrane-bound organelles	Yes	No	No
Nuclear envelope	Yes	No	No
RNA polymerase	Many	One	Many
Cell wall composition	Not always present Plants—cellulose Fungi—chitin	Peptidoglycan	Lacks peptidoglycan
Cell membrane composition	Ester linked lipid with proteins (straight chain)	Ester linked lipids with D-glycerol (straight chain)	Ester linked lipids with L-glycerol (branched chain)

The Tiniest Microbes

There is one group of microbes that were not included in Woese's molecular tree of life, the viruses. Viruses are microscopic organisms that require a living cell, or host, to multiply. They are ubiquitous and may even be the most abundant biological entities on our planet. Viruses are simple in structure, with a genetic material (DNA or RNA) and a protein coat (**Figure 1.15A**). Some sport an additional outer layer, the envelope, which may have spikes that help the virus latch onto and enter a host cell. If the cellular conditions are right, the viruses then multiply within their host, often killing the host cell in the process.

Each type of virus has its own **host range**, which refers to the breadth of hosts it can infect. Some have a narrow host range; for example, *Variola virus*, which causes smallpox, can only infect humans. Other viruses have broad host ranges; for example, SARS-CoV-2, the causative agent of COVID-19, may infect hundreds of different hosts, including humans and other primates, bats, pangolins, ferrets, and camels.

Viruses are generally not given species names, so they don't fit neatly into the Linnaean classification system. In fact, many scientists don't consider them to be alive! They lack some of the basic features we think of when we attempt to define life, such as being cellular, maintaining homeostasis (or a stable internal state), growing, and making or acquiring energy. They do, however, replicate—using the host's replication machinery—and they adapt to their environment. Whether they are alive or not, viruses are one of the most abundant and diverse forms of microorganisms on Earth. They are categorized according to various characteristics they possess, includ-

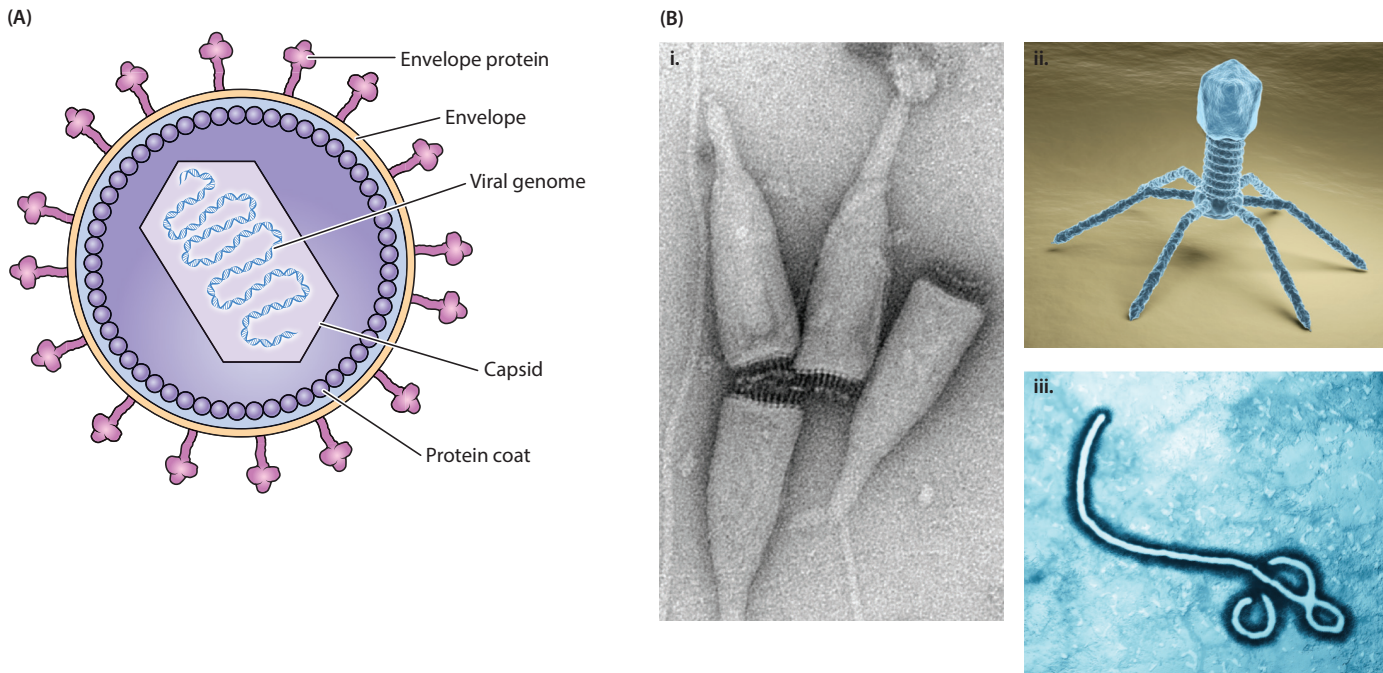


Figure 1.15 Viral Structure and Diversity (A) Most viruses are enclosed by an envelope embedded with proteins, which help the virus enter a host cell. A virus may have a DNA or RNA genome, which may be protected by a capsid. (B) A variety of different viral structures: [i] Acidianus bottle-shaped virus (colorized electron micrograph image), [ii] Bacteriophage on a bacterial cell (computer generated image), [iii] Ebola virus (microscopic view), and [iv] SARS-CoV-2 (computer generated image). (B photos from [i] ICTV International Committee on Taxonomy of Viruses, David Prangishvili, Mart Krupovic, Andrew M. Kropinski, Stuart G. Siddell, CC BY-SA 4.0, via Wikimedia Commons; [ii] extender_01/Shutterstock; [iii] iStock.com/Nixx photography; [iv] iStock.com/Naeblys)

ing their shape and size, the type of genetic material they possess (DNA or RNA), and whether they have an envelope layer. **Figure 1.15B** illustrates the major types of viruses.

It is challenging to identify the origin of viruses, as they don't leave fossils. In addition, some viruses can insert their genetic material into their hosts' genomes, which makes it difficult to untangle viral from host evolutionary histories. Since viruses do not share homologous genes or proteins with members of the three domains (Bacteria, Archaea, and Eukarya), we are not able to place them onto one or more branches of the ToL, leaving their relationships with other life forms in question.

1.3 MAKING THE INVISIBLE VISIBLE

With Woese's transformation of the ToL, microbes took center stage in our understanding of the diversity of life for the first time. In fact, according to Woese, microbes are the core of life on Earth: "If you wiped all multicellular life-forms off the face of the earth, microbial life might shift a tiny bit, if microbial life were to disappear, that would be it—instant death for the planet" (Blakeslee, 1996).

Before the 16S rRNA ToL revolution, we hadn't appreciated the immense diversity of microbes on our planet. In large part this was due to their seemingly simple morphology, which resulted in our tendency to group these simple life forms together. In the five-kingdom view of life, we see the microbial lineages clustered in two pools at the base of the tree (see Figure 1.12B). These pools represent the protists and monera (Bacteria and Archaea) with virtually no branches to represent what we now know is an incredible diversity of microscopic life.

We have known that microbes exist for over 400 years, ever since Robert Hooke invented the first microscope and explored the detailed structure of all sorts of biological entities, such as sponges, seaweed, and wood. Of particular interest here are his observations of mold. He describes its appearance on numerous decaying substances and notes that these creatures "will not be unworthy of our more serious speculation and examination" (Hooke, 1665). In short, Hooke was describing a microorganism's appearance for the first time.

The First Sightings of Bacteria

Inspired by Hooke, Antonie van Leeuwenhoek developed an even more powerful microscope and explored numerous samples from his own body, such as stool. In 1677, he reported to the British Royal Society that he had discovered over 1,000 "**animalcules**," or little animals, that differed from one location in the body to another (**Figure 1.16**) (van Leeuwenhoek, 1677). When he examined scrapings from his teeth, van Leeuwenhoek noted, "I then most always saw, with great wonder, that in the said matter there were many very little living animalcules, very prettily a-moving. The biggest sort . . . had a very strong and swift motion and shot through the water (or spittle) like a pike does through the water. The second sort . . . oft-times spun round like a top . . . and these were far more in number" (van Leeuwenhoek, 1677). These were the very first observations of living bacteria ever recorded, and they inspired the development of an entirely new field of study, **microbiology**, or the branch of science that deals with microorganisms. Van Leeuwenhoek is considered the father of microbiology, and from the

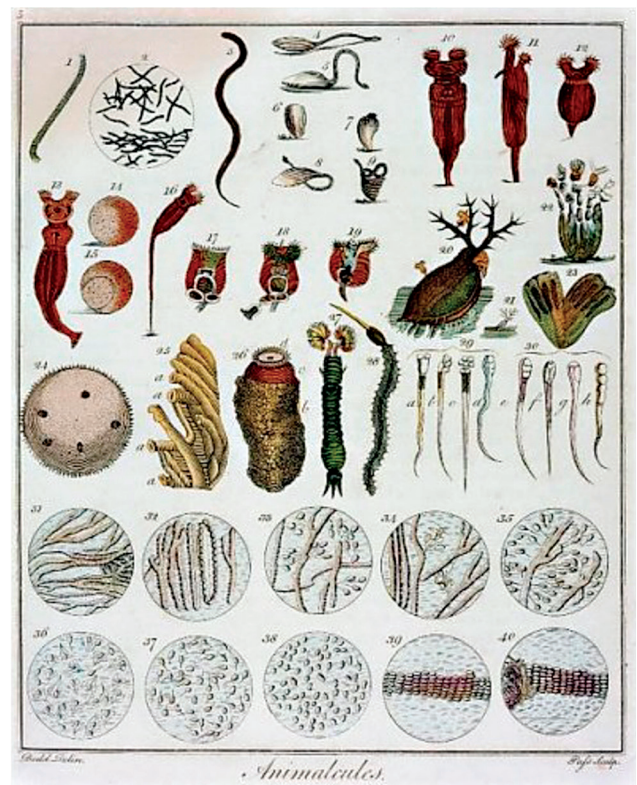


Figure 1.16 **Animalcules** Antonie van Leeuwenhoek was the first person to record observations of the microbiome. He obtained microbiome samples from various body parts and viewed them under a microscope. The "animalcules," or microorganisms, he saw are illustrated in this figure. (Photo from The Picture Art Collection/Alamy Stock Photo)

late 1600s to present day, scientists have been exploring the rich diversity of microbes on Earth.

Culturing the Invisible

Ever since the invention of the microscope, microbiologists have developed a rich toolbox with which to further explore microscopic life forms. The most common approach is to **culture** the cells, which allows them to grow and divide until there are enough for us to see. The basic procedure is straightforward. Say you want to see some of the microorganisms present in a nearby pond. You start with a sample of pond water and spread a drop of it on a rich growth medium. Each cell lands on a unique spot on the growth medium. If its requirements for growth are present, it grows and divides in this spot, and its daughter cells then replicate and eventually form a visible “colony” of hundreds of thousands of identical cells (**Figure 1.17**). In our pond water sample, we might find 50 or more different types of microbes growing on the food source we provide.

By altering the nutrients offered in growth medium to meet different species’ growth requirements, scientists have identified several thousand prokaryotic and protist species. However, that seemingly impressive number pales in comparison with the number that actually inhabit the pond water. If we were to apply Woese’s molecular methods of comparing all the 16S rDNA present in our pond water sample, we might find several thousand microbial species. This discrepancy between what we can grow in artificial media and what microscopic life is present in a sample is known as the **great plate count anomaly**, and it hindered progress in microbiology for decades. We simply didn’t know what (or how much) we didn’t know! For example, it is common knowledge that urine is sterile, unless you have a urinary tract infection. And yet, if you take a sample of supposedly sterile urine from a bladder and sequence the 16S rDNA present, you will find a wealth of different microbes have made urine, or the bladder, their home. For every novel environment we sample, we identify an ever-greater breadth and depth of microbial diversity.

Extremophiles, Life on the Edge

With the advent of molecular tools for identifying microbes, microbiologists engaged in an expansive hunt for novel microorganisms. We now know that microbes exist in



Figure 1.17 Bacterial Culture To isolate a genetically identical group of bacteria, a sample can be spread across a nutrient-filled petri dish to isolate individual cells, which can grow and divide to form visible colonies (A). Every member of a colony is a descendant of the first individual cell that landed on that spot on the petri dish. To obtain a pure culture of each individual cell from the original sample, cells from a colony are transferred to a fresh petri dish and grown in isolation (B). (Photos from [left] iStock.com/aorphoto; [right] iStock.com/Sinhyu)

some of Earth's most extreme environments. Some thrive in ice or salt, in the most acidic or basic conditions, living in organic solvents, consuming heavy metals and even toxic waste. Such **extremophiles** have been found in every imaginable, and even the most unimaginable, conditions on Earth. In every extreme environment investigated, a variety of organisms have been shown to not only tolerate the conditions there, but often require them to survive. **Table 1.2** shows just a sliver of the extreme environments where extremophiles have been identified so far.

The term *extremophile* means “lover of the extreme,” and the Archaea domain is where most extremophiles are found. In fact, when archaeans were unveiled to the world, they were thought of as extremophile weirdos. We now know that archaeans can readily adapt to extreme conditions, which may be due, in part, to the composition of their cell membrane. All cells have a plasma membrane made of a phospholipid bilayer, which evolved from the lipid-based protocell membrane we discussed earlier. The archaeans employ ether bonds in that bilayer, while bacteria and eukaryotes use ester bonds. This distinction is important because ether bonds are more resistant to chemical activity, which permits archaeal cells to survive in more extreme environments.

Some archaeans are among the most extremely thermophilic (heat tolerant), acidophilic (acid tolerant), alkaliphilic (base tolerant), and halophilic (salt tolerant) microorganisms known. **Figure 1.18** shows the location where extremophiles were first discovered, in the hot springs of Yellowstone National Park. The genus *Picrophilus*, a member of Archaea, includes the most acidophilic organisms known, which can grow at a pH of 0.06, which is more acidic than hydrochloric acid. Despite their heat-loving reputation, archaeans are also found in very cold places, like Arctic seawater. Aside from our fascination with how extremophiles adapt to their extreme environments, this relatively unknown domain of life is particularly important to humans, due to its position on the ToL. Eukaryotes share a more recent common ancestor with Archaea than they do with Bacteria. Archaeans are our sister lineage, and there is so much more we must learn from them about them, and thus our own place in the biosphere.

Table 1.2 Types of Extreme Environments

Hot springs
Deep sea hydrothermal vents
Salt lakes
Polar regions
Volcanic areas
Acidic mine drainage
Deserts
Environments with high radiation levels

1.4 THE MICROBES WITHIN US

We now understand that microbes have a long and rich evolutionary history on Earth, one that is essentially as old as the planet itself. They continuously adapt to novel environments, invent new methods of energy capture, and in the process, have transformed our planet. Given this central role of microbes in the biosphere, it may be less surprising to learn that microbes have also adapted to living in and on us. We refer to these invisible residents as members of our **microbiome** (from the Greek terms *micro* meaning “small” and *bios* meaning “life”). The formal definition of a microbiome refers to a characteristic microbial community occupying a defined habitat that has certain properties. We can find microbiomes essentially everywhere we look—in our gut, in the soil surrounding the roots of a plant, in clouds, and even in the plume from a hydrothermal vent.

A Universe of Microbes within Us

The term *microbiome* refers to both the microorganisms present and the functions they provide, while the term **microbiota** refers simply to which species are present. For example, our



Figure 1.18 Extremophiles at Yellowstone National Park
Extremophiles were first discovered in Yellowstone National Park's hot springs, where the water regularly reaches 189°F. The thermophiles that live in the hot springs give the pool its ring of colors. To survive at such high temperatures, these bacteria have evolved very stable membranes and proteins. One of these proteins, Taq polymerase, is now used in an important technique for creating copies of DNA, known as the polymerase chain reaction, or PCR. Taq is able to maintain its structure and function even at the high temperatures required for PCR. We can thank extremophiles for our ability to perform PCR for COVID-19 testing, gene sequencing, forensic testing, and more! (Photo from Framalicious/Shutterstock)

gut microbiome is home to approximately 300 to 500 species of microbes, collectively called the gut microbiota. These members together with the functions they provide, such as digesting some of the food we ingest, are called our gut microbiome. Each microbiome is integrated into its host or ecosystem and is crucial for the proper functioning and health of the organism(s) in that niche.

Our goal in this textbook is to explore what microbes are present in humans, what functions they encode in their genomes, and how those functions impact us, their human hosts, in both healthy and diseased states. This knowledge may force us to redefine what it means to be human. Rather than consider ourselves as distinct biological entities, separate from all other life forms, we must now acknowledge that humans, indeed all multicellular organisms, are composed of numerous complex ecosystems each consisting of a mixture of their own and microbial cells. This new entity, the human with all its microbiomes, is referred to as the **holobiont**, a term derived from the Greek *hólos* or “whole” and *biont* for “unit of life.” The term was coined by Lynn Margulis in the 1990s as she was exploring the endosymbiotic origin of eukaryotes. Her intent was to provide a term that would acknowledge the key role of symbiotic relationships in the evolution and diversification of multicellular eukaryotic organisms, such as when an ancestral prokaryotic cell gave rise to mitochondria or chloroplasts. However, the term is equally appropriate to refer to a human body with its invisible microbial symbionts that, as you will learn, provide the key to our health while at the same time serving as the harbingers of certain diseases.

Each of us consists of about 30 trillion human cells, which carry our genetic blueprint and the machinery required to translate that information into what becomes the visible “us.” These cells form collections of tissues and organs, which play critical roles in keeping our bodies functioning. For example, skin serves as our front-line defense against invading pathogens, while the heart provides the force required to ensure all of our cells receive the oxygen-rich blood they require. For several thousand years physicians and scientists have explored our cells, tissues, and organs in their quest to understand what makes us uniquely human, what keeps us healthy, and what can go wrong in our bodies to cause disease and death.

We have long known that bacteria and viruses could invade our bodies and cause illness; however, they were considered temporary intruders that our bodies, or the medications we took, would fight to eliminate. In just the past 20 years we have gained an entirely new perspective on the important role microorganisms play in keeping our bodies healthy, leading some to argue that the microbiome should be considered the 11th critical organ, equal in importance to our brain! Let’s explore this new organ and learn a bit about its role in keeping us healthy.

How Much of You Is Human?

It’s estimated that we have about 35 trillion microbes in and on our bodies—about 5 trillion more than the number of human cells! This count excludes viruses, whose numbers may dwarf the human and microbial cell counts combined. Those numbers translate into a weight of just over 1 kg (2.5 pounds), with a volume of about 1.5 liters (6 cups) of cells. That’s nearly half a gallon of microbes per human!

Our body hosts numerous, distinct microbiomes (Figure 1.19). We have an oral microbiome in our mouth, one that covers our skin, another in our urinary tract, one in our gut, and even one deep in our lungs. There are far more fine-tuned distinctions we could make. For example, the microbes that inhabit the surface of our tongue are distinct from those that live under our gums, which are different from those that live attached to our teeth, and so on.

These distinct microbial communities also vary greatly in their cell densities. Blood is a virtual microbial desert, while the large intestine contains one of the densest microbial communities on Earth (Bojanova & Bordenstein, 2016)! While the precise number of microbes may differ, each microbiome is highly diverse, with over

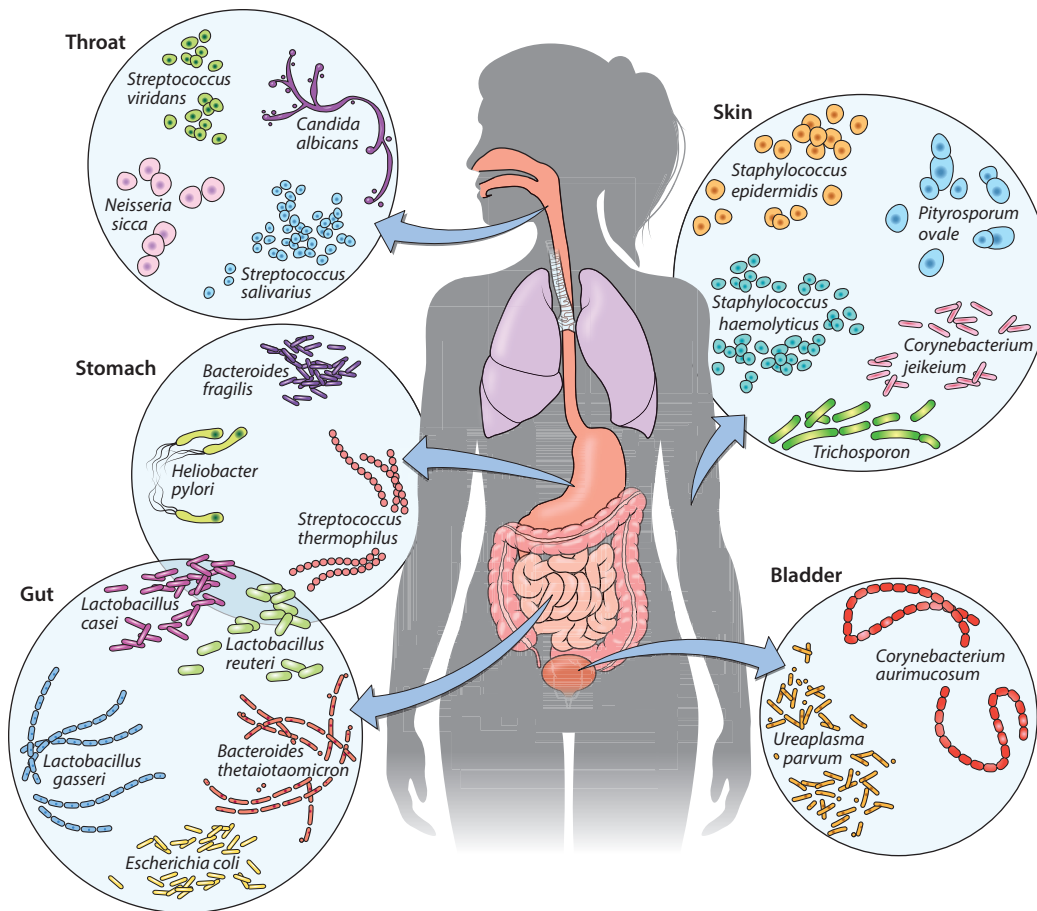


Figure 1.19 So Many Human Microbiomes The human microbiome includes many different microbial communities, each with its own unique composition of species and role in maintaining our health. (After V. D. Appanna, 2018.)

300 distinct bacterial species identified in the human gut microbiome alone (Almeida et al., 2021).

Even more compelling than their sheer numbers is the fact that the genetic information our microbiomes encode far exceeds our own. The human genome encodes 20,000 genes, while our microbiomes provide an additional 45 million, each encoding functions with the potential to impact us, their host. For example, if not for genes carried by certain species of bacteria, we would not be able to digest most of the fiber we consume.

1.5 OUR MICROBIOMES, OUR HEALTH

The rapidly growing field of microbiome science is revealing the complex roles these fellow travelers serve in human health. There is now overwhelming evidence that most functions of our body, such as growth, development, and metabolism, depend on our microbiome. Our immune system is trained first by our mother's microbiome during pregnancy and then by our own microbiome, particularly during the first few years of life. Dysfunctions in the gut microbiome are associated with several autoimmune diseases such as arthritis, fibromyalgia, and multiple sclerosis. Our gut microbiome also plays a role in several intestinal conditions, such as inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS), while obesity is often associated with an imbalance in the members of our gut microbiome.

Microbiomes and Human Nutrition

Another example of the key role our microbiome serves is in nutrition. Sugars and starches are two classes of carbohydrates synthesized by all organisms. The plants we eat contain thousands of different carbohydrates, which are broken down to their simplest components to provide us with energy. The human genome has fewer than 20 **enzymes** involved in digesting carbohydrates. Enzymes are proteins that act as biological catalysts by accelerating chemical reactions. Those carbohydrates we can't digest end up in the large intestine, where our microbiome takes over. The microbes in our gut encode thousands of carbohydrate-digesting enzymes in their genomes, which they employ to break down, or ferment, carbohydrates that are not digestible by humans, for energy.

Microbial Metabolites, Key to Human Health

One outcome of the microbiome's digestive efforts is their waste, some of which is essential for human health. These waste molecules, also known as **by-products**, serve key roles in our nutrition and metabolism. For example, our bodies require vitamins, which are organic compounds that are essential for maintaining various body systems, including the immune and nervous systems. You might have learned that the vitamins our bodies need can only be obtained from the food we eat. In fact, our microbes can produce several key vitamins for us. Many vitamins are **metabolites**, or intermediaries, produced during the fermentation of fibrous foods by the microbes living in our gut. Bacteria in the microbiome also produce **short-chain fatty acids (SCFAs)**, which are fatty acids with fewer than six carbon atoms. They are primarily produced through the fermentation of dietary fibers by gut bacteria in the colon. SCFAs are an essential energy source for our intestinal cells. It is an elegant symbiosis: our gut provides an energy-rich environment that supports an incredible diversity of microbial life, while that life, in turn, provides us with some of the key ingredients required to ensure our health.

Reflections on Your Microbiome

Let's think about our microbiomes from a slightly different perspective. As you walk from one lecture hall to another, passing people who may look very different from you—in height, weight, skin, or eye color—consider this fact: your genome differs by about 0.1% from any other human genome. Regardless of how different you look, you are nearly identical in terms of your DNA content. Now, look again at those passing by, and imagine that you can see the members of their microbiomes as easily as you see their facial features. Each person's microbiome differs by as much as 90% in terms of the species present, not to mention the genetic repertoires those species possess.

All these facts are causing us to reconsider how we think of ourselves as uniquely “us.” Traditional explanations for what makes an individual unique focus on our brain or the contents of our genome. However, as you will learn, our microbial residents communicate directly with our brain, and they provide far more gene functions than does our own genome. We are realizing that humans are not discrete entities of human cells and genes; rather, each of us is a consortium of thousands of organisms that result in a functioning, hopefully healthy, human. Indeed, it takes a microbial village to be a human!

Take a moment to reflect on what this new understanding of our microbial partnerships means to you. Does it scare you (or gross you out) to imagine the astronomical numbers of microbes in and on your body? Do you get excited about the genetic potential we carry inside us? Or do your thoughts turn to the role these microbes have played in our evolutionary history? Perhaps you wonder if you can take advantage of them to improve your health. Simply said, we are not alone, and it can feel empowering to understand that you have a fair bit of help in keeping your body healthy.

CHECK YOUR UNDERSTANDING

1. Approximately when do we think life emerged on this planet?
 - a. 4 billion years ago
 - b. 1 million years ago
 - c. 0.5 million years ago
 - d. 1,000 years ago
2. The Miller-Urey experiment was designed to test whether
 - a. early Earth's conditions could be mimicked.
 - b. organic molecules could be created under early Earth conditions.
 - c. inorganic molecules could create life.
 - d. life could be created in a glass chamber.
3. Which represents the Central Dogma of Molecular Biology?
 - a. RNA → DNA → protein
 - b. Membrane → DNA → protein
 - c. DNA → RNA → protein
 - d. DNA → membrane → protein
4. The advanced protocell created by Szostak's lab was essentially a
 - a. membrane-bound cell containing DNA.
 - b. fragment of RNA that could replicate itself.
 - c. cellular structure that could make copies of itself.
 - d. cellular structure that was unable to replicate itself.
5. Natural selection occurs when
 - a. an individual organism gains new, advantageous traits during its lifespan.
 - b. individuals with advantageous traits are better able to survive and reproduce, and those traits become more common in the population over time.
 - c. random events result in organisms better able to survive and reproduce.
 - d. a population of organisms survives to reproduce.
6. Hydrothermal vents provide a rich nutrient source that some of the earliest life forms likely took advantage of.
 - a. True
 - b. False
7. What are deep-sea hydrothermal vents?
 - a. Magma transmitted from the Earth's core
 - b. The ocean's equivalent of geysers
 - c. Very hot plumes of air at the bottom of the ocean
 - d. Underwater volcanoes
8. The two competing arguments about the origin of life are the replication argument and the cell division argument.
 - a. True
 - b. False
9. The protocell membrane was created with
 - a. DNA.
 - b. RNA.
 - c. fatty acids.
 - d. proteins.
10. What's the difference between autotrophs and heterotrophs?
 - a. An autotroph makes its own food.
 - b. A heterotroph makes its own food.
 - c. A heterotroph uses the sun's energy to fuel itself.
 - d. An autotroph uses the sun's energy to fuel itself.
11. How did the Great Oxidation Event affect life?
 - a. Anaerobic life largely went extinct.
 - b. Aerobic life largely went extinct.
 - c. It created the rust deposits found in some sedimentary rocks.
 - d. It enabled anaerobic life to flourish.
12. Identify 2 characteristics of eukaryotes not found in prokaryotes.
 - a. Cell membranes, flagella
 - b. Nuclei, mitochondria
 - c. Nuclei, flagella
 - d. Golgi bodies, cell membranes
13. Lynn Margulis proposed that eukaryotic cells came from a chance fusion of 2 protists.
 - a. True
 - b. False
14. How did cyanobacteria transform Earth's atmosphere?
 - a. By producing methane
 - b. By consuming all the existing oxygen
 - c. By producing oxygen
 - d. By consuming all the existing carbon dioxide
15. LUCA was the very first organism.
 - a. True
 - b. False
16. What technology allowed the microbiome to be viewed for the first time?
 - a. Telescope
 - b. Microscope
 - c. Electron microscope
 - d. 16S ribosomal sequence

17. What genus are humans members of?
 - a. Eukarya
 - b. Sapiens
 - c. Mammalia
 - d. *Homo*
18. Which kingdom were prokaryotes a part of in the 5-kingdom view of life?
 - a. Monera
 - b. Fungi
 - c. Protists
 - d. Bacteria
19. What did Carl Woese use to infer relationships between prokaryotes?
 - a. Whole genome sequencing
 - b. Phenotypic observations
 - c. Metabolic pathways
 - d. 16S rRNA
20. What are the 3 domains of life?
 - a. Eukarya, Prokarya, and Monera
 - b. Eukarya, Bacteria, and Archaea
 - c. Fungi, Protista, and Bacteria
 - d. Eukarya, Bacteria, and Protista
21. What is the cause of the great plate anomaly?
 - a. Some bacteria have RNA genomes.
 - b. Many bacteria cannot be cultured using available techniques.
 - c. It is difficult to find bacteria in the environment.
 - d. It is impossible to isolate a single species from a sample.
22. Extremophiles are microbes that survive in intense conditions, such as very high or low temperatures.
 - a. True
 - b. False
23. Which human microbiome is less dense than the others?
 - a. Gut microbiome
 - b. Oral microbiome
 - c. Blood microbiome
 - d. Skin microbiome
24. A human and their microbiome have about the same number of enzymes involved in digesting carbohydrates.
 - a. True
 - b. False
25. Vitamins, short-chain fatty acids, and other metabolites are produced when certain microbes digest which compounds in food?
 - a. Simple sugars
 - b. Fatty acids
 - c. Lipids
 - d. Fibers

Answers: 1A, 2B, 3C, 4C, 5B, 6A, 7B, 8B, 9C, 10A, 11A, 12B, 13B, 14C, 15B, 16B, 17D, 18A, 19D, 20B, 21B, 22A, 23C, 24B, 25D

DIVING DEEPER

1. Why were deep-sea hydrothermal vents advantageous locations for early life?
2. How did Miller and Urey show that the organic molecules necessary for life could form from inorganic material?
3. What were the two competing views about the origin of life, and what did Jack Szostak's protocell reveal?
4. What's the difference between autotrophs and heterotrophs?
5. How did the Great Oxidation Event affect life?
6. Can you explain three differences and three similarities between prokaryotes and eukaryotes?
7. According to Lynn Margulis's endosymbiotic theory, how did eukaryotic cells acquire mitochondria and chloroplasts?
8. Identify three differences between the five-kingdoms and three-domains views of life's diversity.
9. Why is the ribosome a good tool to use for inferring the tree of life?
10. Why was Woese's use of 16S rDNA sequencing revolutionary?
11. What technology allowed the microbiome to be viewed for the first time?
12. Why are bacterial culture techniques limited, and what technology solves this problem?
13. Can you give examples of the environments that extremophiles are able to live in?
14. What is a virus's host range?
15. Why can't viruses be placed on the tree of life, and how are they different from Bacteria, Archaea, and Eukarya?
16. What's the difference between the microbiome and microbiota?

17. Lynn Margulis introduced the term holobiont to explain what?
18. Can you list five microbiomes found in/on humans?
19. How does the human microbiome vary by body part?
20. Why is the microbiome necessary for carbohydrate digestion?
21. What are the two main metabolites bacteria produce as waste, and why are they important for human health?

DISCUSSING AND REFLECTING

1. Lynn Margulis's serial endosymbiosis theory was a harbinger of the discovery of the microbiome. Explain what is meant by that statement.
2. Woese's impact on our understanding of biodiversity has been enormous. Describe the key features of biodiversity that we were ignorant about before Woese's research revealed the three-domain tree of life.
3. What can extremophiles tell us about the origin of life on Earth and the possibility of life existing on other planets?
4. Reflection. Carl Woese said, "If you wiped all multi-cellular life-forms off the face of the earth, microbial life might shift a tiny bit, if microbial life were to disappear, that would be it—instant death for the planet" (Blakeslee, 1996). How do you feel now that you know the importance of microbes, and how does this affect your view of life on this planet?

RECOMMENDED READINGS

Popular Science Reviews

- O'Donnell, E. (2019, June 7). How Life Began: Jack Szostak's Pursuit of the Biggest Questions on Earth. *Harvard Magazine*, 40–79.
- Quammen, D. (2018, August 13). The Scientist Who Scrambled Darwin's Tree of Life. *New York Times*, 34.

Popular Science Book

- Sagan, D. (2012). *Lynn Margulis: The Life and Legacy of a Scientific Rebel*. Chelsea Green.

Scientific Reviews

- Gray, M. W. (2017). Lynn Margulis and the Endosymbiont Hypothesis: 50 Years Later. *Molecular Biology of the Cell*, 28(10), 1285–1287. <https://doi.org/10.1091/mbc.e16-07-0509>
- Nasir, A., Romero-Severson, E., & Claverie, J.-M. (2020). Investigating the Concept and Origin of Viruses. *Trends in Microbiology*, 28(12), 959–967. <https://doi.org/10.1016/j.tim.2020.08.003>

Index

- A
- abiogenesis, 4
 - abiotic components, 374
 - ABO gene, 340
 - abstract (article), 147, 149–51
 - abundance. *See* species abundance
 - acetate
 - in gut microbiome, 60–62, 273, 278, 281–82, 285, 386
 - health linked to, 386
 - immune function, 184, 301
 - Acetobacter*, 247
 - Acidianus virus, 16
 - acidic environment
 - oral microbiome, 71
 - skin microbiome, 74–75
 - acidophilic archaeans, 19
 - Acinetobacter*, 247, 362
 - Acinetobacter lwoffii*, 300, 302, 309
 - acne, 75–76
 - acquired (adaptive) immune system, 180–82, 237–38, 296–97
 - ACTH (adrenocorticotropin), 212
 - Actinobacteria
 - colonization resistance, 62
 - female reproductive tract microbiome, 176
 - gut microbiome, 330–31
 - infant microbiome, 188–90
 - in leanness, 277
 - oral microbiome, 69, 70
 - primate microbiome, 325
 - respiratory microbiome, 306–7
 - skin microbiome, 73–74
 - stomach microbiome, 336
 - Actinomyces*, 70
 - active state, 362–63
 - adaptations
 - niche, 45
 - processes specific to, 55
 - adapter regions, 101–2, 105, 117
 - adaptive (acquired) immune system, 180–82, 237–38, 296–97
 - adaptive traits, 7
 - adenine, 99
 - adenocarcinoma, 337
 - adenosine triphosphate (ATP), 8, 60
 - adherens, 73
 - adiposity, 276, 277, 279, 283–84. *See also* obesity
 - adrenal glands, 212
 - adrenocorticotropin (ACTH), 212
 - aerobic bacteria, 37, 69, 71, 188, 190, 395
 - aerobic respiration, 7–8
 - Africa
 - ape diversification, 323–24
 - Malawi study, 324
 - agar, 37–38, 77
 - Aggregatibacter*, 70
 - Aggregatibacter actinomycetemcomitans*, 281
 - agriculture. *See* farming
 - Ahmadi, S., 290
 - air-borne microbes experiment, 30–31
 - air-handling systems, 349, 353–55, 359, 365
 - Akkermansia*, 307–8
 - Akkermansia muciniphila*
 - gut microbiome, 273, 278, 281
 - gut transit times linked to, 380
 - infant microbiome, 194
 - weight loss linked to, 285, 288, 289
 - Aktipis, Athena, 62
 - Alexander, Albert, 34
 - algorithms, similarity-searching, 120, 123
 - aliquot, 97
 - alkaliphilic archaeans, 19
 - allergens, 296
 - allergic cascade, 296–97
 - allergic diseases, 295–319. *See also specific disorder*
 - antibiotics in, 304–5
 - atopic march, 303
 - circle of causality, 315–16
 - environmental impact, 300–303
 - epigenetic changes, 298–99
 - farm effect, 297, 300, 302–3, 308–9, 357–58
 - hygiene hypothesis, 245, 302–4, 333–34, 350, 366–69
 - infant microbiome linked to, 198–99
 - maternal microbiome linked to, 299–300
 - microbiome in, 305–13
 - prevention of, 297–98, 304
 - treatment of, 313–15
 - allergic response, 295–97, 334
 - Alm, E. J., 254–55
 - alpha-aminoadipic acid, 246
 - alpha diversity, 126–29, 141, 255
 - indices, 129–32, 166–69, 382
 - infant microbiome, 196–97
 - in obesity, 280
 - α -amylase, 330
 - α -synuclein, 227–28
 - α -toxin (α -hemolysin), 310
 - altered microbiome, 88. *See also* dysbiosis
 - Alzheimer's disease, 221, 228
 - Amazon River basin study, 349–50
 - Ambystoma mexicanum* (axolotl), 87
 - American Academy of Allergy, Asthma & Immunology, 303
 - American Gut Project, 383
 - amino acids
 - in bile salts, 283
 - in Crohn's disease, 66–69
 - in depression, 224–26
 - origin of, 3–4
 - triplets encoding, 119–20
 - Amish farmers (USA), 302–3, 357–58
 - amniotic sac, 179–80, 243
 - amplification, DNA, 101–6, 117–18
 - AMPs (antimicrobial proteins), 240, 241, 258
 - amylases, salivary, 60, 330
 - amylose, 279
 - anaerobic bacteria, 37–39, 65, 71, 190, 257–60, 395
 - anaerobic respiration, 7–8
 - Anaerostipes caccae*, 314
 - anaphylaxis, 297
 - animalcules, 17, 28
 - animals. *See also specific animal*
 - in built environment, 350, 353–54, 369
 - infant microbiome affected by, 192–93, 297, 300, 302–3, 308–9, 357–58
 - in research (*see* model organisms)
 - in tree of life, 12–13, 19
 - annealing, 101–2, 117
 - anoxic environment, 7–8, 37–38
 - Antharam, V. C., 266
 - anthrax, 33
 - antibacterial mouthwash, 70
 - antibiotics
 - agricultural use of, 335
 - in allergic diseases, 304–5, 310, 312
 - bactericidal, 35
 - bacteriostatic, 35
 - in children, 196–97, 300, 304–5, 335, 337, 360
 - definition of, 34
 - discovery of, 34–35
 - dysbiosis caused by, 39, 57, 76, 196–97, 214, 241, 244, 260, 335, 337
 - increased use of, 201, 245, 335, 365
 - microbiome recovery from, 394–95
 - naturally produced, 331
 - new perspectives on, 339–40
 - preventative use of, 261
 - resistance to, 35, 85, 186–87, 310, 330–31, 335, 337, 360, 362
 - antibodies, 182, 184, 237–38, 242–45, 296
 - antidepressants, 220–21, 229
 - antigen-presenting cells (APCs), 241–42, 296–97
 - antigens, 237, 310
 - antimicrobial proteins (AMPs), 240, 241, 258

- antimicrobials
 - female reproductive tract, 177–79
 - intestinal, 239
 - skin, 309
- antiseptics, 35
- anxiety, 220
- APCs (antigen-presenting cells), 241–42, 296–97
- apple-shaped body, 279
- Appleton, Joseph, 37
- Archaea
 - evolutionary divergence, 103
 - extremophiles, 1, 3, 18–19
 - gut microbiome, 58, 59
 - oral microbiome, 69
 - skin microbiome, 73–75
 - in tree of life, 14–15, 17, 19
- arginine, 73, 394
- arthritis, rheumatoid, 246–47
- artifact, 160–62
- artifact situation, 266
- aryl hydrocarbon receptor agonists, 214
- ASD (autism spectrum disorder), 226–27
- asparagine, 246
- Aspergillus*, 69, 78
- asthma, 198, 306–9
 - birth mode linked to, 86, 300, 304
 - farm effect, 302–3, 308–9, 357–58
 - gut dysbiosis, 245
 - gut-lung axis, 307–8
 - maternal microbiome linked to, 299–300
 - physiological responses in, 306–7
 - tolerance approach, 304
 - treatment of, 314–15
- astrocytes, 214, 221
- atherosclerosis, 247
- atmosphere
 - anoxic, 7–8, 37–38
 - early Earth, 2, 3
- atopic dermatitis (eczema), 75, 198–99, 240, 300, 309–11
- atopic march, 303
- atopy, 198
- ATP (adenosine triphosphate), 8, 60
- authorship (article), 148–49
- autism spectrum disorder (ASD), 226–27
- autoantigens, 237
- autoclave, 37
- autoimmune diseases. *See also specific disorder*
 - CNS, 241–42
 - hygiene hypothesis, 245, 302–4, 333–34, 350, 366–69
 - systemic, 246
- autoimmunity, 182–84, 237
- autonomic nervous system, 210, 217
- autophagy, 222
- autotrophs, 7
- Axial Therapeutics, 226
- axolotl (*Ambystoma mexicanum*), 87
- axon (nerve fiber), 185, 217
- B
 - babies. *See* infant microbiome; newborns
 - Bacillus*, 78
 - Bacillus lactis aërogenes*, 389
 - Bacillus licheniformis*, 309
 - bacteria. *See also specific microbe*
 - aerobic, 37, 69, 71, 188, 190, 395
 - anaerobic, 37–39, 65, 71, 190, 257–60, 395
 - antibiotics produced by, 331
 - appendages, 69–70
 - in built environment, 355, 363
 - cellulose-degrading, 37
 - in core microbiome, 54–55
 - culturing methods, 18, 37–39, 42
 - evolutionary divergence, 103
 - filamentous, 43, 226–27
 - first observations of, 17–18, 28
 - immune responses to, 237 (*see also* immune system)
 - recovery-associated, 394–95
 - saccharolytic, 392
 - tree of life, 15, 17, 19
 - virulence factors, 264–65, 310
 - bacterial infections. *See specific infection*
 - antibiotics for (*see* antibiotics)
 - bacterial vaginosis (BV), 179, 202, 255
 - bactericidal antibiotics, 35
 - bacteriocins, 177, 178
 - bacteriophages (phages)
 - in built environment, 352
 - characteristics of, 16
 - gut microbiome, 63–65, 330–31
 - infant microbiome, 189
 - skin microbiome, 73
 - therapeutic use of, 341
 - bacteriostatic antibiotics, 35
 - Bacteroides*
 - in birth mode study, 128–29, 187
 - in colorectal cancer, 67
 - in coronary heart disease, 247
 - in depression, 225–26
 - dietary impact on, 332
 - in food allergy, 67
 - infant microbiome, 189, 193, 194, 196, 198
 - lung microbiome, 241
 - in obesity, 278–80, 288
 - primate microbiome, 323–24
 - stomach microbiome, 336
 - vaginal microbiome, 186
 - Bacteroides fragilis*, 51, 189, 199, 268, 301
 - Bacteroides thetaiotaomicron*, 60, 69
 - Bacteroidetes
 - in colorectal cancer, 62–64
 - core microbiome, 54
 - in diabetes, 200
 - female reproductive tract microbiome, 176, 183–84
 - gut microbiome, 53, 59, 60, 67, 199–200, 302, 325
 - infant microbiome, 189, 194, 195, 199
 - in obesity, 199, 277, 281, 285
 - oral microbiome, 69, 70, 281
 - primate microbiome, 325
 - respiratory microbiome, 306–7
 - skin microbiome, 73–74
 - stomach microbiome, 336
 - barcodes, 101–2, 117
 - bar plot, 164–66
 - Barrett’s esophagus, 337
 - Bartonella*, 330–31
 - BAs (bile acids), 283
 - baseball team metaphor, 54–55, 385
 - bases, 99
 - Basic Local Alignment Search Tool (BLAST), 120
 - basophils, 181, 238, 296–97
 - Bassi, Agostino, 32
 - bathrooms, 351, 353, 355–56, 363, 364
 - BBB (blood-brain barrier), 212–13, 216–17
 - BC (Bray-Curtis dissimilarity) metric, 135–36, 333
 - B cells, 182, 238
 - in allergic cascade, 296–97
 - development of, 236–37, 243–44
 - in stomach, 337
 - BDNF (brain-derived neurotrophic factor), 221
 - BE. *See* built environment
 - beds, microbes in, 346
 - behavioral abnormalities, 185, 223
 - Belgium, 330–31
 - beta-alanine, 246
 - beta diversity, 135–39
 - definition of, 126
 - dysbiosis defined by, 255
 - female reproductive tract, 176–77
 - gut microbiome, 333
 - visualisations, 140–41, 155–56
 - β-oxidation, 258–59
 - bias
 - codon, 120
 - research, 45, 376
 - Bifidobacterium*
 - in birth mode study, 129
 - cholesterol-lowering effect, 279
 - farm effect, 300
 - in fossils, 327
 - gut microbiome, 62, 64, 188, 198–99, 307–8, 388
 - infant microbiome, 188, 190–201, 203–4, 256–57, 279, 304
 - in lactose digestion, 340
 - in microbiota-gut-brain axis, 219–21, 225
 - in obesity, 288–90
 - probiotic strains, 390, 393
 - Bifidobacterium adolescentis*, 60, 323
 - Bifidobacterium animalis*, 289, 314
 - Bifidobacterium bifidum*, 192, 289
 - Bifidobacterium breve*, 192, 229, 314
 - Bifidobacterium infantis*, 175, 192, 203, 229
 - Bifidobacterium lactis*, 314
 - Bifidobacterium longum*, 203, 229, 256–57, 278, 289, 314
 - bifidus factor, 191
 - bile acids (BAs), 283
 - bile ducts, 241
 - bile salt hydrolases (BSHs), 283
 - bimodal distribution, 93–94
 - binominal (Latin) names, 12, 53–54
 - biodiversity, 126. *See also* diversity
 - biodiversity hypothesis, 304, 366–67
 - biofilms, 67, 70, 71, 265, 327, 351
 - bioinformatics, 38–41, 121
 - biomarkers
 - disease, 281
 - weight loss, 286
 - biomolecules, 5
 - biosphere, early Earth, 8–10
 - biotherapy, 310–11

- birth, preterm, 46, 202–4, 243, 300, 360
 birth mode
 colonization process during, 41, 186–87
 C-section (*see* Cesarean section)
 vaginal delivery, 186–87, 191
 birth mode study
 data analysis, 116–17, 122–25, 128–32
 design of, 86–90, 95
 discussion, 157–58
 literature review, 148–58
 microbiome analysis program, 158–70
 research questions, 86, 121
 results, 154–57
 sample size, 125, 141, 150
 sampling methods, 97–98
 bisphenol A (BPA), 364
 black mold, 345, 355, 359
 bladder cancer, 248
 bladder microbiome, 21
 Blaser, Martin, 334–37
 BLAST (Basic Local Alignment Search Tool), 120
Blastocystis, 59
Blastocystis hominis, 115
Blautia, 225–26, 327
 blood-brain barrier (BBB), 212–13, 216–17
 blood pressure, 275
 blood stem cells, 243
 blood sugar, 212, 275
 blue-green algae (Cyanobacteria), 8–9
 B lymphocytes. *See* B cells
 body mass index (BMI), 199, 274–75, 281
 body odor, 73
 body weight, 274–79. *See also* obesity
 Bogaert, Debby, 196–97
 bone marrow, 236
 bonobos, 322–30, 346
 Booth, A., 224
 Bordetella, 330–31
 bowel movements, 375. *See also* feces
 box and whiskers plot, 134–35
 box plot, 247–48
 BPA (bisphenol A), 364
 brain, 209–33
 development of, 185, 212–17
 expansion in humans, 328–29
 gut interactions, 211, 213–22 (*see also* microbiota-gut-brain axis)
 brain-derived neurotrophic factor (BDNF), 221
 Bray-Curtis dissimilarity (BC) metric, 135–36, 333
 Brazil, 349–50
 breastfeeding. *See* human milk
 Bristol stool chart, 378
 Brudziński, Józef, 389
 Bry, Lynn, 43–44
 BSHs (bile salt hydrolases), 283
 bubonic plague, 348
build back better mantra, 365–66
 built environment (BE), 345–72
 definition of, 345–46
 features of, 349, 353–56, 359–60, 369
 future improvements, 365–69
 history of, 346–48
 lifestyle based on (*see* Western lifestyle)
 metabolomics, 362–65
 microbe tracking in, 358–62
 microbiology of, 350–52 (*see also* microbiomes of the built environment)
 butterfly gut amoeba, 29
 butyrate
 gut microbiome, 60, 61, 193, 258, 267
 health linked to, 386
 immune function, 305, 308, 312, 338
 in obesity, 279, 281–82, 286–87
 in type 1 diabetes, 200
 BV (bacterial vaginosis), 179, 202, 255
 by-products, 22. *See also* metabolites; *specific substance*
 C
Caenorhabditis elegans (nematode), 87
 Callaway, Ewen, 186
 Camarillo-Guerrero, L. F., 103
 Cambrian Explosion, 11–12
Campylobacter, 268
 cancer, 248–50
 adenocarcinoma, 337
 bladder, 248
 colorectal, 67, 249, 261, 265, 340
 liver, 265–66
 microbiome-based therapies, 250
 skin, 73–74
 stomach, 248–49, 337
Candida
 gut microbiome, 220
 oral microbiome, 69
 skin microbiome, 73, 78
Candida albicans, 373
 gut microbiome, 57, 59
 vaginal microbiome, 179
 candidiasis, 179
 Cani, Patrice, 289
 capsaicin, 364
 carbohydrates
 in cavity formation, 71
 dietary, 59–60, 285, 288, 332
 digestion of, 22, 188, 194, 281–82, 329–30, 392
 types of, 22, 59–60 (*see also* fiber; starches; sugars)
 carbon dioxide, 3, 258, 355
 cardiometabolic diseases (CMDs), 247–48.
 See also specific disease
 carpets, 353–54
 Cason, Carolina, 360–61
 cavities (dental caries), 71, 394
 CD-HIT, 154, 158
 celiac disease, 245
 cell density, 20–21
 cell-mediated immunity, 237
 cells
 culturing methods, 18, 37–39, 42
 eukaryotic (*see* eukaryotes)
 origin of, 4–6, 20
 plasma membranes, 18
 prokaryotic (*see* prokaryotes)
 cellular respiration, 7–8
 cellulose, 37, 59–60, 315, 345, 355
 Center for Microbiome Innovation, 170
 Central Dogma of Molecular Biology, 4–7
 central nervous system (CNS), 185, 210, 241–42. *See also* brain
 Cesarean section (C-section), 186–87
 allergic disease linked to, 300, 304, 312
 avoidance of, 340
 dysbiosis linked to, 200–201
 NICU use after, 360
 studies of (*see* birth mode study)
 vaginal microbiome transplant after, 202, 340
 c-FOS enzyme, 224–25
 Chain, Ernst, 34
Chaos (formless) genus, 28
 CHD (coronary heart disease), 247–48
 Checherta (Peru), 349–50
 chemical communication, gut-immune system, 63–64, 180, 239
 chemical lysis, 101
 chemoautotrophs, 8
 chemolithoautotrophy, 7
 chemolithotrophs, 2
 chemoorganotrophs, 1
 childbirth. *See* birth mode
 chimpanzees, 322–30, 346
 chlamydia, 33
 Chlamydiae, 330–31
 chloroplasts, 11
 Chng, K. R., 394–95
 cholesterol, 275, 279, 282, 283, 285, 376
Christensenella minuta, 285–86
 chromatin, 298
 chromosome structure, 4–5
 chronic heart disease, 247
 chronic periodontitis (CP), 281
 Church, George, 109
 circle of causality, 315–16
 citations (article), 152
 cities. *See* urban lifestyle
Citrobacter rodentium, 224–25
 classification system, Linnaean, 12–17, 28, 53–54
 cleaning practices, 333–35, 356, 359–62
 Clostridiales, 78
Clostridioides difficile, 253, 369, 384
Clostridioides difficile infection
 disorders caused by, 57, 261
 FMT for, 39–40, 260, 290, 314, 341, 377
Clostridium
 in depression, 226
 immune function, 308, 312
 infant microbiome, 194, 198–99, 214–15
 in liver cancer, 265
Clostridium leptum, 386
Clostridium neonatale, 307
 clumping factors A and B, 310
 cluster, 154
 CMDs (cardiometabolic diseases), 247–48.
 See also specific disease
 CNS (central nervous system), 185, 210, 241–42. *See also* brain
 codon bias, 120
 codons, 119–20
 coevolution, 219, 229–30, 322–23
 coin toss example, 92
 colic, 200, 203
 colitis, 40, 65
 enterocolitis, 39–40, 200, 203
 ulcerative, 66–67, 248, 258–59

- Collinsella*, 246–47
colonization process
 during birth, 41, 186–87
 during infancy, 189–90, 196
 recolonization, 337–38
colonization resistance, 259
 gut microbiome, 36–37, 62–63, 196–97, 204, 259
 infant microbiome, 196–97
 lung microbiome, 240–41
 oral microbiome, 70
 skin microbiome, 74–75, 240–41, 309
colonocytes, 65
color coding, 123
colorectal cancer (CRC), 67, 249, 261, 265, 340
colostrum, 245
commensal interaction, 230, 259
community state types (CSTs), 177–78
competition, diversification driven by, 7
competitive exclusion, 179
complementary supplements, 394
confidence intervals, 140
confounding variables, 95
consortia, 388
constant regions, 103
contamination of samples, 118
contig (contiguous sequence), 119
control
 experimental, 77–79, 95–96, 125, 223, 247, 254, 277
 quality, 118
 sterility, 37–38, 77–78
cooling systems, 349, 353–55, 359, 365
coprolites, 326–27
coprophagy, 95, 226–27
coprostanol, 376
core microbiome, 54–57, 187–90, 254
coronary heart disease (CHD), 247–48
correlation, 86
corticotrophin-releasing hormone (CRH), 212
cortisol, 212
Corynebacterium, 70, 73–75
Corynebacterium accolens, 74–75
COVID-19 virus, 16, 356, 365–66
cow milk allergy, 312, 314
CP (chronic periodontitis), 281
CRC (colorectal cancer), 67, 249, 261, 265, 340
CRH (corticotrophin-releasing hormone), 212
Crick, 38
critical window, 196, 201, 235, 245, 297–98, 334–35, 357
Crittenden, Alyssa, 332
Crohn's disease, 66–69, 257–58
cross-feeding interactions, 188, 192, 338
cross-sectional study, 96
crown species, 15
Cryan, John, 227
crypts, 257
C-section. *See* Cesarean section
CSTs (community state types), 177–78
culturing
 fecal samples, 97
 methods, 18, 37–39, 76–78
 oral microbiome, 42
 samples for (*see* sampling methods)
 skin microbiome, 78–80
Curatola, Gerry, 72
Cutibacterium, 73–75
Cutibacterium acnes, 73, 75–76
Cyanobacteria (blue-green algae), 8–9
cyclic causality, 315–16
cytokines, 217
 activation of, 237
 in allergic response, 297
 in autism spectrum disorder, 226–27
 in human milk, 244
 in MGBA pathway, 221
 in obesity, 283–84
 in rheumatoid arthritis, 247
cytosine, 99
cytotoxins, 182
D
Darwin, Charles, 12–13
data analysis, 88, 115–44
 microbiome, 121–25
 overview, 115–18
 quality control, 118
 reconstruction of genes and genomes, 118–20
 reporting on, 153–57 (*see also* literature)
 software, 121, 140, 145, 154, 158–70 (*see also specific program*)
 species diversity measures, 126–39
 species diversity visualisations, 139–41, 155–56, 163–64
data distribution, 93–94
data organization, 88
datasets. *See also specific study*
 genome reference, 119, 121–23, 154, 163, 376
 KOALA Birth Cohort Study, 195
 public (Qiita), 159–60
data transformation, 163–64
DCs (dendritic cells), 181, 239, 296
dead zones (ocean), 9
deceased state, 362–63
defensins, 256, 257
degranulation, 296
deidentification, 151
Deinococcus, 353
delta toxin, 75
dementia, 222
demineralization, 71
demultiplexing, 118
denaturing, 101–2
dendritic cells (DCs), 181, 239, 296
de novo reconstruction, 119
dental caries, 71, 394
dental plaque. *See also* oral microbiome
 creation of, 70
 early studies of, 17, 28, 37, 41–42
 fossilized, 327–28
deoxyribonucleic acid. *See* DNA
deoxyribose, 99
dependent variables, 89
depression, 220, 223–26, 229
dermatitis, atopic (eczema), 75, 198–99, 240, 300, 309–11
desensitization, 313
Desnues, Christelle, 331
deterministic (selection) process, 266–67
De Vlaminc, Iwijn, 110
diabetes
 type 1, 200, 245
 type 2, 46, 247, 280
diarrheal diseases, 33, 197–98, 253, 261.
 See also specific disorder
diet
 antibiotics in, 335
 body weight management, 287–91
 carbohydrates (*see* carbohydrates)
 evolved dependence, 229–30, 328–29
 fermented food, 288, 388–89
 fiber (*see* fiber)
 food additives, 258
 food allergies (*see* food allergies)
 food as medicine, 396
 gut transit time, 379–80
 healthy, 387–88
 human milk, 191–94
 in obesity, 199, 275, 278, 285–91
 oral microbiome impact, 70–71
 plants in, 323, 328, 332, 340, 352, 388, 394
 prebiotic foods (*see* prebiotics)
 during pregnancy, 182–84, 244, 299–300
 probiotic foods (*see* probiotics)
 professional advice on, 377–78
 solid food transition, 194, 257, 303
 Western, 287, 303, 332–33, 335–36, 340, 365, 388, 392
dietary emulsifiers, 258
dietary supplements
 prebiotics, 392–93
 probiotics, 389–92
 synbiotics, 393–94
digital object identifier (DOI), 148
Dinan, T. G., 228–29
Dinophysis algae, 9
disappearing-microbiota hypothesis, 334–37, 341
discovery metabolomics, 214
discussion section (article), 148, 149, 153, 157–58
disease. *See also specific disease*
 versus dysbiosis, 260, 266–69
 ecological perspective on, 258–59, 268, 374, 395
 environmental impact (*see* built environment)
 germ theory of, 31–32, 333
 humoral theory of, 254–55
 Koch's postulates about, 32–33
 microbiome associations, 260–69
 microbiome-based therapies, 39–41, 201–4, 228–29, 250 (*see also specific therapy*)
 most common and deadly, 33
 spontaneous generation theory of, 29–31
 susceptibility to, 196, 201, 235, 376–77 (*see also* immune system)
disease markers, 281
disinfectants, 35, 356
dissimilarity, measurement of, 135–39
distance matrix, 156
distribution of data, 93–94
diversity, 126
 biodiversity hypothesis, 304, 366–67

- Cambrian Explosion, 11–12
 cataloguing methods, 43
 competition driving, 7
 in core microbiome, 56–57, 189, 254
 Cyanobacteria, 9
versus function, 266–67
 as health indicator, 384–85
 meadow metaphor, 374, 383–84
 measurement of, 126–39, 141, 166–69, 255, 382
 viruses, 16
 visualisations, 139–41, 155–56, 163–64
 diversity index, 129
 DNA
 amplification, 101–6, 117–18
 chemistry of, 98–99
 epigenetic changes, 298–99
 extraction, 38–39, 99–101, 117
 methylation, 298–99
 noncoding, 119
 origin of, 4
 replication, 4–7, 99–100
 ribosomal (*see* ribosomal DNA)
 versus RNA, 107
 shearing, 104
 structure of, 38, 98–99
 DNA isolation kits, 101
 DNA methyltransferase (DNMT), 298
 DNA sequence read, 117
 DNA sequencing, 96, 98. *See also specific method or study*
 contig (contiguous sequence), 119
 cost of, 150
 data analysis, 116–18
 of fossils, 327
 function prediction, 120
 high-throughput, 104–6, 117
 metagenomic library, 104
 of primate microbiome, 322–24
 purpose of, 38–39
 ribosomal, 41–42
 shotgun, 106
 by synthesis (next-generation), 117–18
 target gene amplicon, 101–2, 381 (*see also specific target*)
 DNMT (DNA methyltransferase), 298
 DOI (digital object identifier), 148
 domains of life, 14–15
 Dominguez-Bello, M. G., 148–70, 186, 202
 Doolittle, W. F., 224
Dorea, 327
 dormant state, 362–63
 double helix, 99
Drosophila melanogaster (fruit fly), 87, 225
 Dukes, C. D., 202
 dust
 farm, 308–9, 357–58 (*see also* farm effect)
 house, 353–55, 357–58, 363
 Duvallet, Claire, 261–62
 dysbiosis, 253–71
 circle of causality, 315–16
 definition of, 58–59, 254–55, 266
 versus disease, 260, 266–69
 gut microbiome (*see* gut microbiome dysbiosis)
 indices of, 267–69
 infant microbiome, 175, 196–201 (*see also* birth mode)
 lung microbiome, 241, 307, 308
 maternal microbiome, 213, 226
 oral microbiome, 71–72, 262–65
 self-management of (*see* personal microbiome)
 shared, 265–66
 skin microbiome, 75–76, 240, 309–11
 smoking-related, 46
 vaginal microbiome, 179
 dysentery, 36, 39
Dysosmobacter welbionis, 279
 E
 Earth
 microbes as core of life on, 17
 origin of life on, 2–12
 tree of life on, 12–17, 19, 132
 Earth Microbiome Project (EMP), 106
 Easy Microbiome Analysis Platform (EzMAP), 170
 Ebola virus, 16
 ecological core, 55–56
 ecological Koch's postulates, 267–69
 ecological perspective, 255–60, 374, 395
 ecosystem, 374, 386–87, 395
 eczema (atopic dermatitis), 75, 198–99, 240, 300, 309–11
 education, scientific, 86
 EECs (enteroendocrine cells), 219
 effectors, 211
Eggerthella, 246
 Eiseman, Ben, 39–40
 Elinav, Eran, 46
 EMP (Earth Microbiome Project), 106
 emulsifiers, 258
 endocrine pathway (MGBA), 218–19
 endocrine system, 211–12, 217
 endosymbiont, 11
 endosymbiosis, 10–12, 15, 20, 52, 223
 endotoxins, 357–58
 ENS (enteric nervous system), 211, 217, 219, 220
Entamoeba, 69
 enteric bacteria. *See* Enterobacteriaceae
 enteric nervous system (ENS), 211, 217, 219, 220
Enterobacter, 225, 261
 Enterobacteriaceae
 gut microbiome, 388
 infant microbiome, 193, 194, 304
 in obesity, 280–82, 284–85
 in ulcerative colitis, 259
Enterococcus, 220, 304
Enterococcus faecalis, 145, 340
 enteroendocrine cells (EECs), 219
 enterotypes, 325–26
 envelope, viral, 16–17
 environment
 in allergic disease, 300–303, 312
 anoxic, 7–8, 37–38
 built (*see* built environment)
 early Earth, 2, 3
 gene expression affected by, 298–300, 322, 357–58
 health care, 186–87, 356, 359–62
 infant microbiome impacted by, 194–95, 300–303
 environmental metagenomics, 38–39, 41–43
 enzymes. *See also specific enzyme*
 carbohydrate-digesting, 22, 60
 definition of, 22
 eosinophils, 181, 237–38, 296, 306, 315
 epigenetic changes, 298–99
 epithelial cells, in allergic response, 296–97
 EPS (extracellular polymeric substances), 263
 error bars, 92–93
 errors, process, 118, 121
 Escherich, Theodor, 36
Escherichia coli, 209
 classification of, 53–54
 digestive function of, 60
 discovery of, 36
 disease caused by, 57
 gut microbiome, 220, 258, 268
 infant microbiome, 204
 in microbiota-gut-brain axis, 220, 224–25
 Nissle 1917 strain, 36–37, 39
 in obesity, 278–79
 O157:H7 strain, 53, 57
 esophageal reflux, 337
 esophagus, 21, 58. *See also* gut microbiome
 ester bonds, 18
 estrogen, 176–77, 256
 ether bonds, 18
 ethics, research, 150–51
Eubacterium, 67, 225–26
Eubacterium coprostanoligenes, 376
Eubacterium cylindroides, 287
Eubacterium nodatum, 265, 281
Eubacterium rectale, 60, 380, 386
 eubiosis, 254, 260, 267
 Eukarya, 14–15
 eukaryotes
 classification of, 15
 definition of, 10
 gut microbiome, 59
 oral microbiome, 69–70
 origin of, 10–12, 20
 Euler's number, 130
 evenness (species), 126. *See also* alpha diversity
 evolutionary distance, 132
 evolutionary divergence, 103
 evolutionary tree (phylogeny), 12, 132, 138, 154, 322–23
 evolved dependence, 229–30, 328–29
 evolving microbiome, 321–44
 ancestral origins, 322–31
 healthful microbiota development, 339–41
 industrialization, 331–38, 348, 376 (*see also* built environment; Western lifestyle)
 missing-heritability problem, 339
 experiment
 design, 30–31, 88–89 (*see also* research)
 methods, 97–106 (*see also* culturing; sampling methods)
 experimental controls, 77–79, 95–96, 125, 223, 247, 254, 277
 experimental data, *versus* metadata, 96–97
 experimental treatment, 30
 experimental variables, 89, 95
 extant species, 7

- extension phase of PCR, 102
- extinction
 - loss of microbiota, 334–38, 341
 - mass events, 9
- extracellular polymeric substances (EPS), 263
- extremophiles, 1, 3, 18–19
- EzMAP (Easy Microbiome Analysis Platform), 170
- F
- facultative anaerobic bacteria, 65, 258–60, 395
- Faecalibacterium*, 247, 307, 314–15, 327
- Faecalibacterium prausnitzii*, 194–95, 198–200, 267, 386
- Faecalicatena lactaris*, 340
- FAIR principles, 90
- Faith's phylogenetic diversity metric, 132–35
- families, 12
- farm effect, 297, 300, 302–3, 308–9, 357–58
- farming
 - antibiotics used in, 335
 - introduction of, 328
- FASTA file, 122–23
- fasting-induced adipose factor, 277
- FastTree, 154
- fat
 - absorption of, 283
 - adiposity, 276, 277, 279, 283–84 (*see also* obesity)
 - dietary, 285
 - measurement of, 274–75
 - production of, 60–61, 282
 - storage of, 283–84
 - subcutaneous layer, 73, 275
- fat-loving (lipophilic) yeast, 73
- fatty acids, 5
 - free, 200
 - short-chain (*see* short-chain fatty acids)
- F/B ratio, 277, 281, 285
- FDA (Food and Drug Administration), 290, 377, 391
- fecal microbiota transplantation (FMT), 39–41, 253, 260, 261, 290–91, 305, 314, 341, 377, 388
- feces
 - amino acids in, 68–69
 - consumption of, 95, 226–27
 - fossilized, 326–27, 330–31
 - obesity transmission through, 44
 - quality assessment, 375, 378–79
 - sampling methods, 97–98
- female reproductive tract microbiome, 176–79. *See also* vaginal microbiome
 - during pregnancy (*see* birth mode; pregnancy)
- fermented food, 288, 388–89
- fermenters, 60–61, 65, 385–87, 392
- fetal microbiota transplant (FMT), 202
- fetal programming hypothesis, 196
- fetal stem cells, 217
- fetus
 - brain development, 185, 212–17
 - delivery of (*see* birth mode; newborns)
 - immune system development, 180–87, 195, 217, 242–44, 297–300
 - mother's microbiome (*see* pregnancy)
- FFAs (free fatty acids), 200
- fiber (dietary), 59–60
 - body weight link, 44, 277–80, 288, 321
 - in gut health assessment, 379–80, 385–88
 - immune function, 311–12
 - maternal microbiome, 182–84, 244, 299–301
 - prebiotic (*see* prebiotics)
 - in Western diet, 332–33, 340, 392
- Fibrobacter*, 323–24
- fight-or-flight response, 217
- filamentous bacteria, 43, 226–27
- filtration systems, 355–56
- financial incentives, for research participants, 94
- findings section (article), 148, 149, 151
- Finland, 304
- Firmicutes
 - in colorectal cancer, 62–64
 - in core microbiome, 54
 - in diabetes, 200
 - female reproductive tract microbiome, 176
 - gut microbiome, 53, 59, 60, 62, 67, 188, 198–200, 302, 325, 330–31
 - gut transit time, 380
 - infant microbiome, 188–91, 194, 195, 198–99
 - in obesity, 199, 277, 281, 285
 - oral microbiome, 69, 70
 - primate microbiome, 325
 - respiratory microbiome, 306–7
 - skin microbiome, 73–74
 - stomach microbiome, 336
- Fischbach, Michael, 70
- five-kingdom tree of life, 12–13, 17, 19
- 5' (five prime), 99
- Fleming, Alexander, 34, 335
- A Flora and Fauna within Living Animals* (Leidy), 29
- Florey, Howard, 34
- fluorescent labels, 42–43, 104, 110, 117
- FLVR, 314–15
- fly larvae experiment, 29–30
- FMT (fecal microbiota transplantation), 39–41, 253, 260, 261, 290–91, 305, 314, 341, 377, 388
- FMT (fetal microbiota transplant), 202
- folic acid, 216
- food. *See* diet
- food additives, 258
- food allergies, 311–13
 - antibiotics in, 304
 - infant microbiome, 193, 198, 303
 - physiological response to, 297
 - treatment of, 313–15
- food allergy oral immunotherapy (OIT), 313
- Food and Drug Administration (FDA), 290, 377, 391
- food desert, 275
- forensics, microbiome used in, 352
- formless (*Chaos*) genus, 28
- forward primers, 101–2
- fossils
 - dental plaque, 327–28
 - feces, 326–27, 330–31
 - microbial, 2–3
- Foster, Jane, 223
- Foster, K. R., 230
- Foster, Kevin, 256
- free fatty acids (FFAs), 200
- freezing of samples, 98
- French Academy of Sciences, 30–31
- Friedland, Robert, 228
- fructooligosaccharides, 289, 392–94
- fruit fly (*Drosophila melanogaster*), 87, 225
- functional core, 55–56, 329–30
- functional redundancy, 262–65
- function *versus* diversity, 266–67
- funding, research, 94, 150
- fungi. *See also* specific microbe
 - antibiotics produced by, 331
 - in built environment, 351, 355, 363
 - gut microbiome, 59, 381
 - immune responses to, 237 (*see also* immune system)
 - oral microbiome, 69–70
 - silkworm studies, 32
 - skin microbiome, 73–74
 - in tree of life, 12–13
- furnishings, 353–54
- Fusarium*, 69
- Fusobacteria
 - infant microbiome, 189
 - in obesity, 280
 - respiratory microbiome, 207
 - stomach microbiome, 336
- Fusobacterium*, 70, 261
- Fusobacterium nucleatum*, 249, 265, 281
- G
- GABA (gamma-aminobutyric acid), 220, 224–26
- galactooligosaccharides, 289, 392–93
- gamma-aminobutyric acid (GABA), 220, 224–26
- ganglia, 210
- garbage in, garbage out* expression, 118
- Gardner, H. L., 202
- Gardnerella*, 179
- Gardnerella vaginalis*, 202
- GasPak™, 38
- gastric acid, 257
- gastric cancer, 248–49, 337
- gastroenteritis, 259
- gastrointestinal (GI) tract, 58. *See also* specific organ
 - bowel movements, 375 (*see also* feces)
 - digestion in, 60–61
 - enteric nervous system, 211, 217, 219, 220
 - immune function, 63–64, 180, 239, 245
 - leash effect, 257–58
 - microbes in (*see* gut microbiome)
 - mucin (*see* mucin layer)
 - transit time, 379–80
- Gaussian (normal) distribution, 93
- GBA (gut-brain axis), 211
- GenBank, 120
- Generally Regarded As Safe (GRAS) status, 391
- general practitioner (GP), advice from, 375–78
- genes
 - expression of, 298–99, 322, 357–58
 - reconstruction of, 118–20

- genetic code, 120
- genetic databases, 120, 154
- genetic dictionary, 119–20
- genetics
 - allergic disease linked to, 299
 - versus* environment, 322
 - infant microbiome impacted by, 188
 - missing-heritability problem, 339
 - in obesity, 43–44, 275
 - primate evolution, 322–25
- genetic variant (strain), 53, 278, 390–94
- genome, reconstruction of, 118–20
- genome reference sequences, 119, 121–23, 154, 163, 376
- genome scaffold, 119
- genome-wide association studies (GWASs), 339
- genomics, 38–41
- genus, 12, 53
 - identification of, 121–24
- germ-free mice, 40–41, 43–44, 87
 - allergic disease studies, 300, 305, 308–9, 312–14
 - host regulatory mechanisms, 338
 - nervous system studies, 214–15, 223
 - obesity studies, 43–44, 199, 268, 276–77, 283
- germs, 34
- germ theory of disease, 31–32, 333
- Gerrard, J. W., 333–34
- ghrelin, 337
- Giardia intestinalis*, 27, 268
- Gilbert, Jack, 46–47, 260–61, 352
- GI tract. *See* gastrointestinal tract
 - microbes in (*see* gut microbiome)
- Global Microbiome Conservancy, 341
- glucose intolerance, 275
- glucose production, 212
- glutamate, 220
- glycans. *See* polysaccharides
- glycan degradation strategy, 60–61
- glycine, 283
- glycolysis, 258
- glycoprotein, 70, 255–56
- glycosidic linkages, 59
- GMHI (Gut Microbiome Health Index), 376–77, 384
- gnotobiotic (germ-free) animals, 40–41, 87. *See also* germ-free mice
- goblet cells, 257
- GOE (Great Oxidation Event), 9–10
- gonorrhea, 85
- Google Scholar, 90, 152
- Gordon, Jeffrey, 43–44, 46, 268, 276–77
- Gorenflo, Neal, 366
- gorillas, 322–30
- GP (general practitioner), advice from, 375–78
- graphs, 141, 155
- GRAS (Generally Regarded As Safe) status, 391
- great apes, 322–27. *See also specific species*
- Great Oxidation Event (GOE), 9–10
- great plate count anomaly, 18
- green cities, 365–69
- Greengenes, 121, 154, 158, 163
- gross change of microbiota diversity
 - category, 261
- growing state, 362–63
- growth medium
 - preparation of, 77
 - species requirements, 18
 - sterile, 37–38, 77–78
- guanine, 99
- gum disease (periodontitis), 69–72, 261–65, 281
- gut-brain axis (GBA), 211
- gut-liver axis, 241–42
- gut-lung axis, 307–8
- gut microbiome, 21, 58–69. *See also specific microbe*
 - in allergic disease, 300–301, 305–6, 311–12
 - birth mode impact (*see* birth mode)
 - brain interactions, 211, 213–22 (*see also* microbiota-gut-brain axis)
 - colonization resistance, 36–37, 62–63, 196–97, 204, 259
 - common species in, 52–54
 - definition of, 20
 - dysbiosis (*see* gut microbiome dysbiosis)
 - early observations of, 29
 - ecological perspective on, 255–56, 259–60, 268, 374, 395
 - example organisms, 27, 51, 85, 115, 145, 175, 209, 235, 273, 321, 373
 - functions of, 43–44, 58
 - genetic composition of, 58, 60
 - health linked to, 37, 254, 374–75, 396
 - immune system interactions, 63–64, 180, 239, 242, 244–50, 300–301, 305–6, 311–12
 - infant, 187–94, 196–97, 300, 304–5
 - lifestyle impacts, 331–38 (*see also* Western lifestyle)
 - in neuropsychiatric disorders, 222–28
 - in obesity (*see* obesity)
 - oral microbiome connection, 266, 281
 - phageome, 63–65
 - during pregnancy, 179–80, 186, 299
 - in primates, 322–26
 - resilience of, 57
 - self-management of (*see* personal microbiome)
 - spatial omics, 110
 - species count, 58–59
 - therapies based on, 39–41, 228–29
 - transplantation of, 268, 277
- gut microbiome dysbiosis
 - allergic diseases linked to, 198–99, 305–6
 - antibiotic-associated (*see* antibiotics)
 - intestinal disease linked to, 21, 64–69, 258–59, 267
 - malnutrition linked to, 197–98
 - obesity linked to, 21, 267, 278
 - self-management of (*see* personal microbiome)
- Gut Microbiome Health Index (GMHI), 376–77, 384
- Gut Phage Database, 103
- gut transit time, 379–80
- GWASs (genome-wide association studies), 339
- György, Paul, 191
- gyrB, 322–24
- H
 - Haahtela, T., 315
 - Hadza people (Tanzania), 331–32
 - Haemophilus*, 265, 307–8
 - HAIs (healthcare-associated infections), 186–87, 356, 359–62
 - halophilic archaeans, 19
 - halotolerance, 73
 - Handelsman, Jo, 38–39
 - handwashing, 358–59
 - Harvard Healthy Eating Plate, 387–88
 - HAT (histone acetyltransferase), 298
 - hay fever, 297, 300, 334
 - HDL (high-density lipoprotein cholesterol), 275, 285
 - health, microbiome linked to, 21–22, 37, 56–57, 72, 254, 374–75, 396. *See also* normal microbiome
 - healthcare
 - professional advice, 375–78
 - self-management (*see* personal microbiome)
 - healthcare-associated infections (HAIs), 186–87, 356, 359–62
 - health inequities, 365–66
 - healthy gut criteria, 375, 385–86
 - healthy gut phageome, 64–65
 - heating systems, 349, 353–55, 359, 365
 - hedgehog structure, 42–43
 - Helicobacter pylori*, 235, 248–49, 334, 336–38
 - helper T cells, 182, 226–27, 296–97, 308
 - hematopoietic stem cells, 243
 - heritability rate, 275. *See also* genetics
 - herpes, 352
 - Heterocephalus glaber* (naked mole rat), 97
 - heterotrophs, 7
 - high-density lipoprotein cholesterol (HDL), 275, 285
 - high microbiome diversity, 56
 - high-pressure liquid chromatography (HPLC), 108
 - high-throughput DNA sequencing, 104–6, 117
 - Hippocrates, 396
 - histamine, 296
 - histogram, 93–94
 - histone acetyltransferase (HAT), 298
 - histone deacetylases, 312
 - history
 - of human microbiome, 322–31
 - of microbiology, 17–18, 27–38
 - of microbiome research, 41–47
 - Hitchcock, Thomas, 76
 - HIV/AIDS, 33
 - HMOs (human milk oligosaccharides), 191–92
 - HMP (Human Microbiome Project), 45–47, 54, 254
 - holobiont, 51–83
 - definition of, 20, 51–52, 254
 - ecological perspective on, 255–60, 268, 374, 395
 - genetic composition, 53
 - host-microbiota interactions, 338
 - species count, 53
 - Home Microbiome Project, 351–52. *See also* built environment

- homeostasis, 58, 64–66, 259
 - disruption of (*see* dysbiosis)
- hominids. *See also specific species*
- microbiome in, 322–27
- homogenization, 97, 99
- homologs, 103
- Homo neanderthalensis* (Neanderthals), 71, 322, 326–30
- Homo sapiens*. *See* human
- Hooke, Robert, 17
- hormones, 211–12. *See also specific hormone*
 - female, 176–77
- hospital environment, 186–87, 356, 359–62
- Hospital Microbiome Project, 361–62
- host-adapted core, 55–56
- host-microbiota interactions. *See also*
 - holobiont
 - types of, 338
- host range, 16–17
- hot springs, archaeans in, 19
- housekeeping tasks, of core microbiome, 55
- House Observations of Microbial and Environmental Chemistry Project, 364–65
- howler monkeys, 327–30
- HPA (hypothalamic-pituitary-adrenal) axis, 212, 217
- HPLC (high-pressure liquid chromatography), 108
- human (*Homo sapiens*)
 - classification of, 12, 322–24
 - evolution of, 322–30
 - microbial clouds, 350
 - microbiomes associated with (*see* microbiomes of the built environment)
 - relationship with microbiome (*see* holobiont)
- human genome-wide association studies (GWASs), 339
- human microbiome. *See also specific site*
 - altered, 88 (*see also* dysbiosis)
 - core, 54–57, 187–90, 254
 - definition of, 19
 - evolution of (*see* evolving microbiome)
 - functional role of, 45, 54–55, 329
 - health linked to, 21–22, 37, 56–57, 72, 254, 374–75, 396 (*see also* normal microbiome)
 - host relationship with (*see* holobiont)
 - research on (*see* research; *specific study*)
 - self-management of (*see* personal microbiome)
 - size of, 20–21
 - therapeutic use of, 39–41, 201–4, 228–29, 250, 291, 313–15, 341, 388–94 (*see also specific therapy*)
 - uniqueness of, 22, 54–55, 156, 376, 384
- Human Microbiome Project (HMP), 45–47, 54, 254
- human milk, 191–94
 - antibiotics in, 196–97
 - composition of, 191–94, 244–45, 256, 289
 - immune function, 244–45, 338, 340
 - microbiome, 189–90, 256–57, 338
- human milk oligosaccharides (HMOs), 191–92
- human subjects, 91
 - deidentification of, 151
 - financial incentives for, 94
 - metadata collected from, 97
- humidity, 353–55, 362, 363
- humoral immune responses, 237
- humoral theory of disease, 254–55
- Hungate, Robert, 37–38
- Hungate technique, 38
- hunter-gatherer lifestyle, 331–33
- Hutterite farmers (USA), 302–3, 357–58
- Hyalosphenia papilio*, 29
- hydrogen, in early Earth atmosphere, 3
- hydrogen peroxide, 178, 359
- hydrothermal vents, 1, 2, 348
- hygiene hypothesis, 245, 302–4, 333–34, 350, 366–69
- hygiene practices, 333–35, 348
- hypertension, 275
- hyperthermophiles, 1, 19
- hypothalamic-pituitary-adrenal (HPA) axis, 212, 217
- hypothalamus, 212
- hypothesis, 30
 - biodiversity, 304, 366–67
 - disappearing-microbiota, 334–37, 341
 - fetal programming, 196
 - hygiene, 245, 302–4, 333–34, 350, 366–69
 - microbiome rewilding, 366–69
 - null, 88–89, 91, 135, 139
 - old friends, 245, 303–4, 366–67
 - testable, 76, 87–88
- hypoxia, 258
- I
- IBD (inflammatory bowel disease), 46, 66–69, 246, 248, 261, 265. *See also specific disorder*
- IBS (irritable bowel syndrome), 220–21, 229, 260
- if/then format, 88
- IgA (immunoglobulin A), 64, 241, 244–45, 256
- IgE (immunoglobulin E), 192–93, 238, 296–97
- IgG (immunoglobulin G), 243, 245
- ILCs (innate lymphoid cells), 237
- IL-6 (interleukin-6), 283–84, 288
- IL-17 (interleukin-17), 226–27, 247
- Illumina adapters, 101–2, 105
- immune disorders, 187, 245–50. *See also specific disease*
- immune pathway (MGBA), 219, 221
- immune system, 235–52
 - activation of, 237–38
 - allergic response, 295–97 (*see also* allergic diseases; *specific disorder*)
 - autophagy, 222–23
 - components of, 180–82, 236–38
 - development of, 21, 180–87, 194–96, 200, 201, 217, 242–45, 297–300, 312–13, 334–35, 357
 - epigenetic changes, 298–99
 - gut microbiome, 63–64, 180, 239, 242, 244–50, 300–301, 305–6, 311–12
 - host-microbiota interactions, 338
 - lung microbiome, 240–41, 306–9
- mucosal firewall, 239–40
- oral microbiome, 71–72
- during pregnancy, 180–82, 195, 217, 242–44, 299–300
- skin microbiome, 73–76, 240–41
- stomach microbiome, 337
- immune tolerance, 304, 312, 313
- immunoglobulin A (IgA), 64, 241, 244–45, 256
- immunoglobulin E (IgE), 192–93, 238, 296–97
- immunoglobulin G (IgG), 243, 245
- immunotherapy, 313
- independent variables, 89
- indole, 284
- industrialization, 331–38, 348, 376. *See also*
 - built environment; Western lifestyle
- infant formula, 192–93, 200, 201, 203–4
- infant microbiome, 187–91
 - antibiotics in, 196–97, 300, 304–5, 335, 337, 360
 - dysbiosis, 175, 196–201 (*see also* birth mode)
 - environmental impacts on, 194–95, 300–303
 - immune function, 244–45, 297–303, 313, 334–35, 338, 357
 - milk-oriented, 191–94, 256–57
 - newborn (*see* birth mode; newborns)
 - solid food transition, 194, 257, 303
- inflammatory bowel disease (IBD), 46, 66–69, 246, 248, 261, 265. *See also specific disorder*
- inflammatory cascade, in obesity, 282–85, 288, 338
- inflammatory skin disorders, 240. *See also specific disorder*
- influenza, 33, 352, 355
- inheritance. *See* genetics
- innate immune system, 180–82, 237–38, 296–97, 301
- innate lymphoid cells (ILCs), 237
- inorganic compounds, 3
- insect gut microbiome, 29
- insulin, 212
- insulin resistance, 275–76
- integrated HMP (iHMP), 45–46
- integration, 211
- interleukins, in allergic response, 297
- interleukin-6 (IL-6), 283–84, 288
- interleukin-17 (IL-17), 226–27, 247
- internal capsule, 214
- interquartile range, 135
- intestines. *See* large intestine; small intestine
 - microbes in (*see* gut microbiome)
- intriguing association, 260
- introduction (article), 147, 149, 152
- inulin, 315
- investigational new drug application, 290
- ions, 108
- Iquitos (Peru), 349–50
- irreproducibility, 93
- irritable bowel syndrome (IBS), 220–21, 229, 260
- J
- Johnson, K V.-A., 229–30
- Jorth, Peter, 262–65

- journals, 146–47, 152. *See also* literature
Justinianic Plague of 541, 348
- K
- keratinocytes, 74–75
- keystone species. *See also specific microbe*
female reproductive tract microbiome, 176
gut microbiome, 273, 278, 281, 286, 384, 394–95
loss of, 336
oral microbiome, 71
recovery-associated, 394–95
- kidney failure, 247
- killer T cells (KTCs), 182
- kingdoms, 12
- kitchens, 355–56, 363–64
- Klebsiella*, 225
- Klebsiella pneumoniae*, 221
- Knight, Rob, 46, 137, 150
- KOALA Birth Cohort Study, 195
- Koch, Robert, 32–33, 224, 267, 333
- Koch's postulates, 32–33, 255, 268
depression study using, 224
ecological, 267–69
- KTCs (killer T cells), 182
- L
- Lachnospira*, 307, 314–15
- Lachnospiraceae, 194, 261
- lactase, 340
- lactate, 179
- lactic acid, 176–78, 390
- Lactocaseibacillus rhamnosus*, 394
- Lactobacillus*
in birth mode study, 128–29
in built environment, 353
in colorectal cancer, 67
farm effect, 300
gut microbiome, 62–64, 307–8, 388
infant microbiome, 192, 194
in microbiota-gut-brain axis, 219, 220, 225
in obesity, 278, 283, 288–90
oral microbiome, 70
probiotic strains, 390, 393
vaginal microbiome, 176–79, 186, 201, 256
- Lactobacillus acidophilus*, 229, 389
- Lactobacillus brevis*, 122–23, 129
- Lactobacillus casei* Shirota, 289
- Lactobacillus crispatus*, 177
- Lactobacillus delbrueckii* subsp. *bulgaricus*, 229
- Lactobacillus gasseri*, 177, 278
- Lactobacillus helveticus*, 229
- Lactobacillus iners*, 177–79
- Lactobacillus jensenii*, 177–78
- Lactobacillus paracasei*, 229, 278
- Lactobacillus plantarum*, 229
- Lactobacillus reuteri*, 60, 203, 226, 278, 299
- Lactobacillus rhamnosus*, 201
- Lactococcus*, 70
- Lactococcus lactis*, 302, 309
- lactose digestion, 340
- lactulose, 392
- large intestine, 58
- bacteriophages in, 64–65
- digestion in, 60–61
- dysbiosis in, 64–69, 259, 276 (*see also* gut microbiome dysbiosis)
- immune function, 63–64, 180, 239, 245
- leash effect, 257–58
- microbes in, 59, 61–63, 273 (*see also* gut microbiome)
- mucin (*see* mucin layer)
- Last Universal Common Ancestor (LUCA), 7
- Latin (binomial) names, 12, 53–54
- latrine deposits, 326–27, 330–31
- Lawley, Trevor, 186–87
- LDL-C (low-density lipoprotein cholesterol), 275
- leaf-associated microbes, 346
- leanness, 44, 277–79, 281, 289
- learned immune response, 237–38
- leash effect, 256–57
- Leeuwenhoek, Antonie van, 17, 27–28, 37, 41
- Legionella*, 355–56
- Legionella pneumophila*, 359
- Legionnaires' disease, 359
- Leidy, Joseph, 29
- leptin, 277, 337
- leucine-rich repeats (LRRs), 301
- Lewy bodies, 227–28
- Ley, Ruth, 277
- Li, D., 224
- Li, Huiying, 76
- life
microbes as core of, 17
origins of, 2–12
tree of, 12–17, 19, 132
- lifestyle
hunter-gatherer, 331–33
industrialization, 331–33, 348, 376 (*see also* built environment; Western lifestyle)
- light, 355–56, 359
- limited pathogens category, 261
- Limi Valley (Nepal), 341
- Linnaean classification system, 12–17, 28, 53–54
- Linnaeus, Carolus, 12, 28
- lipid imbalance, 275
- lipolysis, 282
- lipophilic yeast, 73
- lipopolysaccharides (LPS), 221–22
in allergic disease, 301–3, 308
immune response, 338
in lungs, 241
in obesity, 276, 282–85
in type 1 diabetes, 200
- literature, 145–74
article format, 147–49
evaluation of, 89–90, 148–58
peer review, 90, 146–47, 157
primary, 89–90, 141, 146–48
searching, 90, 152
secondary, 146
tertiary, 146
types of, 146
- Liu, Albert, 201
- liver cancer, 265–66
- liver microbiome, 241–42
- Lloyds Bank coprolite, 326–27
- longitudinal study, 96
- loss of health-associated bacteria category, 261
- loss of microbiota, 334–38, 341
- low-density lipoprotein cholesterol (LDL-C), 275
- low microbiome diversity, 56
- Lozupone, C., 137
- LPS. *See* lipopolysaccharides
- LRRs (leucine-rich repeats), 301
- LUCA (Last Universal Common Ancestor), 7
- lumen, intestinal, 63–64
- lung microbiome, 240–41, 306–9
- lymphatic cells, 236, 243
- lymph nodes, 236, 243
- lymphocytes. *See* B cells; T cells
- lymphoid progenitor cells, 238
- Lynch, Susan, 314–15
- lysis, 100–101
- lysosomes, 222–23
- M
- macrophages, 181, 241, 243–45, 283–84
- maggot experiment, 29–30
- magnesium, 5
- magnetic beads, 101
- magnification, 28, 42
- major depressive disorder (MDD), 220, 223–26, 229
- major histocompatibility complex (MHC), 238
- Malassezia*, 73–75
- Malawi, 324
- malnutrition, 197–98, 244, 268
- maltooligosaccharides, 392
- MAMPs (microbe-associated molecular patterns), 301–2
- Manaus (Brazil), 349–50
- manuscripts, 146. *See also* literature
- Margulis, Lynn, 11, 20, 52, 223
- marker food, 379
- Marshall, Barry, 336
- mass extinction events, 9
- mass spectrometry, 107–8
- mast cells, 238, 296–97, 299
- maternal microbiome. *See* birth mode; pregnancy
- Matsés people (Peru), 333
- maximum value, 134
- Mayneris-Perxachs, J., 224–25
- McCright, Sam, 284
- MDD (major depressive disorder), 220, 223–26, 229
- MDRP (multidrug-resistant pathogens), 362
- meadow diversity metaphor, 374, 383–84
- mean, 92
- mechanical lysis, 100–101
- median value, 134–35
- medical professionals, advice from, 375–78
- medieval microbiome, 330–31
- Med13L* gene, 340
- Meisel, P., 281
- melatonin, 212
- membrane argument, 4–5
- mental disorders. *See also specific disorder*
microbiota-gut-brain axis in, 220–21
psychobiotics for, 228–29

- messenger RNA, 107
metabolic modules, 54
metabolic states, 362–63
metabolic syndrome (MetS), 275–76, 289
metabolism, 61
metabolites. *See also specific substance*
 in asthma, 314–15
 in built environment, 363–64
 in Crohn's disease, 66–69
 ecological perspective on, 256–58, 395
 gut transit time, 379
 health linked to, 22, 385–86
 immune function, 239, 241
 infant microbiome, 188–90, 192, 214–15
 maternal microbiome, 180, 182, 213, 242–43, 299
 in microbiota-gut-brain axis, 219, 221, 338
 in obesity, 278, 281–82
 of starch digestion (*see* short-chain fatty acids)
metabolome, 109
metabolomics, 106–7, 109, 214, 362–65, 375, 382
Metabolomics Standards Initiative, 109
Metabolomics Workbench, 109
metadata, 90, 96–97
metagenome, 104
metagenomics, 38–39, 41–43
 in built environment, 363
 DNA amplification, 101–6, 117–18
 DNA extraction, 99–101, 117
 personal screening, 375–77
 spatial transcriptomics, 109–10, 263
metagenomic sequence library, 104
metagenomic (shotgun) sequencing, 106
metaproteomics, 106–8, 375, 382
metatranscriptome, 107
metatranscriptomics, 106–7, 382
Metchnikoff, Élie, 389
Methanobrevibacter, 69
Methanobrevibacter smithii, 69, 323–24
methanogenesis, 3, 7
methanogens
 classification of, 14–15
 skin microbiome, 74–75
Methanopyrus kandleri, 3
methanotrophs, 9
methicillin-resistant *S. aureus* (MRSA), 295, 337
methods section (article), 147–48, 153, 154
Methylobacterium, 351
MetS (metabolic syndrome), 275–76, 289
MGBA. *See* microbiota-gut-brain axis
MHC (major histocompatibility complex), 238
Mian, 170
miasma theory (spontaneous generation), 29–31
mice. *See* mouse
micelles, 5
microbe(s)
 as core of life on Earth, 17
 definition of, 2–3
 metabolic states, 362–63
 metabolites (*see* metabolites; *specific substance*)
 research on (*see* research)
microbe-associated molecular patterns (MAMPs), 301–2
microbial clouds, 350
microbial ecology, 37
microbial guilds, 279–81
microbial leash metaphor, 256–57
microbially produced volatile organic compounds (MVOCs), 364
microbial seed bank, 341
microbiology
 definition of, 32
 history of, 17–18, 27–38
 modern developments in, 38–41
microbiome
 in humans (*see* human microbiome)
 in primates, 322–27
microbiome analysis programs, 170. *See also* Qiita
MicrobiomeAnalyst, 170
microbiome rewilding hypothesis, 366–69
microbiomes of the built environment (MoBE), 345
 constituents of, 351–52
 control of, 348, 355–56
 early studies of, 349–50
 future, 365–69
 health impacts of, 348, 356–58
 history of, 347–48
 metabolomics, 362–65
 microbial transport in, 350–51
 physical factors influencing, 349, 353–56, 359–60, 369
 tracking methods, 358–62
microbiota
 definition of, 19–20, 52
 transfer of (*see* transplantation)
microbiota-gut-brain axis (MGBA), 209, 217–22, 338
 autophagy, 222
 endocrine pathway, 218–19
 immune pathway, 219, 221
 neural pathway, 219–21
Micrococcus, 78
microglial cells, 185, 213–14, 221, 241–42
microRNAs (miRs), 284, 298–99
Middle Ages, microbes from, 330–31
milk
 cow, allergy to, 312, 314
 human (*see* human milk)
 probiotic, 202
milk-oriented microbiome (MOM), 192
Miller, Stanley, 3–4
minimum value, 134
miRs (microRNAs), 284, 298–99
missing-heritability problem, 339
mitochondrion, 11
MoBE. *See* microbiomes of the built environment
model organisms, 87. *See also specific organism*
 Crohn's disease, 67
 germ-free, 40–41, 87 (*see also* germ-free mice)
 obesity studies, 276–77
 variables, 95
molar ratio, 61
mold
 Hooke's observations of, 17
 toxic, 345, 355, 359
molecular networking, 109
molecular photocopying, 101
molecular probing, 42–43
molecular therapies, 226–27
molecular tree of life, 13–14, 132
MOM (milk-oriented microbiome), 192
monera, 13
monocytes, 238
monosaccharides, 59
Moraxella, 307
Morganella, 225
mother's first gift, 186. *See also* birth mode; pregnancy
mother's milk. *See* human milk
mothur, 121, 140
motor function of the CNS, 211
mouse (*Mus musculus*), 87, 91
 allergic disease studies, 300–302, 305, 307–9, 312–15, 357
 autism spectrum disorder studies, 226
 brain studies, 214–16, 221, 223
 Crohn's disease studies, 67
 depression studies, 224–25
 germ-free (*see* germ-free mice)
 maternal microbiome, 180–71, 183–85, 244
 obesity studies, 43–44, 199, 268, 276–77, 279, 281, 283–85, 289, 290
 rheumatoid arthritis studies, 246
 spatial omics, 110
 variables, 95
mouth, 58. *See also* oral microbiome
mouth-body connection, 72
mouthwash, antibacterial, 70
MRSA (methicillin-resistant *S. aureus*), 295, 337
mucin layer
 host-microbiome interactions in, 256–57, 273, 380
 infant microbiome, 188, 194, 204
 in obesity, 278, 284–85
mucosal firewall, 239–40, 245
mucus escalator, 257
Mullis, Kary, 101
multicellularity, origin of, 10–12
multidrug-resistant pathogens (MDRP), 362
multi-omics, 109–10, 154, 224–25
multiple sclerosis, 221
multiplexing, 117–18
Mure, Nancy, 199
Mus musculus. *See* mouse
MVOCs (microbially produced volatile organic compounds), 364
Mycobacterium, 355
Mycobacterium neoaurum, 224
Mycobacterium tuberculosis, 347
myelination, 217
myeloid cells, 236, 243

N
Nagler, Cathryn, 311
naive T cells, 182, 296–97, 305
Nakajima, Akihito, 183
naked mole rat (*Heterocephalus glaber*), 87

- Namur (Belgium), 330–31
nasopharynx microbiome, 21, 58, 337, 360–61
NAST, 154, 158
National Institutes of Health (NIH), 45, 254
Natufians, 346–47
natural environment, *versus* indoor, 346. *See also* built environment
natural killer T cells, 181, 237–38
natural log, 130
natural selection, 7
nature-based solutions, 366–69
naturopaths, 377–78
nausea, during pregnancy, 201–2
Neanderthals, 71, 322, 326–30
necrotizing enterocolitis, 200, 203
Neisser, Albert, 85
Neisseria, 307–8
Neisseria gonorrhoeae, 85
nematode (*Caenorhabditis elegans*), 87
neonatal intensive care unit (NICU), 360–61
neonates. *See* newborns
Nepal, 341
nerve fiber (axon), 185, 217
nerve impulses, 211
nervous system, 210–12. *See also* brain
Netherlands, 195
network workspace (Qiita), 161–64, 167
neural pathway (MGBA), 219–21
neural tube defects, 216
neurodegenerative disorders. *See also specific disorder*
microbiota-gut-brain axis in, 221–22
neurodivergence, 226–27
neuroendocrine system, 211–12, 217–19
neurogenesis, 219
neuroinflammation, 214, 219, 222, 225
neuropeptides, 213
neuropsychiatric disorders, 222–28. *See also specific disorder*
neurotransmitters, 220
neurotrophic factors, 221
neurotrophic signals, 213
neutrophils, 181, 237–38, 296
newborns
antibiotics in, 196–97, 300, 304–5, 335, 337, 360
birthing process (*see* birth mode)
dysbiotic microbiome, 196–200
feeding (*see* human milk; infant formula)
immune system, 21, 180–87, 194–95, 217, 242, 244–45, 297–304, 312–13, 334–35
microbiome, 186–91, 300, 313
preterm, 46, 202–4, 243, 300, 360
next-generation sequencing, 117–18
niche adaptation, 45
niche modification, 259–60
niche preemption, 259
NICU (neonatal intensive care unit), 360–61
Nightingale, Florence, 359–60
NIH (National Institutes of Health), 45, 254
nisin, 177
Nissle, Alfred, 36
nitric oxide, 70
nitrogen, metabolism of, 74–75
noncoding regions, 119
noncoding RNAs, 284, 298–99
normal (Gaussian) distribution, 93
normal microbiome
core taxa, 54–56
definition of, 52
hallmarks of, 56–57
research on, 45–47, 54
Norman (Oklahoma), 333
nosocomial infections, 186–87, 356, 359–60
nucleosides, 99
nucleotides, 98–99
fluorescent labeling, 104, 117
origin of, 4
triplets of (codons), 119–20
null hypothesis, 88–89, 91, 135, 139
nutrient cycling, in oral microbiome, 70
nutrient medium. *See* growth medium
nutrition. *See also* diet
microbiome in, 22, 197–98, 244, 268
nutritionists, 377–78
O
obesity, 273–94
definition of, 274–75
epidemic of, 274–76, 337
genetic mutations in, 43–44
gut microbiome in, 43–44, 60–61, 199–200, 268, 276–85, 338
infants, 199–200
versus leanness, 277–79, 281, 289
microbial guilds in, 279–81
oral microbiome in, 281
treatment of, 40, 275–76, 285–91
weight loss markers, 281–85
obligate anaerobic bacteria, 65, 257–59
observational studies, 86, 202
oceans
dead zones, 9
hydrothermal vents, 1, 2, 348
Ochman, Howard, 322–25
OIT (food allergy oral immunotherapy), 313
Oklahoma, 333
old friends hypothesis, 245, 303–4, 366–67
Olesen, S. W., 254–55
oligosaccharides, 191, 289, 392–94
Olle, Bernat, 341
Olsen, I., 281
omics, 106–10. *See also specific type*
one pathogen-one disease paradigm, 267
online data analysis programs, 121, 140, 145, 154, 158–70. *See also specific program*
open-access journals, 152
open reading frames (ORFs), 119–20
open-source software, 158
operational taxonomic units (OTUs), 121–24, 154–55, 162–63
oral immunotherapy, 313
oral microbiome, 69–72
in built environment, 351–52
cataloging of, 42–43
colonization resistance, 70
common species in, 69–70
DIY assessment kits, 381
dysbiosis, 71–72, 262–65
early studies of, 17, 28, 37, 41–42
evolution of, 70–71
functions of, 70, 329–30
gut microbiome connection, 266, 281
in liver cancer, 265–66
in obesity, 281
in primates, 327–30
site differences, 52
species count, 69
teeth (*see* dental plaque)
orangutans, 322–25
ORFs (open reading frames), 119–20
origin
of human microbiome, 322–31
of organic molecules, 3
of species, 12–13
Oscillospira, 192, 286
OTUs (operational taxonomic units), 121–24, 154–55, 162–63
outcome, 86
outdoor environment, *versus* indoor, 346. *See also* built environment
outliers, 94
oxygen
in early Earth atmosphere, 2, 7, 9–10
environment without (anoxic), 7–8, 37–38
in gut microbiome, 189–90, 257–60, 267, 395
in large intestine, 65
in oral microbiome, 69, 71
ozone layer, 2
P
Pace, Norm, 351
Palforzia, 313
pancreas, 275
Pandorina algae, 9
Paneth cells, 64–66, 257–58
parasitic worm infections, 297, 308, 330–31, 381
Parkinson, James, 227
Parkinson's disease (PD), 221, 227–28
Parrish, Rosia, 378
participants. *See* human subjects
Parvimonas, 261
passive immunity, 245
Pasteur, Louis, 30–32
pathobionts, 267
pathogens. *See also specific pathogen*
in built environment, 346, 355–56 (*see also* built environment)
defenses against (*see* colonization resistance; immune system)
pathogen trapping, 179
pattern recognition receptors (PRRs), 301
PCA (principal component analysis), 139–41, 169–71, 176, 325–26, 329–30, 333
PCoA (principal coordinate analysis), 156–57, 176–77
PCR (polymerase chain reaction), 19, 101, 117
PCR (polymerase chain reaction) amplification, 101–6, 117–18
PD (Parkinson's disease), 221, 227–28
PD (phylogenetic diversity), 132–35
peanut allergy, 313–14. *See also* food allergies
pear-shaped body, 279
peer review, 90, 146–47, 157
penicillin, 34, 335

- Penicillium notatum*, 34
Peptostreptococcus, 261
 perfluorooctane sulfonic acid (PFOS), 364
 perforins, 182, 240
 periodontitis, 69–72, 261–65, 281
 peripheral nervous system (PNS), 210
 personal microbiome, 373–99
 antibiotic recovery, 394–95
 food as medicine, 396
 Gut Microbiome Health Index, 376–77, 384
 gut microbiome kits, 380–84
 gut transit time, 379–80
 health indicators, 384–87
 healthy diet, 387–88
 healthy gut criteria, 375, 385–86
 microbiome-based therapeutics, 388–94
 professional advice, 375–78
 stool quality assessment, 378–79
 Peru, 333, 349–50
 petri dishes, 77
 pets
 in built environment, 350, 353–54, 369
 infant microbiome affected by, 192–93, 297, 300, 350, 353–54
 microbiome assessment kits, 381
 Peyer's patches, 243
 PFOS (perfluorooctane sulfonic acid), 364
 phageome, gut, 63–65
 phages. *See* bacteriophages
 phagocytes, 237–38
 phagocytosis, 11, 181
 phenotypes, 13
 phenylalanine, 226
 phosphate groups, 99
 phospholipid bilayer, 18
 photosynthesis, 8–9
 phyllosphere, 352–53
 phylogenetic diversity (PD), 132–35
 phylogenetic tree (phylogeny), 12, 132, 138, 154, 322–23
 phylum-level diversity, 382
 phytochemicals, 287–88
Picrophilus, 19
 pili, 69–70
 pilot study. *See* birth mode study
 pioneer (primary) species, 394–95
 pituitary gland, 212
 placenta, 180, 184, 242, 299
 plague, 29, 348
 planetary habitability, 5
 plants
 in built environment, 353–54, 362, 365–69
 chloroplasts, 11
 in diet, 323, 328, 332, 340, 352, 388, 394
 microbiomes, 352–53
 photosynthesis, 8–9
 phytochemicals, 287–88
 in tree of life, 12–13
 plaque. *See* dental plaque
 plasma membrane, 18
 plumbing, 355–56
 PNS (peripheral nervous system), 210
 polymerase chain reaction (PCR), 19, 101, 117
 polymerase chain reaction (PCR) amplification, 101–6, 117–18
 polymicrobial synergy and dysbiosis (PSD), 261–65
 polyphenols, 288, 388
 polysaccharide A, 189, 301
 polysaccharides (glycans), 59
 biological functions, 246, 288
 degradation strategy, 60–61
 glycan degradation strategy, 60–61
 infant microbiome, 188–89
 primate microbiome, 323–24
Porphyromonas, 70–72, 261
Porphyromonas gingivalis, 71–72, 262–65, 281
 portal vein, 241
 postbiotics, 313
 postpartum sepsis, 358–59
 power, statistical, 91, 141
 power analysis, 94–95
 prebiotics, 203, 228
 for allergies, 313, 315
 artificially produced, 392–93
 in breast milk, 191, 203
 definition of, 289, 392
 for depression, 229
 dietary sources, 340, 388, 392–93
 in infant formula, 203–4
 for obesity, 289–90
 synbiotics, 313, 393–94
 predatory journals, 147
 predictable association, 260
 pregnancy
 delivery (*see* birth mode)
 dysbiosis during, 213, 226
 immune system during, 180–87, 195, 217, 242–44, 299–300
 inflammation and infection during, 243–44
 microbiome during, 46, 179–80, 212–17, 299–300, 336
 postpartum sepsis, 358–59
 probiotics during, 201–2
 vaginal sampling during, 97–98
 preterm birth, 46, 202–4, 243, 300, 360
Prevotella, 179, 186, 277–79, 336
 Prevotellaceae, 194, 332
Prevotella copri, 279, 321
Prevotella histicola, 247
Prevotella intermedia, 265
 primary literature, 89–90, 141, 146–48
 primary (pioneer) species, 394–95
 primary starch degraders, 60–61
 primates. *See also specific species*
 microbiome in, 322–27
 primer pad region, 101–2
 primers, 101–2, 117
 primordial soup, 4
 principal component analysis (PCA), 139–41, 169–71, 176, 325–26, 329–30, 333
 principal coordinate analysis (PCoA), 156–57, 176–77
 priority, 188
 probability, 92
 probiotics, 228, 341
 for allergies, 313–14
 brain effects, 220
 for cholesterol levels, 279
 definition of, 288, 389
 for depression, 229
 for diabetes, 200
 dietary supplements, 389–92
 foods containing, 388–89
 in infant formula, 193–94
 for inflammatory bowel disease, 261
 for obesity, 288–89
 during pregnancy, 201–2
 for preterm babies, 203
 for rheumatoid arthritis, 247
 synbiotics, 313, 393–94
 unregulated production of, 204
Proceedings of the National Academy of Sciences (PNAS), 148
 process errors, 118, 121
 proinflammatory cells, 221
 prokaryotes
 classification of, 15
 definition of, 10
 origin of, 10
 proline, 224–25
 propionate, 60–62
 health linked to, 386
 immune function, 308
 infant microbiome, 193
 in obesity, 273, 278, 281–82
Propionibacterium, 73–74, 128–29, 351
 proteases, 73, 310
 proteins
 databases of, 120
 metaproteomics, 106–8, 375, 382
 misfolding, 227–28
 origin of, 4
 tree of life based on, 13–14
 Proteobacteria
 in built environment, 351
 core microbiome, 54
 female reproductive tract microbiome, 176
 gut microbiome, 53, 188, 198, 200, 261–62, 325, 330–31, 384
 infant microbiome, 188–90, 198, 200
 in obesity, 277–79, 284–85
 oral microbiome, 69
 primate microbiome, 325
 respiratory microbiome, 307–8
 skin microbiome, 73–74
 stomach microbiome, 336
Proteus mirabilis, 278–79
 protists
 in oral microbiome, 69–70
 in tree of life, 13
 protocell, 5–7
 PRRs (pattern recognition receptors), 301
 PSD (polymicrobial synergy and dysbiosis), 261–65
 pseudomembranous enterocolitis, 39–40
Pseudomonadota, 70
Pseudomonas, 265, 362
Pseudomonas aeruginosa, 221
Pseudomonas fluorescens, 265
 psoriasis, 240
 psychobiotics, 228–29
 psychological disorders. *See also specific disorder*
 microbiota-gut-brain axis in, 220–21
 psychobiotics for, 228–29
Public Studies section (Qita), 159–60

- PubMed, 90
 Pueblos (American Southwest), 347
 Puerto Almendras (Peru), 349–50
 pulmonary microbiome, 240–41, 306–9
 p-value, 91–92
Pyrococcus furiosus, 1
- Q
 QIIME 2 (Quantitative Insights into Microbial Ecology), 121, 124, 140
 QIIMP (Quick and Intuitive Interactive Metadata Portal), 97
 Qiita, 145, 158–70
 alpha diversity analysis, 166–69
 basics, 158–63
 data transformation, 163–64
 PCA analysis, 169–71
 taxonomic distribution analysis, 164–66
 quality control, in data analysis, 118
 quality scores (QS), 118
 quorum sensing, 230
- R
 RA (rheumatoid arthritis), 246–47
 RABs (recovery-associated bacteria), 394–95
 random (stochastic) process, 266–67
 rarefaction (species accumulation) curves, 124–25, 169–70
- rats
 autoimmune disease studies, 241–42
 depression studies, 224, 229
 naked mole rat, 87
 Parkinson's disease studies, 228
 plague spread by, 348
- rDNA. *See* ribosomal DNA
 receptor attachment specificity, 69–70
 recolonization, 337–38
 recovery-associated bacteria (RABs), 394–95
 red blood cells, 339
 Redi, Francesco, 29–30
 references (article), 148, 152
 reference sequences, 119, 121–23, 154, 163, 376
 regulatory pathways, 54
 regulatory T cells (Tregs), 182–84, 240, 244, 297, 299–301, 305, 308, 312, 314
 Relman, David, 41–42
 replication
 DNA, 4–7, 99–100
 viral, 16
 replication argument, 4–7
 reproductive tract, female, 176–79. *See also* vaginal microbiome
 during pregnancy (*see* birth mode; pregnancy)
 research, 41–47, 85–113. *See also specific study*
 ethics in, 150–51
 funding for, 94, 150
 Human Microbiome Project, 45–47, 54, 254
 metagenomics, 41–43
 origins of, 17, 27–35, 43–44
 reports on (*see* literature)
 volume of, 45
 research design, 86–88, 90–97
 analysis phase (*see* data analysis)
 bias in, 45, 376
 examples of, 95–96, 151, 153 (*see also* birth mode study)
 experimental phase, 97–106 (*see also* experiment)
 hypothesis (*see* hypothesis)
 literature review, 89–90, 146–58
 power analysis, 94–95
 sample size, 91–95, 125, 141, 150, 254, 267
 subjects, 91 (*see also* human subjects; model organisms)
 training in, 86
 research questions, 85, 86, 116, 121
 resilience, 54, 56–57
 resistance, 56
 antibiotic, 35, 85, 186–87, 310, 330–31, 335, 337, 360, 362
 colonization (*see* colonization resistance)
 resistant starch, 60–61, 229–30, 279, 286–87, 388
 resistomes, 360, 362
 respiration, cellular, 7–8
 respiratory syncytial virus (RSV), 309
 respiratory tract
 in built environment, 351, 356–57, 359–60
 infections, 33, 345
 microbiome, 240–41, 306–9, 337
 restrooms, 351, 353, 355–56, 363, 364
 results section (article), 148, 149, 153–54
 retention rates, 94
 reverse primers, 101–2
 review articles, 146
 rewinding hypothesis, 366–69
 rheumatoid arthritis (RA), 246–47
 rhinovirus, 309
 ribosomal DNA (rDNA), 41
 sequencing of, 41–42, 183–84, 375, 381–82 (*see also specific method or study*)
 16S subunit, 18, 41, 133, 183–84
 ribosomal RNA (rRNA)
 classification by, 14–15
 18S subunit, 14, 103
 reference data, 121–23, 154, 163, 376
 sequencing, 44, 96, 101–4, 121, 158, 163 (*see also specific study*)
 16S subunit, 14, 18, 41–42, 44, 96, 98, 101–4, 121, 132, 158, 163, 322, 375, 381
 tree of life based on, 14–15, 132
 variable regions, 103
 ribosome, tree of life based on, 13–14, 132
 richness (species), 126–27, 169–70, 266, 313, 382
- RNA
 versus DNA, 107
 messenger, 107
 noncoding, 284, 298–99
 origin of, 4–7
 ribosomal (*see* ribosomal RNA)
 sequencing, 41–42, 107, 123
 tree of life based on, 14–15, 132
 rock, ancient, 2–3, 9–10
 Rogers, Sherry, 200
 roll-tube, 37–38
Romboutsia, 315
 Rook, Graham, 303
- room temperature, 353–55, 362
Roseburia, 267, 279, 284–85, 327, 386
Roseomonas mucosa, 74–75
Rothia, 307, 314–15, 336
 Royal Society of London, 28
 rRNA. *See* ribosomal RNA (rRNA)
 RSV (respiratory syncytial virus), 309
 rugs, 353–54
 Ruminococcaceae, 261
Ruminococcus, 192, 247, 279, 327
Ruminococcus bromii, 60, 279
Ruminococcus gnavus, 280
 rust, 9–10
- S
 saccharolytic bacteria, 392
 saliva, 281, 327
 salivary amylases, 60, 330
Salmonella typhimurium, 259
 sample size, 91–95, 125, 141, 150, 254, 267
 sampling methods, 98. *See also* culturing
 DNA extraction, 99–101, 117
 fecal, 97–98
 quality control, 118
 skin, 78–80
 vaginal, 97–98
 sanitation practices, 333–35, 356, 359–62
 SARS-CoV-2 virus, 16, 352, 355, 365
 satiety signal, 62, 277, 282
 SBS (sick building syndrome), 345, 356–57
 SCD (sickle cell disease), 339
 SCFAs. *See* short-chain fatty acids
 Schaedler, Russell, 40–41
Schistosoma haematobium, 248
 scientific education, 86
 scientific literature. *See* literature
 seasonal patterns, 332
 sebaceous glands, 73–76
 sebum, 73–76
 secondary literature, 146
 secondary species, 394–95
 secondary succession, 395
 second brain (ENS), 211, 217, 219, 220
 second quartile, 134
 sedimentary rock, 9–10
 seed bank (microbial), 341
 selection, 187–88, 230, 266–67
 selection (deterministic) process, 266–67
 self-management. *See* personal microbiome
 self-tolerance, 182
 semaphorin 5, 248
 semiconservative replication, 99–100
 Semmelweis, Ignaz, 358–59
 sensitized immune system, 297
 sensorimotor deficits, 214
 sensory receptors, 210–11
 sequence alignment, 122–23
 sequence annotation, 109
 sequence functions, prediction of, 120
 sequence ID (OTU), 162–63
 sequence read, 117
 serial endosymbiosis, 11
 serotonin, 220
 sexually transmitted infections (STIs), 178
 Shannon diversity index, 130–32, 166–69, 363
 shareable cities, 366
 shared dysbiosis, 265–66

- Sharif, Maimunah Mohd, 365–66
- Shiga toxin, 53
- Shigella*, 36–37, 39
- short-chain fatty acids (SCFAs), 22, 60. *See also specific acid*
- ecological perspective on, 256–58, 395
- function of, 61–62, 64
- health linked to, 385–86
- immune function, 239, 241, 246, 299, 301, 311–12
- infant microbiome, 190, 194, 200, 204, 256–57
- in microbiota-gut-brain axis, 219, 221–22, 229, 338
- in obesity, 199, 276, 278, 281–82, 286, 288
- oral microbiome, 70
- during pregnancy, 182–83, 187, 213–14, 244, 299
- production of, 65
- shotgun sequencing, 106
- siblings, 193, 300, 334
- sick building syndrome (SBS), 345, 356–57
- sickle cell disease (SCD), 339
- significance, statistical, 91–94
- silica columns, 101
- silkworm studies, 31–32
- SILVA, 121–23, 154
- similarity-searching algorithms, 120, 123
- single-line identifier, 122
- single nucleotide polymorphisms (SNPs), 339–40
- Sinha, Rashmi, 384
- skin cancer, 73–74
- skin infections, 74–75. *See also specific disorder*
- skin microbiome, 21, 73–76
- in built environment, 351–53, 362
- colonization resistance, 74–75, 240–41, 309
- common species in, 73–74, 78, 295
- dysbiosis, 75–76, 240, 309–11
- functions of, 74–75, 240–41
- maternal, 186, 189–90
- newborn, 190–91
- as nutritional desert, 73
- sampling methods, 76–80
- species count, 73
- small intestine, 58
- digestion in, 60
- immune function, 239
- leash effect, 257–58
- microbes in, 59 (*see also gut microbiome*)
- smallpox, 16
- smoking, 46
- SNPs (single nucleotide polymorphisms), 339–40
- software packages, data analysis, 121, 140, 145, 154, 158–70. *See also specific program*
- soil-associated microbes, 346, 353, 362, 367
- somatic (voluntary) nervous system, 210
- Sonnenburg, Justin, 332–33
- spatial transcriptomics, 109–10, 263
- specialized functions, of core microbiome, 55, 329–30
- species, 12, 53
- diversity of (*see diversity*)
- identification of, 121–24
- keystone (*see keystone species*)
- origin of, 12–13
- species abundance
- definition of, 127
- measurement of, 124–29, 155, 164–65
- in personal microbiome, 382
- in primate microbiome, 325–26
- species accumulation (rarefaction) curves, 124–25, 169–70
- species evenness, 126. *See also alpha diversity*
- species recovery, 395
- species richness, 126–27, 169–70, 266, 313, 382
- Sphingomonas*, 351
- spinal cord, 210
- Spirochaetaceae, 332
- Spirulin algae, 9
- spontaneous generation (miasma theory), 29–31
- spores, 40
- stability, 56
- Stachybotrys*, 355, 359
- stack plot, 127–29, 154–57, 164–65
- standard deviation, 92
- Staphylococcus*, 295
- in birth mode study, 128–29
- in built environment, 351, 353, 362
- infant microbiome, 193
- nasal microbiome, 360
- in skin microbiome, 73–75, 78
- Staphylococcus aureus*
- enterocolitis caused by, 39
- infections, 33, 74–75, 240, 295, 309–11, 337
- penicillin mold in, 34
- Staphylococcus epidermidis*, 73–75, 240, 311
- Staphylococcus hominis*, 73, 311
- Staphylococcus sciuri*, 309
- starches, 59–60
- digestion of, 22, 43–44, 328–29
- resistant, 60–61, 229–30, 279, 286–87, 388
- start codon, 119–20
- startle response, 214–16
- statistical power, 91, 141
- statistical significance, 91–94
- statistical tests, 139–41
- stem cells, 217, 243
- sterility control, 37–38, 77–78
- STIs (sexually transmitted infections), 178
- stochastic (random) process, 266–67
- stomach, 21, 58, 257
- immune system in, 337
- microbiome, 21, 59, 235, 336–37 (*see also gut microbiome*)
- stomach cancer, 248–49, 337
- stool. *See feces*
- stop codon, 119–20
- Strachan, D. P., 334
- strains, 53, 278, 390–94
- Streptococcus*
- in cancer treatment, 250
- in hospital environment, 250
- in liver cancer, 265
- nasal microbiome, 360
- in obesity, 280
- oral microbiome, 70, 71, 328–30
- penicillin, 34
- respiratory microbiome, 307
- stomach microbiome, 336
- Streptococcus anginosus*, 330
- Streptococcus gordonii*, 263
- Streptococcus mitis*, 265, 330
- Streptococcus mutans*, 71, 330, 394
- Streptococcus oralis*, 265
- Streptococcus pneumoniae*, 337
- Streptococcus pyogenes*, 330
- Streptococcus salivarius*, 330
- Streptococcus sanguinis*, 330
- Streptococcus thermophilus*, 229
- stress response, 212, 217, 220, 224–25, 257, 378
- stromatolites, 2–3
- subcutaneous fat layer, 73
- subjects
- animal (*see model organisms; specific organism*)
- human (*see human subjects*)
- subscription model, 152
- Succinivibrionaceae, 332
- sugars
- blood levels, 212, 275
- dietary, 22, 59–61, 392
- sulfate-reducing microbes, 7–8
- sunlight, 355
- superantigens, 310
- super bug, 85
- surface area of intestines, 58
- surprising associations, 260
- Svedberg units, 14
- swan-neck flask experiment, 30–31
- sweat, 73
- symbiosis, 11, 20, 22, 34, 322–23, 388
- synbiotics, 313, 393–94
- synergistic supplements, 394
- synthesis (next-generation) sequencing, 117–18
- syntrophy, 69
- Szostak, Jack, 4–5
- T
- tagmentation, 104
- Taleb, Nassim Nicholas, 391–92
- Tannerella forsythia*, 262
- Tanzania, 331–32
- Taq polymerase, 19, 102
- targeted metabolomics, 109
- target gene amplicon sequencing, 101–2, 381. *See also specific target*
- target gene amplification, 105–6
- taste receptors, 71
- taurine, 283
- taxonomic distribution analysis (Qiita), 164–66
- taxonomic identities, assignment of, 121–24
- taxonomy, 12–17, 28, 53–54
- TB (tuberculosis), 347
- T cells, 182, 236–38
- in allergic response, 296–97, 299, 305
- development of, 243–44
- helper, 182, 226–27, 296–97, 308

- killer, 181–82
naive, 182, 305
regulatory (Tregs), 182–84, 240, 244, 297, 299–301, 305, 308, 312, 314
in stomach, 337
temperature
early Earth, 2
extremophiles, 1, 3, 18–19
PCR, 102
room, 353–55, 362
sampling protocols, 98
temporal core, 55–56
tertiary literature, 146
tertiary species, 394–95
testable hypothesis, 76, 87–88
testosterone, 224
therapies, microbiome-based, 39–41, 201–4, 228–29, 250. *See also specific therapy*
Theriot, Casey, 283
thermocycler, 102
thermophilic archaeans, 1, 19
thioalcohols, 73
Thion, Morgane, 185
third quartile, 134
Thomas, Lewis, 33
3' (three prime), 99
throat, 21, 58, 337, 360–61. *See also gut microbiome*
thymine, 99, 107
thymus, 236
thymus-dependent cells. *See* T cells
tight junctions (TJs), 246, 276
tipping points, 56
title (article), 147–49
TJs (tight junctions), 246, 276
TLRs (toll-like receptors), 283–84, 301
T lymphocytes. *See* T cells
TNF- α (tumor necrosis factor alpha), 283–84
toll-like receptors (TLRs), 283–84, 301
tooth plaque. *See* dental plaque
toxic black mold, 345, 355, 359
training, scientific, 86
trans-galactooligosaccharide, 229
transit time (gut), 379–80
transplantation
fecal microbiota, 39–41, 253, 260, 261, 290–91, 305, 314, 341, 377, 388
fetal microbiota, 202
gut microbiome, 268, 277
vaginal microbiome, 202, 340
transportation, 365–66
tree of life (ToL), 12–17, 19, 132
Tregs (regulatory T cells), 182–84, 240, 244, 297, 299–301, 308, 312, 314
Treponema denticola, 262
Trichinella, 29
trichinosis, 29
Trichomonas, 69
triglycerides, 275
trophic interactions, 188
tryptophan, 214, 220, 226
t-test, 139
tuberculosis (TB), 347
tumor microbiomes, 248–49
tumor necrosis factor alpha (TNF- α), 283–84
Tunapuco people (Andes), 333
Turcimonas, 247
Turvey, Stuart, 314
twin studies, 199, 275, 277
type 1 diabetes, 200, 245
type 1 T helper cells (Th1), 296–97, 308
type 2 diabetes, 26, 247, 280
type 2 T helper cells (Th2), 296–97, 308
typhoid fever, 333
U
ulcerative colitis (UC), 66–67, 248, 258–59
ultrasound, 104
ultraviolet (UV) light, 355–56, 359
umbilical cord, 181, 242
UniFrac (unique fraction) metric, 137–39, 141, 176–77
UniProt, 120
United Nations Human Settlements Programme, 365–66
University of California, San Diego, 46–47
University of Chicago hospital, 361–62
untargeted metabolomics, 109
uracil, 107
urban lifestyle, 315–16, 348–50, 357, 365–69. *See also* built environment; Western lifestyle
urease, 67, 336
Urey, Harold, 3–4
urinary tract infections (UTIs), 177–78
UV (ultraviolet) light, 355–56, 359
V
vaccines, 337
vacuoles, 222–23
vaginal delivery, 186–87, 191. *See also* birth mode study
vaginal microbiome, 176–79, 201
community state types, 177–78
diversity in, 255
DIY assessment kits, 381
dysbiosis, 179
functions of, 178–79
leash effect, 256
vaginal microbiome transplant (VMT), 202, 340
vaginal sampling, 97–98
vaginosis, bacterial, 179, 202, 255
vagus nerve, 211, 219, 228
VAMPS (Visualization and Analysis of Microbial Population Structures), 170
van der vossen, E. W. J., 280
variability, data, 134–35, 140
variable regions, 103
variables, 89, 95
Variola virus, 16
Veillonella, 307, 314–15, 328, 336
Veillonellaceae, 179
ventilation, 349, 353–55, 359–60, 365
Vermes (worms) phylum, 28
Verrucomicrobia, 194, 325
vertical loss, 336–37
Vidal, Daniel Ramón, 394
Viking coprolite, 326–27
violin plot, 247–48, 377
virome, 352
Virtue, Anthony, 284
virulence factors, 264–65, 310
viruses. *See also specific microbe*
asthma linked to, 309
in built environment, 351–52, 355, 365–66
characteristics of, 16–17
genomes, 103
gut microbiome, 63–64, 330–31
immune responses to, 237, 245 (*see also* immune system)
infant microbiome, 189
skin microbiome, 73
visualisations
diversity estimates, 139–41, 155–56, 163–64
microbial guilds, 280
phylogenetic trees, 12, 154, 322–23
Visualization and Analysis of Microbial Population Structures (VAMPS), 170
vitamins, 22, 258
Vivomixx, 229
VMT (vaginal microbiome transplant), 202, 340
volatile organic compounds, microbially produced (MVOCs), 364
voluntary (somatic) nervous system, 210
vomiting, during pregnancy, 201–2
vortex, 99
VSL#3, 289
Vuong, H. E., 185, 214–16
W
Wadwah, Arun, 203
waist-to-hip ratio (WHR), 279, 289
Walker, Allan, 389, 391
Wang, G. P., 261–62
Wang, Y., 392
Warinner, Christina, 327–29
Warren, J. Robin, 336
Washington University (St. Louis), 46
waste molecules, 22. *See also* metabolites; *specific substance*
waterborne microbes, 355–56, 363
water supply, 333–35
Watson, 38
weight, body, 274–79. *See also* obesity
Weizmann Institute, 46
Welch, Jessica, 42
Western lifestyle, 287, 303
allergic diseases linked to, 315–16
diet, 287, 303, 332–33, 335–36, 340, 365, 388, 392
environment (*see* built environment)
healthful microbiota development, 340–41
microbiota loss caused by, 334–38, 341
white blood cells, 237–38, 296–97. *See also specific cell type*
White HMP, 45
whole-genome reconstruction, 119
WHO (World Health Organization), 340, 390
WHR (waist-to-hip ratio), 279, 289
windows, 355, 359–60, 362
Woese, Carl, 13–17, 41–42, 96, 132

- workspace (Qiiita), 161–64, 167
- World Health Organization (WHO), 340, 390
- worm infections, 297, 308, 330–31, 381
- worms (Vermes) phylum, 28
- wound healing, 74–75, 240
- Wu, Gary, 67, 280
- X
- Xycrobe, 76
- Y
- Yamazaki, K., 281
- Yang, J., 225
- Yates, J.A.F., 328–30
- yeast
 - gut microbiome, 59, 381
 - skin microbiome, 73
 - vaginal microbiome, 179
- Yellowstone National Park, 19
- Yersinia pestis*, 348
- Yost, S., 265