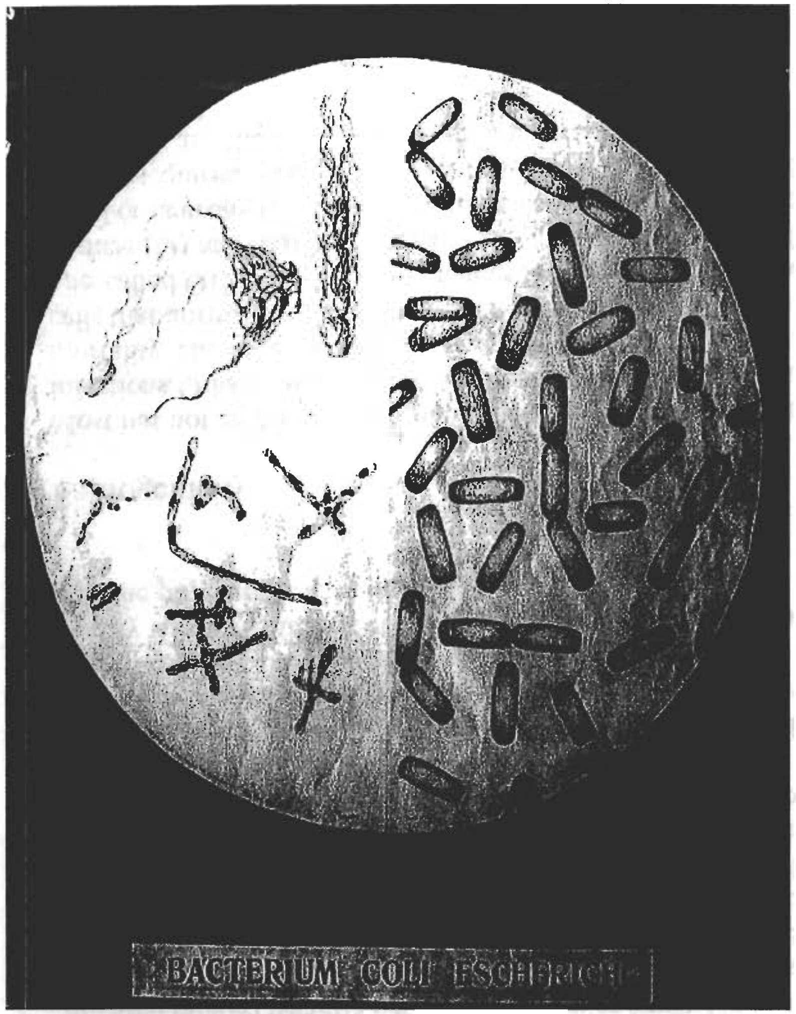

E. coli, circa 1900. A color poster used in lectures by Martinus W. Beijerinck, founder of the Delft School of Microbiology, drawn by his sister Henriëtte. Courtesy of Lesley A. Robertson.

1 Why *E. coli*?

Heritage

E. coli (*Escherichia coli*) is a bacterium that lives in your gut. It is one of the simplest and best understood living things, yet remarkably sophisticated. Fossil remains of bacteria are found in rocks that are billions of years old. Thus, creatures of *E. coli*'s kind are a thousand times older than we are. Yet we are closely related. *E. coli* stores genetic information in the same way that we do, reads that information in the same way, and synthesizes the same kinds of molecular tools for carrying out basic cellular functions. Many of the enzymes (catalytic proteins) designed for harvesting energy or crafting molecular building blocks have nearly identical structures. Thus, a number of early solutions to life's problems found by bacteria have been passed down to us.

Size and Shape

E. coli is very small. Its cells are rod-shaped, about 2.5 micrometers (μm) long—10,000 end to end span 1 inch—by about 0.8 μm in diameter, with hemispherical end caps. Imagine a microscopic cocktail sausage. As the cell grows, it gets longer and then divides in the middle. In a warm, rich nutrient broth, this takes only 20 minutes. The cell has a thin three-layered wall enclosing a relatively homogeneous molecular soup, called the cytoplasm. It does not have a nucleus, other membrane-enclosed organelles, or any cytoskeletal elements (rope-like or rod-like components) typical of higher cells, such as those composing the human body. However, some elements of this kind are built into the cell wall. And *E. coli* does have external organelles, thin straight filaments, called pili, that enable it to attach to specific substrata, and thicker, longer helical filaments, called flagella, that enable it to swim.

Habitat

E. coli lives a life of luxury in the lower intestines of warm-blooded animals, including humans. Once expelled, it lives a life of penury and hazard in water, sediment, and soil. *E. coli* is a minor constituent of the human gut. A typical stool contains as many as 10^{11} (100 billion) bacteria per cubic centimeter (cm^3). Up to 10^9 (1 billion) of these are *E. coli*. The majority of the other bacteria are strictly anaerobic, and thus unable to live in the presence of oxygen outside of the body. Cells of *E. coli* can live with or without oxygen, and thus survive (with luck) until they find another host. The particular species that we are going to learn about is called K-12. It lives in the laboratory. It was isolated in 1922 from the feces of a convalescent diphtheria patient and maintained at Stanford University, beginning in 1925, in a departmental culture collection. It has been in captivity for so long that it is no longer able to colonize the human gut. Fed well, however, it grows to a density similar to that of its siblings there, to some 10^9 cells per cm^3: the population of India in a spoonful.

Pathogenicity

Most but not all *E. coli* are friendly. But some cause urinary tract infections. Others cause diarrheal diseases and contribute to infant mortality. The latter strains carry islands of DNA not present in cells that normally inhabit the human gut. An exceptionally nasty one, called O157:H7—these are names for particular types of cell-surface (O) and flagellar antigens (H)—can cause severe or fatal renal or neurological complications. It also carries genes encoding toxins acquired from a relative, *Shigella*, a dysentery bacillus. But these are the exceptions. Common strains such as K-12 are our friends. Among other things, they help prevent invasion of the gut by yeast and fungi, organisms that are far less benign.

Preeminence

E. coli was first identified in the intestinal flora of infants by the German pediatrician Theodor Escherich (1885), who called it *Bacterium coli commune*. It was named for Escherich in 1920. For a review of Escherich's work, see Bettelheim (1986). *E. coli* was a useful organism for studies of bacterial physiology, because it was readily accessible, generally benign, and grew readily on chemically defined media. Thus, it came to be used for dissection of biochemical pathways; for studies of bacterial viruses, of bacterial and viral genetics, of the regulation of gene expression, of the nature of the genetic code, of gene replication, and of protein synthesis; and, in the present age of genetic engineering, for the manufacture of proteins of commercial value.

Motile Behavior

E. coli also has been a model organism for the study of the molecular biology of behavior, the primary focus of this book. *E. coli* swims. It modifies the way in which it swims to move toward regions in its environment that it deems more favorable. Each flagellum is driven at its base by a reversible rotary motor, driven by a proton flux. The cell's ability to migrate in a particular direction results from the control of the direction of rotation of these flagella. This control is effected by intracellular signals generated by receptors in the cell wall that count molecules of interest that impinge on the cell surface. What were the chemical and physical constraints that *E. coli* had to meet to devise such mechanisms? How does all of this work? Indeed, what is it like being a microscopic organism living in an aqueous environment? Can we understand *E. coli*'s world? The answers to these questions are fascinating, in part, because that world is so very different from our own. We will try to come to grips with the life of this distant yet intimate relative, and step, as it were, into *E. coli*'s shoes.

This is a cross-field endeavor. Physicists seek precise descriptions of how cells move and of the kinds of measurements that they make on their environment. Biochemists are interested in the structures and interactions of molecules that monitor the external environment, pass information from the outside to the inside of the cell, process sensory data, and effect a response. Geneticists identify the genes that specify these molecules and learn how these genes are turned on and off. With *E. coli*, the physics, biochemistry, and genetics are all readily accessible.

Simplicity

In grappling with such basic questions, one has to start somewhere, preferably with something simple. Compare the sizes and dates of origin of various nervous systems outlined in Fig. 1.1. We are astonishingly complex. The neocortex in humans is a multilayered sheet of cells, about 1 millimeter (mm) thick, almost large enough to cover your desk top. Each cubic millimeter contains about 40,000 cells, each making some 20,000 connections. The axons that make the connections in each cubic millimeter total several kilometers (km) long! A pyramidal cell in the olfactory cortex of the cat is shown in Fig. 1.2. *E. coli* is about the size of one synaptic spine, one of the little bumps seen on the enlarged views of the dendrites.

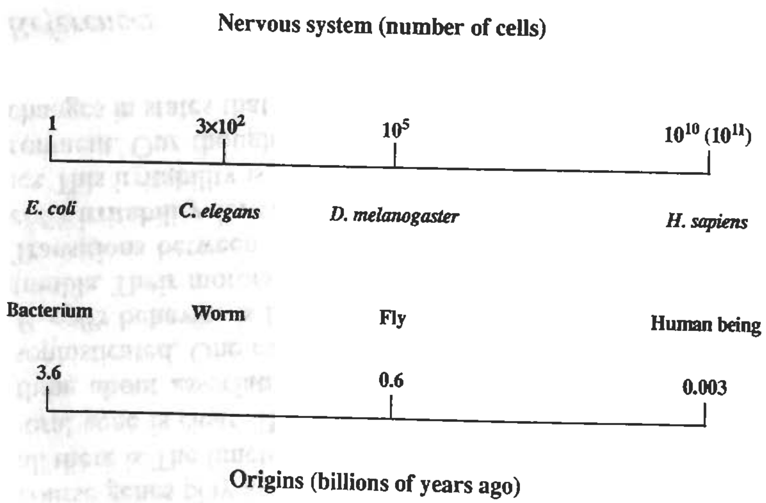

FIGURE 1.1. Approximate number of cells in different nervous systems, shown on a logarithmic scale. The estimate for humans is low. The species that are best understood are *E. coli*, *Caenorhabditis elegans*, *Drosophila melanogaster*, and *Homosapiens sapiens*, respectively. The scale is also historic: bacteria go back a few billion years, worms and flies a few hundred million, and humans only a few million.

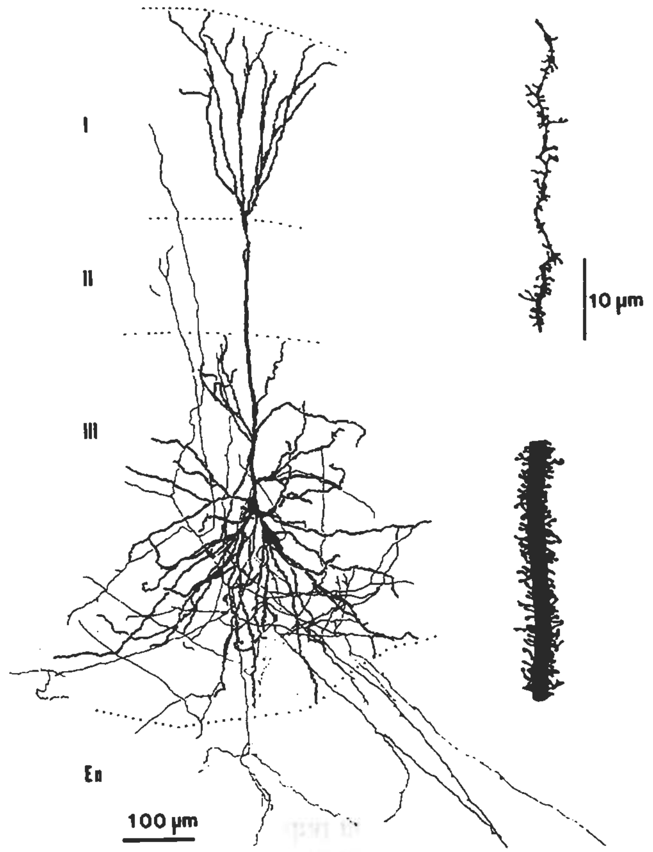

FIGURE 1.2. One pyramidal cell from the olfactory cortex of the cat. The main body of the cell is at the center, the dendrites (branched extensions that receive synaptic inputs) are at the top, and the axon (a filamentous extension that sends signals to other cells) is at the bottom. Segments of dendrites are shown enlarged at the right, covered with synaptic spines, each about the size of *E. coli*. (Tseng & Haberly, 1989, Fig. 2, reprinted with permission.)

To understand *E. coli*'s behavior, we will touch on a number of other topics of interest in cellular and molecular biology. The total extent of this knowledge is vast. For *E. coli*, the "bible" is a book called *Escherichia coli and Salmonella: Cellular and Molecular Biology* (Neidhardt et al., 1996). This is a two-volume work put together by 237 authors with the help of 10 editors comprising 155 chapters: 3008 pages in 8½ × 11-inch format. There is more information there than can be fathomed by any one human brain.

Genes and Behavior

When one starts with *E. coli*, debates about the importance of genes for behavior (Weiner, 1999) have an air of unreality. Of course genes play an essential role in behavior: for *E. coli*, that is all there is. The function of the product of essentially every behavioral gene is clear. There is no evidence that *E. coli* knows anything about associative learning, yet its behavior is remarkably sophisticated. One can even approach the question of free will. *E. coli's* behavior is fundamentally stochastic: cells either run or tumble. Their motors spin either counterclockwise or clockwise. Transitions between the latter states are thermally activated. *E. coli's* irritability derives from the basic laws of statistical mechanics. This irritability is modulated by the cell's reading of its environment. Our thoughts might be triggered in the same way, by changes in states that are thermally activated.

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2
Larger Organisms

Seventeenth Century

Antony van Leeuwenhoek was the first person to see bacteria, and it was their motion that captured his attention. However, he was not the first person to use a microscope or to describe cells. But the single-lens instruments that he made himself had fewer aberrations than the compound instruments of his day, so he was able to see more. And his curiosity was insatiable. His work on little animals—he called them animalcules—is available to the modern reader through translations from the archaic Dutch by the British microbiologist Clifford Dobell (1932), who published them on the 300th anniversary of van Leeuwenhoek's birth. Van Leeuwenhoek described what he saw in letters written in ink, still jet black, sealed with red wax, and sent from Delft to London, to Henry Oldenberg, the secretary of the Royal Society. Oldenberg translated bits and pieces and published them in the *Transactions of the Royal Society*. My favorite is the 18th letter in which van Leeuwenhoek describes animalcules in water from his well. He was curious about the effect that pepper might have, so he ground up some in a blue porcelain pot and mixed it in. A number of larger animalcules died out, until on 6 August 1676 he saw large numbers of very small ones:

> I now saw very plainly that these were little eels, or worms, lying all huddled up together and wriggling; just as if you saw, with the naked eye, a whole tubful of very little eels and water, with the eels a-squirming among one another: and the whole water seemed to be alive with these multifarious animalcules. This was for me, among all the marvels that I have discovered in nature, the most marvellous of all; and I must say, for my part, that no more pleasant sight has ever yet come before my eye than these many thousands of living creatures, seen all alive in a little drop of water, moving among one another, each several creature having its own proper motion.