Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Chapter 8

Changing how we think about infectious diseases

Section 8.1 Abandoning Koch's postulates

It isn't that they can't see the solution. It's that they can't see the problem.

G.K. Chesterton

Robert Koch's postulates, published in 1890, are a set of criteria that establish whether a particular organism is the cause of a particular disease. Today, Koch's postulates are taught in high school and college classrooms as a demonstration of the rigor and legitimacy of clinical microbiology. To review, the four postulates of Koch are as follows:

–1. The microorganism must be found in the diseased animal, and not found in healthy animals.
–2. The microorganism must be extracted and isolated from the diseased animal and subsequently grown in culture.
–3. The microorganism must cause disease when introduced to a healthy experimental animal.
–4. The microorganism must be extracted from the diseased experimental animal and demonstrated to be the same microorganism that was originally isolated from the first diseased animal.

Let's go over these four postulates once more, this time explaining how they ignore or contradict what we now know about infectious diseases.

–1. The microorganism must be found in the diseased animal, and not found in healthy animals.

As previously discussed, lots of pathogenic organisms are found in healthy animals, producing disease in only a tiny fraction of the individuals who are infected. For example, Bartonella species can live in blood without causing disease, producing an asymptomatic bacteremia in the wide assortment of animals that they may infect. Hence, we can no longer assume that blood samples from healthy animals are sterile. The mechanism of Bartonella transmission from animal to animal is not fully understood, but arthropod vectors (ticks, fleas, and...
lice) are suspected, as well as scratches and bites from infected animals (e.g., cats and rats) [1] [Glossary Vector].

There are now about eight species of Bartonella that are known or suspected to be human pathogens. Until just a few decades ago, only two such species were known. Today, the species of Bartonella, which are ubiquitous among mammals, are known or suspected to cause a variety of phenotypically dissimilar diseases [1]:

- Bartonella bacilliformis → Carrion disease
- Bartonella quintana → Bacillary angiomatosis, trench fever, endocarditis
- Bartonella henselae → Bacillary angiomatosis, cat-scratch disease, peliosis hepatis B. henselae
- Bartonella clarridgeiae → Cat-scratch disease [2]
- Bartonella elizabethae → Endocarditis
- Bartonella vinsonii var berkhoffii → endocarditis
- Bartonella vinsonii var arupensis → fever and a valvulopathy
- Bartonella grahamii → uveitis

The precise diagnosis of Bartonella species in human blood and lesions has provided us with the names of infectious organism associated with a number of diseases, but this new knowledge has not shed much light on why Bartonella can circulate in the blood without causing any reaction, for indefinite periods of time, or why any given Bartonella species may be associated with any of several diverse clinical manifestations. Furthermore, Koch's third postulate fails miserably for genus Bartonella; injecting any of these Bartonella species into experimental animals, will more than likely produce no symptoms.

2. The microorganism must be extracted and isolated from the diseased animal (and grown in culture).

Many pathogens do not grow in nutrient medium culture. This applies generally to common Mollicute bacteria, including Erysipelothrix, Mycoplasma, and Ureaplasma. This would also apply to viruses, none of which grow in cell-free media. Paradoxically, some of the organisms known to produce bacteremias in human blood grow very poorly in blood cultures, and this would include the aforementioned Bartonella species and the HACEK organisms [1, 3]. The HACEK organisms are a group of proteobacteria, found in otherwise healthy individuals, that are known to cause some cases of endocarditis, especially in children, and which do not grow well in culture. The term HACEK is created from the initials of the organisms of the group: Haemophilus, particularly Haemophilus parainfluenzae; Aggregatibacter, including Aggregatibacter actinomycetemcomitans and Aggregatibacter aphrophilus; Cardiobacterium hominis; Eikenella corrodens; and Kingella, particularly Kingella kingae.

3. The microorganism must cause disease when introduced to a healthy experimental animal.
Again, some of the worst microorganisms will not produce disease in healthy animals. To confuse matters further, we now have examples of nonliving agents that will produce transmissible disease in healthy animals (prions).

This third postulate of Koch presumes that each occurrence of an infectious disease has a particular organism that is “the cause” of the disease. We must return here to our often-repeated theme that diseases do not have “a cause,” and infectious diseases are no exception to the rule that pathogenesis is a multistep process. We have already seen that myocardial infarction results from a multitude of conditions that occur through time. In some cases, the last event is infectious, wherein a focal bacterial endocarditis precipitates a thrombus that blocks a narrowed coronary artery. It would be folly to believe that the sequence of events that lead to a myocardial infarction can be precipitated simply by injecting an organism into an animal. Later in this chapter, we will see two examples of rare infections for which several conditions must prevail before a disease emerges [4, 5].

4. The microorganism must be extracted from the infected experimental animal and demonstrated to be the same microorganism that was originally isolated from the original diseased animal.

Many infections, considered the underlying cause of a disease, are absent from the lesions that ultimately develop. For example, Group A streptococcus infection is considered to be the underlying cause of rheumatic fever. The infection is long gone prior to the appearance of the valvular and endocardial lesions of rheumatic fever. As another example, several species of human papillomavirus are considered to be the underlying cause of nearly all cases of squamous carcinoma of the uterine cervix. Morphologic cytopathic effects are visible in the earliest precancers that precede the development of invasive carcinoma. The cancers, which may occur years following the early papillomavirus infections, may lack recoverable virus.

Let’s look at an example of an infectious disease that violates every one of Koch’s postulates. Whipple disease, previously a disease of unknown etiology, is characterized by organ infiltration with foamy macrophages (i.e., specialized reticuloendothelial cells that “eat” bacteria and debris). The organ most often compromised in Whipple disease is the small intestine, where infiltration of infected macrophages in the lamina propria (i.e., a strip of loose connective tissue subjacent to the epithelial lining of the small intestine) causes malabsorption. Whipple disease is rare. It occurs most often in farmers and gardeners who work with soil.

Whipple disease was first described in 1907 [6], but its cause was unknown until 1992, when researchers isolated and amplified, from Whipple disease tissues, a 16s ribosomal RNA sequence that could only have a bacterial origin [7]. Based on molecular features of the ribosomal RNA molecule, the researchers
assigned it to Class Cellulomonadacea, and named the species Tropheryma whipplei, after the man who first described the disease, George Hoyt Whipple.

Particularly noteworthy, in the case of Whipple disease, is that Koch's postulates never came close to being satisfied. For the experimentalist, the most important of Koch's postulates require the extraction of the organism from a lesion (i.e., from diseased, infected tissue), the isolation and culture of the organism in the laboratory, and the consistent reproduction of the lesion in an animal injected with the organism. In the case of Whipple disease, none of these criteria were satisfied. The consistent identification in Whipple disease tissue of a particular molecule, characteristic of a particular species of bacteria, was deemed sufficient to establish the infectious origin of the disease.

In the general scheme of events, bacteria in the human body are eaten by macrophages, wherein they are degraded. In the case of T. whipplei, only a small population of susceptible individuals lack the ability to destroy T. whipplei organisms. In susceptible individuals, the organisms multiply within macrophages. When organisms are released from dying macrophages, additional macrophages arrive to feed, but this only result in the local accumulation of macrophages bloated by bacteria. Whipple disease is a good example of a disease caused by an organism but dependent on a genetic predisposition, expressed as a defect in innate immunity; specifically, a reduction of macrophages expressing CD11b (also known as macrophage-1 antigen) \[8\]. Whipple disease cannot be consistently reproduced in humans or any other animals, because it can only infect and grow in a small portion of the human population.

As we learn more and more about the complexity of disease causation, formerly useful paradigms, such as Koch's postulates, seem burdensome and useless. When we encounter rare diseases of infectious cause, we might expect to find that the pathogenesis of disease (i.e., the biological steps that lead to a clinical phenotype) may require several independent causal events to occur in sequence. In the case of Whipple disease, the infected individual must be exposed to a soil organism, limiting the disease to farmers and gardeners. The organism, residing in the soil, must be ingested, perhaps by the inhalation of dust. The organism must evade degradation by gut macrophages, limiting disease to individuals with a specific type of defect in cell-mediated immunity, and the individual must have disease that is sufficiently active to produce clinical symptoms. It is unlikely that we could reproduce a complex sequence of steps, leading to a disease, by simply inoculating an organism into an experimental animal [Glossary Underlying cause, Proximate cause, Root cause].

Side-stepping Koch's postulates has become de rigueur in the practice of modern medicine. For example, the United States has experienced a recent increase in cases of acute flaccid myelitis, a rare disease of children \[9\]. Diagnosis is based on a metagenomic analysis (i.e., culture-independent sequence searches conducted on an assemblage of microbial gene sequences in a biologic sample)
of DNA obtained from nasopharyngeal swabs. The organism that is present in most of the examined cases is enterovirus-D68, and this virus is the presumed causal organism of acute flaccid myelitis, until proven otherwise.

Genotyping species of organisms has become quite easy, but there are many millions of microorganism species, and it may never be feasible to complete a database of genome sequences of all living species. Though the number of individual species is too large to sequence, we can do a fair job at sequencing most of the different genera of living species. We now have a fairly accurate way of identifying the genus of any organism found within a tissue sample, by sequencing its ribosomal RNA and comparing the sequence against references sequences in public databases [10–13]. There are limitations to this technique, but when we combine our analysis of ribosomal RNA with our accumulated knowledge of clinical features of the infection, we can often arrive at candidate pathogen [11, 14, 15].

Modern medicine has changed the vocabulary of infection. Familiar terms such as primary pathogen, opportunistic infection, and immunocompetent patient need to be reexamined in light of what we have come to know. Even a fundamental concept, such as “the organism causing the disease” should probably be abandoned in light of the multistep pathogenesis of all diseases. Because a microorganism may contribute to the pathogenesis of a disease at a single moment of time, long before the disease becomes clinically manifest, we can expect to see cases in which screening tests for a putative causal organism will be negative in affected patients [16]. Koch, in his own time, understood the practical limitations of his postulates. Maybe it's time to reconsider Koch's postulates in light of the analytic methods now available that assign a taxonomic class to an infective organism, without isolating or characterizing the agent [17].

Section 8.2 Prion diseases: Fulfilling Koch's postulates, but without an organism

*Life is a concept.*

Patrick Forterre [18]

Everyone has heard the aphorism: “One bad apple spoils the bunch.” This trite adage seems to be the principle underlying the prion diseases. A prion is a misfolded protein that can somehow serve as a template for proteins of the same type to misfold, producing collections of nonfunctioning protein globs that accumulate, causing cells to degenerate. The cells of the body that are most vulnerable to prion-produced disease are the neurons of the brain. The reason for the particular sensitivity of neurons to prion disease relates to the limited ability of neurons to replicate (i.e., to replace damaged neurons with new neurons), and to repair damage occurring in their uniquely long cytoplasmic extensions (e.g., axons).
The term prion was introduced in 1982, by Stanley Prusiner [19]. Prions are the only infectious agents that contain neither DNA nor RNA. Though few scientists would consider prions to be organisms, living or otherwise, they are included here to ensure that readers are aware of these biological agents. Prions are not confined to mammals, and not confined to the brain [20]. They have been observed in fungi, where their accumulation does not seem to produce any deleterious effect, and may even be advantageous to the organism [21].

One peculiar feature of the prion diseases is that they fulfill Koch’s postulates. Let’s review Koch’s postulates, substituting the word “agent” for “microorganism.”

1. The agent must be found in the diseased animal, and not found in healthy animals.
2. The agent must be extracted and isolated from the diseased animal (and subsequently grown in culture).
3. The agent must cause disease when introduced to a healthy experimental animal.
4. The agent must be extracted from the diseased experimental animal and demonstrated to be the same agent that was originally isolated from the first diseased animal.

Allowing a bit of leeway for the interpretation of these four requirements, in the particular case of prion molecules, we can contrive a fairly convincing argument that the prion agent satisfies all of Koch’s postulates, and that prions are the infection causing Creutzfeld-Jakob disease in humans, scrapie in sheep, and bovine spongiform encephalitis in cows. Referring to the requirements, we have a large literature in which the transmissibility of prion extracts from human to nonhuman animal, and from nonhuman animal to nonhuman animal has been demonstrated [22, 23]. The prion agents have been extracted and studied. Prions can be examined in growing yeast cultures, and the propagation of prions can be observed in controlled, experimental settings [24–26]. In culture and in ex vivo systems, we can now study how various cellular processes may participate in the conversion of normal prion proteins into infectious prion agents [26, 27].

The key difference between prion infections and infections caused by living microorganisms is that prions propagate without replicating. It would seem that the mere presence of a prion molecule in company with normal prion proteins is sufficient to produce a characteristic misfolding of the normal form of the protein, which can propagate to other normal prion proteins in the cell, and from one cell to another.

Because the prion protein, in its proper molecular configuration, is a normal constituent of cells, conventional terminology seeks to avoid confusion by labeling the infectious prion protein as “PrP(Scr)” (i.e., prion protein as it might occur in scrapie) and the normal prion protein as either “PrP” or as “PrP(C)” (i.e., prion protein as it might occur in normal cells).
The normal prion protein (PrP(C)) serves many different purposes, including the regulation of myelin maintenance, and seems to have a role in various processes wherein cellular differentiation is controlled [28]. It is significant that PrP(C) knockout mice [i.e., mice with no PrP(C)] are essentially normal at birth, and survive over the following months with only marginal behavior deficits [29]. Animals that lack PrP(C) are completely resistant to all forms of prion-induced disease, simply because they lack any protein that can be converted to a pathogenic form. Hence, it is important to understand the role of PrP(C), if we plan to develop drugs that treat or prevent prion diseases based on targeting the PrP(C) molecule.

Unlike most of the infectious diseases we have discussed so far, the prion diseases occur in three pathogenetic forms [30]:

- **1. Transmitted.** Caused by an infectious prion (e.g., PrP(Scr)) that is introduced into a host.

  In the prion disease known as Kuru, members of the Fore tribe in New Guinea practice a form of ritualistic cannibalism. Kuru was contracted when tribe members ate the brains of individuals harboring the Kuru infection. When the practice of ritualistic cannibalism was stopped, the incidence of Kuru fell.

  In the case of the so-called variant Creutzfeldt-Jakob disease, the disease is contracted after individuals eat the meat of cows infected with bovine prions.

  In the case of iatrogenic Creutzfeldt-Jakob disease, disease is contracted when prion-contaminated blood products (e.g., human growth hormone preparations) or tissues (e.g., dura mater grafts, pituitary extracts) are injected or transplanted into recipient patients.

- **2. Genetic**

  Genetic prion disease results from inherited germ-line mutations of the PRNP gene (i.e., the gene that codes for PrP(C)). The genetic diseases include familial Creutzfeldt-Jakob disease, fatal familial insomnia, and Gerstmann-Straussler-Scheinker disease.

- **3. Sporadic**

  Little is known about sporadic prion diseases, which includes sporadic Creutzfeldt-Jakob disease, sporadic fatal insomnia, and variable protease-sensitive prionopathy. The two mechanisms that seem to be most credible involve: (1) a somatic mutation of the PRNP gene within a single cell, which yields new molecules of PrP(Scr), which propagate through the nervous system to produce a prionopathy and (2) an acquired conformational change of PrP(C) into PrP(Scr), which then propagates to produce a prionopathy [26]. The clinical form of the prionopathy that would result from either of these hypothetical mechanisms would be somewhat dependent on how the disease
spreads through the brain [31]. This, in turn, may depend on where in the central nervous system (CNS) the process begins (i.e., which neurons are the first to be altered).

In all the three pathogenetic forms, the process seems to take decades to develop. In the case of kuru, infections may require as long as 50 years to become clinically evident [32]. All forms of prionopathy are progressive, with clinical signs dominated by decreasing cognitive ability and impaired motor coordination. Currently, all of the prion diseases are 100% fatal. All forms of prionopathy lead to the same morphologic changes in cells, this being a spongiform encephalopathy [33] (Fig. 8.1).

When we think of the prionopathies as a disease of a self-propagating misfolded protein that accumulates in neurons, and we stop thinking in terms of any particular protein as being the defining agent of disease, then we begin to see additional diseases that might fit the definition of a prionopathy. In particular, it has been suggested that the disease known as multiple system atrophy (MSA) with parkinsonism may qualify. MSA is a CNS disorder that develops very slowly, and produces a progressive loss of autonomic nervous system function. In MSA, there is always an accumulating ball of sticky, misfolded alpha-synuclein protein, observed as cytoplasmic inclusion bodies in glial cells. In 2015, it was shown that a neurodegenerative disease could be transmitted to transgenic mice expressing normal human alpha-synucleoprotein, after injection with a brain homogenate prepared from human MSA cases [34]. Hence, MSA can be considered a type of prionopathy produced by an altered protein other than PrP(Scr).

**FIG. 8.1** Spongiform encephalopathy (brain tissue section, hematoxylin-eosin stain). Numerous vacuolated neurons are seen (i.e., spongiform change), along with small degenerate cells and scattered inflammatory cells. *(Source, a public domain image prepared at the U.S. Department of Agriculture, by Dr. Al Jenny.)*
If we accept that prion diseases can be produced by self-propagating proteins other than PrP(Scr), then what other diseases might we now investigate as potential prion diseases. Without diverting too far from the subject of this book, we can say that there seems to be a newly described class of diseases characterized by misfolded self-propagating and, under some circumstances, transmissible proteins, which may include the prionopathies, the tauopathies (including Alzheimer disease), and the amyloidoses [31, 35–37].

Section 8.3 Diagnostic challenges

In fact, diseases that exhibit simple Mendelian patterns of inheritance tend to be rare. Rather, complex diseases arise from numerous genetic and environmental factors working together.

Johanna Craig [38]

Diagnosis of infectious disease isn't easy; the chief problem being that patients with early signs of infection will often present with nonspecific symptoms that could accompany the common cold, or the so-called “intestinal” flu, or as any other common condition producing generalized malaise and mild fever. American health-care workers will not soon forget the first US case of Ebola. Thomas Duncan first arrived at the Emergency Room of the Texas Health Presbyterian Hospital, on the evening of September 25, 2014, complaining of fever, abdominal pain, dizziness, and nausea. After a few hours in the emergency room, Mr. Duncan was discharged with the diagnosis of sinusitis and a prescription of antibiotics. Mr. Duncan returned to the same emergency room 2 days later, much sicker. It turns out that Mr. Duncan had arrived in the United States just days previously, after having resided in Liberia, Africa. This time around, the correct diagnosis of Ebola virus infection was rendered. On October 8, Mr. Duncan died from Ebola virus hemorrhagic fever. Before his death, two health-care workers from the hospital were infected; they were the first to contract Ebola virus infection while on US soil. Both were diagnosed in early stages of the disease, and both survived.

Let's list some of the reasons why diagnosing an infectious disease can be very difficult, even for the most astute physicians.

- Huge variety of potential clinical presentations for a single organism.

As mentioned, the clinical presentation of an infectious disease is often nonspecific and may closely mimic other infectious and noninfectious conditions, particularly in the early stages of the disease. Many infections produce mild, self-limited disease, and are not worth investigating clinically.

Infectious diseases may closely mimic one another, leading the unwary physician to mistakenly apply a common diagnosis to an uncommon infection. For example, Neorickettsia sennetsu causes a rare disease that closely mimics infectious mononucleosis, a common disease caused by the Epstein Barr virus. As another example, patients with HIV/AIDS are susceptible to
two different skin conditions that closely resemble one another: bacillary angiomatosis and Kaposi sarcoma. Bacillary angiomatosis is an exaggerated overgrowth of small vessels of the skin, produced by infection with species of Bartonella (i.e., B. quintana and Bartonella henhenselae). Kaposi sarcoma is a cancer of vascular origin (i.e., a type of angioscarcoma) that is caused by Herpesvirus-8. Both bacillary angiomatosis and Kaposi sarcoma look very similar by gross examination and by microscopic examination with standard histological stains (i.e., Hematoxylin and eosin stains). Both bacillary angiomatosis and Kaposi sarcoma occur in AIDS patients, but their respective prognoses and treatments are very different. The correct diagnosis requires an astute pathologist who understands and anticipates the rare and the common causes of vascular proliferative lesions in immune-compromised patients [Glossary Hematoxylin and eosin].

The list of nonpathogenic organisms is growing shorter.

In 1950, the United States navy conducted an ill-advised experiment on the unsuspecting citizens of San Francisco [39]. Large hoses sprayed out a fog of Serratia marcescens and Bacillus globigii to determine whether this kind of dispersal mechanism might be an effective way of exposing a large population to a biological warfare agent. S. marcescens and B. globigii were used because these organisms were considered to be completely harmless. From the viewpoint of the navy, this experiment was a success in that the bacteria were distributed widely over the Bay area, delivering a small dose of organisms to the target population.

The US navy declared a victory for itself in its undeclared war on San Francisco. The generals did not suspect that there would be any collateral damage. Unexpectedly, a small epidemic of S. marcescens infections was reported among the exposed population. In all, 11 individuals required hospitalization and one individual died. No cases of S. marcescens infections had been previously reported in the hospital where the death occurred, and no clusters of S. marcescens infections had occurred following the epidemic that coincided with the navy's experiment. It seems that S. marcescens, though harmless to most individuals, was pathogenic to a tiny subpopulation of the population. Presumably, genetic susceptibility accounted for the shift from harmless organism to deadly pathogen, in at least one hapless victim. At the time, nobody understood why this mini-epidemic had hit San Francisco. It was not until 1976, when the navy experiment was declassified, that the truth came to light.

What does it take to be a pathogen? Basically, any organism that can grow in human blood, in human tissues, on human endothelial or serosal surfaces, or in any internal sources of fluid (i.e., joint fluid, pleural fluid, and urine) can be a pathogen. Even organisms that don't grow well in human blood and tissues can be pathogenic in a select group of individuals.
The proteobacteria Eikenella corrodens is a normal inhabitant of the mouth that is harmless under most, but not all, conditions. When the organism is mechanically forced into the blood stream (e.g., by accidentally biting through the oral mucose while eating), it can produce a cellulitis or a bacteremia with endocarditis. It is included with the HACEK group of endocarditis-producing organisms. E. corrodens can also produce disease in diabetics and immunocompromised individuals, apparently without inadvertent biting. Genus Prevotella contains oral inhabitants that can produce plaque, halitosis, and periodontal disease. Prevotella dentalis, like E. corrodens, produces the so-called bite infections, wherein oral bacteria are inoculated, by a bite or abrasion, into adjacent tissues, producing abscesses, wound infections, or bacteremia. P. dentalis bacteremia can lead to disseminated infections.

We now encounter instances wherein once-obscure organisms have risen to the level of common pathogens. Blastocystis hominis was a eukaryotic organism seen as an incidental finding, of no known significance, on stool examinations. For a long time, the proper taxonomic classification of this organism was undetermined, and it has been variously referred to as a yeast, a fungus, an amoeba, a flagellated single-celled eukaryote, or a sporozoan (former name for apicomplexan), at various times [40]. Today, Blastocystis is considered a genus belonging to the heterokonts, and is the only heterokont known to produce a human infection. Infection follows ingestion of the cyst through the fecal-oral route. Most infections do not result in any clinical symptoms, but sometimes, a syndrome mimicking irritable bowel syndrome may occur. Among individuals who have microscopic school examinations, for any reason, up to 25% of specimens contain Blastocystis [41]. Because Blastocystis is found in the stools of healthy individuals, the finding of the organism in the stool of a symptomatic patient does not necessarily establish a causal relationship. Treatment with metronidazole, an antibiotic effective against eukaryotes and prokaryotes, has its advocates [42, 43], but can we do better? Blastocystis is the only heterokont known to cause disease in humans, and we know almost nothing about the heterokonts that would help us design a drug that would be effective against Blastocystis. Our experience with Blastocystis reminds us that as we may discover pathogens belonging to classes of organisms that were previously thought to be devoid of infectious agents. In such cases, we will need to find new, class-specific antibiotics. Let's look at another example wherein a taxonomic change requires us to develop a new approach to treatment.

Growing number of rare infectious diseases

While the list of common infections is growing slowly, the list of rare infectious diseases is exploding. Improvements in the taxonomic designations of infectious organisms, the availability of highly advanced reference laboratories capable of accurately identifying infectious organisms, increases in the number of immune-compromised patients susceptible to infections by organisms that are
not otherwise pathogenic, and the ease with which infections can be transported from place to place throughout the modern world, have all contributed to the increase in newly encountered rare infectious diseases.

A source of new, rare infections is invasive instruments and catheters, particularly those that dwell inside the body for prolonged periods, such as bladder catheters, ventilator tubes and pulmonary assistive devices, shunts, venous and arterial lines, and indwelling drains and tubes. These devices provide a path of entry to a wide variety of organisms that would otherwise be halted by normal anatomic barriers. Of the different organisms that invade via indwelling devices, most are bacteria. Fungal disease has occurred in adults who receive intravenous parental nutrition; the fungi growing in the lipid-rich alimentation fluids [44]. The bacterial organisms that invade via indwelling devices include species of Pseudomonaiales, Bacillales, Bacteroidetes, Fusobacteria, and Legionallales. Despite their taxonomic diversity, all these organisms seem to share an ability to secrete biofilms over surfaces, and to glide through the biofilms they create. Biofilms are invisible, slimy coatings, composed of polysaccharides and cellular debris that provide sanctuary from the antibacterial sprays and solutions used in hospitals. Bacterial species that can glide through a biofilm can track a catheter into the body. For example, Staphyloccocus epidermidis is a commensal organism that lives on human skin. Some of the organisms now known to cause catheter-associated hospital infections were previously obscure [e.g., Leclercia adecarboxylata [45]. The list of such organisms is constantly growing.

Most of the newly recognized rare infections have a fungal origin. Approximately 54 fungi account for the vast majority of fungal infections, but the total number of fungi that are pathogenic to humans is much higher, and growing rapidly [46]. With advanced typing techniques, it is now possible to identify new species of fungi. For example, 34 new species of Aspergillus have been isolated from clinical specimens Aspergillus fumigatus, a common cause of severe pulmonary infections in immune-compromised patients [46]. We can now identify the specific fungal species responsible for cases that would formerly have been impossible to diagnose accurately [47].

– Properly classifying infectious diseases

For a long time, brain infections due to Naegleria fowleri were lumped with the amoebic encephalitides, and Naegleria was classified as an Acanthameoba, under Class Amoebozoa. We now know that N. is a member of Class Percolozoa, and the encephalitis caused by Naegleria fowleri is a percolozoan encephalitis. Why is this significant? Naegleria happens to be the only pathogenic species in Class Percolozoa, and we know almost nothing about the Percolozoan pathways that might render Naegleria sensitive to antibiotics. Currently, Naegleria encephalitis is treated as though it were one of the amoebic encephalitides, with
amphotericin B. With or without amphotericin B treatment, nearly all cases of percolozoan encephalitis are fatal [48]. Clearly, we need to learn a lot more about the biological pathways of members of Class Percolozoa, so that we can design a class-based strategy to prevent and treat Percolozoan encephalitis. Most importantly, we need to stop pretending that Naegleria is a genus in Class Amoebozoa, simply because it looks like an amoeba.

In the past, the rational basis for splitting a group of organisms into differently named species required, at the very least, heritable functional or morphologic differences among the members of the group. Gene sequencing has changed the rules for assigning new species. For example, various organisms with subtle differences from Bacteroides fragilis have been elevated to the level of species based on DNA homology studies. These include Bacteroides distasonis, Bacteroides ovatus, Bacteroides thetaiotaomicron, and Bacteroides vulgatus [3, 49].

There is a growing list of infections known to be resistant to most types of antibiotic treatments. For the most part, these are not rare diseases; they are common diseases that happen to be resistant to antibiotics. Examples are resistant strains of Staphylococcus aureus, Acinetobacter baumanii, and Klebsiella pneumoniae. New techniques for subtyping strains based on antibiotic resistance or susceptibilities are being developed and will probably replace older agar growth tests [50] [Glossary Serotype, Serovar].

Genus Plasmodium is responsible for human and animal malaria. About 300–500 million people are infected with malaria worldwide. About 2 million people die each year from malaria [51, 52]. There are several hundred species of Plasmodium that infect animals, but only a half dozen species are known to infect humans [52]. Newly emerging species, causing human disease, may arise from animal reservoirs. For example, Plasmodium knowlesi, a known cause of malaria in macaque monkeys, has emerged as a cause of human malaria in Southeast Asia, where it has grown in incidence to the point that it currently accounts for about two-thirds of malarial cases in this region. Malaria is commonly diagnosed with an antigen test developed against the common forms of human plasmodia (e.g., Plasmodium falciparum). Patients with P. knowlesi may have a negative reaction to the standard Plasmodium antigen test [53]. If this were to occur, a P. knowlesi infection may go undiagnosed, and the patient might not be provided with needed antimalarial medication. Careful examination of blood will usually indicate the presence of parasites in the cases of P. knowlesi malaria, and a specific diagnosis can be confirmed with advanced molecular tests. Here is an example of a previously rare infection, emerging as an endemic infection, whose diagnosis can be missed with testing methods designed for the common forms of disease.

Technical advances in the past decade have greatly improved our ability to diagnose species and subtypes (i.e., serotypes or serovars) [54, 55]. A striking case in point was reported in 2014, when DNA was extracted from the spinal fluid of a child with meningitis of undetermined cause [56]. After 2 days of
sequencing and computer searches through multiple DNA databases, a match was found with Leptospira. The patient was started on penicillin, and recovered soon thereafter. In this case, modern genetic analysis helped rescue a gravely ill child. Nevertheless, our ability to diagnose a specific species present within a sample specimen (e.g., tissue, blood, body fluid) will always be limited by our incomplete pathogen database. There are just too many potential pathogens to include every organism's genome, and the list of pathogens keeps growing longer. Fortunately, microbial taxonomy provides some relief to this seemingly intractable problem.

While the number of potential pathogenic organisms is large and unknowable, the number of genera that contain pathogens is quite small. A genomic database that provides the characteristic sequences for every genus of pathogenic organism would, in theory, allow us to determine whether a clinical sample contains organisms belonging to a genus that is known to contain known pathogens. Such information would be helpful in several ways:

- If clinical findings suggest a particular pathogen, then knowing that the clinical sample contains organisms belonging to the genus of the suspected pathogen would provide a level of corroboration for our clinical impression.
- If genetic analysis of the clinical sample indicates that the sample contains organisms belonging to a single genus known to contain pathogens, then we might consider initiating treatment with a drug that is known to be effective against organisms of the genus.
- If genetic analysis of the clinical sample indicates that genetic analyses of multiple clinical samples fail to match against any known genus of micro-organism, including viruses, then the clinician might begin to search for noninfectious causes of the patient's condition.

In point of fact, the genus of an organism can often be determined by examining the sequence of the rRNA gene, and such an approach has proven useful in the diagnosis of bacteria and fungi [2, 10–14]. Not only has this methodology proven useful in identifying the genus of organisms in a sample, but an extension of the method has also been developed to locate individual organisms within a mixed clinical sample of organisms. Roughly, here is how it works [57, 58]:

1. Genus-specific rRNA oligonucleotides are prepared as fluorescent probes.
2. The rRNA probes are incubated with a mixture of organisms.
3. The target organisms are detected (via fluorescence in situ hybridization).
4. The fluorescent organisms are extracted and examined by ancillary methods (e.g., scanning electron microscopy, culture) to determine the species name of the organism.
It should be noted that genetic analyses, powerful as they are, can often be circumvented by clinical acumen. In the aforementioned case of gene-based diagnosis of childhood meningitis caused by leptospirosis, we note that an astute clinician may have reached the same diagnosis sooner, and without state-of-the-art technology. Empirically, it is known that children with meningitis whose cerebrospinal fluid (CSF) specimen does not grow organisms will have leptospirosis in about a third of cases [59]. The diagnosis could be confirmed quickly using older technology that directly tested for the presence of the suspected organism (rather than laboriously searching through a large database) [59]. We should be prepared to accept that there will always be circumstances wherein a gene-based diagnosis must give way to common sense.

- Some diagnoses can only be established by highly specialized laboratories. Some of these laboratories were created to find the cause of epidemics, not of isolated illnesses. Under normal conditions, empiric treatments may be a practical alternative to precision diagnoses.
- Sometimes, it is faster and more effective to deduce a diagnosis than to resort to sequence analyses.
- Sometimes, precision diagnosis can be overly sensitive, detecting sequences of contaminants or detecting organisms that are present in such low numbers that they could not have caused the disease.
- Sometimes precise diagnoses are mistaken. Aside from sample contamination, which is a persistent problem whenever tiny quantities of diagnostic material are analyzed, we must be prepared to encounter instances when DNA sequences, thought to be characteristic of a species, are found in other organisms [60, 61].
- Sometimes precise diagnoses will be irreproducible by other laboratories examining samples of the same specimen. The difficulties in verifying and reproducing the results obtained through precision measurements are a matter of deep concern to those who regulate new diagnostic tests [62–77].

Section 8.4 Discovering new infections among the diseases of unknown origin

*That which can be asserted without evidence, can be dismissed without evidence.*

Christopher Hitchens

What shall we do with all the human diseases whose pathogenesis is unknown, despite our best efforts? We can start by grouping them to see if they share any common biological properties. Here is a partial list of diseases, some being common but most being rare, that are mysteries of modern medicine:

- Acrocyanosis
– Acute flaccid myelitis
– Alzheimer disease
– Aphthous ulcers
– Balanitis xerotica obliterans
– Behcet disease
– Benign fasciculation syndrome
– Brainerd diarrhea
– Cardiac syndrome X
– Chronic fatigue syndrome
– Chronic prostatitis/chronic pelvic pain syndrome
– Cluster headache
– Complex regional pain syndrome
– Copenhagen disease
– Cronkhite-Canada syndrome
– Cyclic vomiting syndrome
– Dancing mania
– Danubian endemic familial nephropathy
– Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)
– Electromagnetic hypersensitivity
– Encephalitis lethargica
– Exploding head syndrome
– Fibromyalgia
– Fields' disease
– Functional colonic disease
– Giant cell (temporal) arteritis
– Gluten-sensitive idiopathic neuropathies
– Gorham vanishing bone disease
– Granuloma annulare
– Granulomatosis with polyangiitis (Wegener syndrome)
– Gulf War syndrome
– Hallermann-Streiff syndrome
– Heavy legs
– Henoch-Schonlein purpura
– Interstitial cystitis
– Irritable bowel syndrome
– Kashin-Beck disease
– Kawasaki disease
– Lichen sclerosus
– Lytico-Bodig disease
– Mesoamerican nephropathy
– Microscopic polyangiitis
– Morgellons disease
– Mortimer disease
– Myofascial pain syndrome
Changing how we think about infectious diseases

Chapter | 8

New daily persistent headache
Nodding disease
Picardy sweat
Pigmented villonodular synovitis
Pityriasis rosea
Polyarteritis nodosa
Posterior cortical atrophy
Prurigo nodularis
SAPHO syndrome
Sarcoidosis
Sick building syndrome
Sjogren's syndrome
Spontaneous cerebrospinal fluid leak
Stiff person syndrome
Sudden unexpected death syndrome
Sweating sickness
Synovial osteochondromatosis
Takayasu arteritis
Torticollis
Trichodynia
Trigger finger
Tropical sprue

We do not know the root causes, the steps of development, or the fundamental biological properties of these diseases. Based on our experiences with diseases of known origin, is there anything that we can say that may help us to understand and classify these strange diseases? Most certainly, yes. If the diseases occur primarily in children, and if the disease runs in families, then we can say that, in all likelihood, a strong genetic influence is at work. If the disease causes fever and signs of inflammation and responds to anti-inflammatory medication, then we can infer that the condition involves a primary disorder of the inflammatory system, or a secondary disorder (such as the response to an infection). If the disease arises as an epidemic, then an infection or a newly introduced environmental toxin is likely to blame. Most importantly, if all of the medical research at our disposal is brought to bear on a disease, and no root cause is found, then it's a very safe bet that multiple conditions and events converge to produce the disease, and that a single cause will never be assigned. Our attention should be focused on finding the factors that contribute to the development of the disease.

In point of fact, if we look at former diseases-in-waiting, we find that most are diseases whose causes are amalgamations of infectious, genetic, and environmental conditions. Let's consider Whipple disease, discussed previously in this chapter. The disease is only observed in tillers of the soil (i.e., an occupational disease), who ingest the T. whipplei organism (i.e., an...
infectious disease), and who also happen to have a rare immune defect (i.e., a genetic disease). The multiplicity of events and conditions contributing to the development of Whipple disease confused early generations of medical researchers and earned it a prominent spot on the list of diseases-in-waiting. Using modern laboratory techniques and the knowledge that diseases are sequential, multievent processes, the mystery of Whipple disease was solved, 85 years after the first report of a human infection.

Celiac disease, a former disease-in-waiting, remains shrouded in biological ambiguity. Regardless, medical researchers believe that they know enough about this disease to drop it from the list. Celiac disease is triggered by the ingestion of gluten, a component of wheat (i.e., an environmental disease), and occurs in individuals who inherit Human Leucocytic Antigens DQ2 and DQ8 (i.e., a genetic disease) [78]. Gluten peptides are resistant to complete proteolytic digestion and enter the small intestinal lamina propria (i.e., the layer just beneath the epithelial cells lining the gut) where they elicit a strong, local immune reaction [78] (i.e., a disease of immunity). Recent literature suggests that the inflammatory response to gluten is primed by reovirus infection (i.e., a microbial infection) [79]. Despite the complex etiology of the disease, symptoms of the disease can be ameliorated by omitting gluten from the diet.

Another disease that seems to follow a pathogenesis similar to that of celiac disease is reactive arthritis, formerly known as Reiter's syndrome. This inflammatory condition affects the joints, eyes, urethra, and skin. Symptoms from these different tissues may occur asynchronously, and the disease may occur as a succession of remissions and relapses. As in celiac disease, there seems to be a genetic component to the syndrome, with about 75% of affected individuals having the Human Leucocytic Antigens B27 marker. Human Leucocytic Antigen B27 is a major histocompatibility locus that has been associated with several other inflammatory conditions, including ankylosing spondylitis and acute anterior uveitis [80, 81]. As in celiac disease, Reiter’s syndrome seems to have an infectious component, with most new cases following sexually transmitted infection by Chlamydia trachomatis or Ureaplasma urealyticum. Disease can also arise after gastrointestinal infection with shigella, salmonella, yersinia, or campylobacter bacteria.

Nodding disease, which may soon be removed from the list of diseases-in-waiting, is a frightening condition, first documented in the 1960s, that occurs almost exclusively in young children and adolescents living in regions of South Sudan, Tanzania, and Uganda. The disease stunts normal growth of the brain, and produces seizures. During the seizures, the neck muscles do not support the weight of the head, resulting in a characteristic nod, emphasized in the name of the disease. It was noticed that nodding disease occurs in areas where river blindness is endemic. River blindness is the second most common cause of infectious blindness worldwide and occurs in individuals infected by the filarial nematode Onchocerca volvulus [82]. The nematode migrates to the eyes,
where a peculiar secondary infection takes control of the pathogenic process. Wolbachia pipientis happens to be an endosymbiont that infects most members of the filarial Class Onchocercidae [83]. It is the Wolbachia pipientis living within O. volvulus that causes the local inflammatory reaction that leads to blindness.

A recent paper found that patients with nodding disease have antibodies to Onchocerca volvulus proteins that cross-react with leiomodin-1, a protein expressed in areas of the brain affected by the disease [84]. If this early research is confirmed, then nodding disease will be seen as an infectious disease that elicits an antibody response, which subsequently elicits a neurologic disorder. If so, nodding disease should be preventable by the avoidance or early treatment of O. volvulus infections. Hopefully, another disease with a complex etiology will be removed from the list of diseases-in-waiting.

Keshan disease was a disease of unknown etiology that has been tentatively removed from the list of diseases-in-waiting. Endemic to the Keshan region of Northeastern China, this disease, first reported in 1935, produces a cardiomyopathy, mostly in boys under 15 years old and women of childbearing age. This disease is often fatal, and thousands of deaths were reported in its peak incidence years (1960–70). Knowing that the region with the highest incidence of disease corresponded to a region with selenium deficiency, Chinese authorities treated spring crops with sodium selenite. It worked. The incidence of Keshan disease dropped in the areas where the crops were sprayed [85]. In 1981, a report came out indicating that Keshan disease patients had high levels of antibodies against Coxsackie virus, a virus known to produce cardiomyopathy [85, 86]. Current thinking would suggest that Keshan disease occurs in individuals whose hearts are weakened by selenium-deficient individuals, and who subsequently become infected with a virulent and cardiotoxic strain of Coxsackie virus [4].

Last but not least, we should consider Alzheimer disease, a common condition whose cause is unknown, and for which we have no prevention, no cure, and no way to impede the relentless progress of the disease [87]. We have already discussed Alzheimer disease in Section 8.2, “Prion Diseases: Fulfilling Koch's Postulates, but Without an Organism.” In our earlier discussion, we observed that misfolded amyloid, as extracellular amyloid plaques, and tau proteins, as intracellular neurofibrillary tangles, accumulate in the areas of the brain most affected by the neurodegeneration of Alzheimer disease. Although the origin of aggregates of misfolded protein in Alzheimer disease is unknown, we see such changes, to some degree, in the brains of virtually every individual who dies at an advanced age. We tend to credit such changes to long-term effects that accumulate in aging (i.e., nonrenewing or postmitotic) cells. Like many of the diseases of unknown origin, there seems to be a genetic component of indeterminate significance. We observe that individuals who have inherited two copies of the ApoE4
gene, sometimes called the Alzheimer gene, have a much increased risk of developing the disease.

Having found both nongenetic (aging) and genetic (ApoE4) risk factors for Alzheimer disease, might we not expect an infectious etiology is also involved? In fact, a specific organisms, Porphyromonas gingivalis (Class Bacteroidetes), an oral bacteria that can produce gingivitis, is currently being investigated as a potential cause of Alzheimer disease. The evidence so far would seem to indicate that individuals with chronic gingivitis have higher than normal incidence of the disease, the organism can infect brains, and that toxins produced by the organism and found in the brain are neurotoxic [88, 89]. We need not speculate on the potential significance of finding that a bacterium is an underlying cause of Alzheimer disease. Clinical trials, as they say, are underway. The point emphasized here is that diseases of unknown origin are often caused by a combination of genetic, environmental, and infectious conditions that work in steps, over time. Sometimes the best approach to prevent these types of diseases relies on a multifront effort. Such an approach has been attempted, by enhancing the diet, physical fitness, and metal activity of at-risk individual; with positive results [90].

Summarizing, the diseases-in-waiting seem to fit a common pattern as follows:

- Complex chain of causal events
- Tend to occur in rather specific populations, often based on age, geographic location, and occupation
- Unraveling their pathogenesis requires advanced diagnostic methodologies
- Hard to absolutely prove (there could be more to the story or the story could be wrong)
- Provide multiple interventional opportunities to stop or slow the development of disease (i.e., treatments can be aimed at any of the multiple steps in pathogenesis)
- Most importantly, an infectious agent is often involved somewhere in the process

We should think of pathogenesis as a sequence of biological events that occur over time, and that eventually produce a clinical phenotype that we recognize clinically as a disease. When infectious agents are involved in one step of a sequence of steps that eventually lead to disease, we can no longer equate the infectious agent with the “cause” of the disease. It may be difficult to understand how we might diagnose, prevent, or treat a disease that has no single, assignable cause. Nonetheless, the diseases of unknown origin seem to be teaching us that diseases often have complex pathogeneses. Identifying a disease-related organism is often just the beginning of a long discovery processes that will lead to a full understanding of these challenging diseases.
Section 8.5 Unstable taxonomies

I learned very early the difference between knowing the name of something and knowing something.

Richard Feynman

A taxonomy is a theoretical construct. As such, it needs to be constantly tested to determine whether the defined properties of each class actually extend to all of the members of the class, and whether the hierarchy of the classes is true. As new information is acquired, taxonomies will need to change.

Some of the recent changes in the taxonomy of living organisms have involved the highest classes in the hierarchy. The first division of the Eukaryotes was assigned to Class Bikonta and Class Unikonta (analogous to dicot and monocot division in Class Angiospermae) [91]. Class Protoctista has been dropped from the formal taxonomy. Class Microsporidia was moved from Class Protoctista to Class Fungi. The parasitic myxozoans have been added to Class Cnidaria (which includes sea anemones, corals, jellyfish, and hydra-like animals). Class Chlorophyta was moved from Class Protoctista to Class Archaeplastida.

Class Fungi has recently undergone profound changes, with the exclusion of myxomycetes (slime molds) and oomycetes (water molds), and the acquisition of Class Microsporidia. The instability of fungal taxonomy negatively impacts the practice of clinical mycology. When the name of a fungus changes, so must the name of the associated disease. Consider “Allescheria boydii,” people infected with this organism were said to suffer from the disease known as allescheriasis. When the organism’s name was changed to Petriellidium boydii, the disease name was changed to petriellidosis. When the fungal name was changed, once more, to Pseudallescheria boydii, the disease name was changed to pseudallescheriasis [46]. All three names appear in the literature (past and present).

The fungi are known for wide variations in the morphologic appearance of a single species. Pathogenic fungi grow within human tissues without reproduction (i.e., in an asexual morphologic phase). For the most part, pathologists see hyphae or yeast forms, and these forms and most of the many species of infectious fungi can look more or less equivalent when observed in tissue. As a partial remedy for this situation, pathologists have discovered a wide range of subtle clues that may help them distinguish one fungus from another: width of hyphae, angle of hyphal branching, septation of hyphae, the presence or absence of pigment, the size of yeasts and the morphology of budding, the type of host response to the fungal organisms (e.g., granuloma, acute inflammation), the anatomic site of infection, and so on. Clever as they may be, the definitive diagnosis for fungal species is determined in the clinical mycology lab, whenever feasible. Fungal specimens successfully grown in culture often have a different morphology from
that of the same fungus growing in human tissue. This situation is very different from that of bacterial infections, which have about the same morphology in tissues as they have in the culture dish (Fig. 8.2).

Fungal organisms have two options for reproduction: sexual and asexual. Both these forms of reproduction have their own morphologic appearances, in the same species of organism. Factors that determine the mode of reproduction for a cultured fungus are a mystery. It is possible for one mycologist to observe a fungus that reproduces exclusively asexually, while another mycologist, observing the same species in a culture dish or growing in the wild, may observe sexual reproduction (e.g., fruiting bodies). Depending on the phase of reproduction observed, and ignorant of the existence of an alternate morphologic form, taxonomists have assigned different names (sexual and asexual) to the same organism. Rather than harmonizing a dichotomous nomenclature under one preferred name, the International Code of Botanical Nomenclature (ICBN) had ruled, in the past, that it is acceptable to assign two different binomials to an organism: a sexual (also called teleomorphic, perfect, or meiotic form) and an asexual (also called anamorphic, imperfect, or mitotic form). For instance, two binomials legitimately apply to the same organism: Filobasidiella neoformans (the teleomorphic form) and Cryptococcus neoformans (the anamorphic form). Clinical mycologists typically use the asexual name, because it is the asexual form that grows in human tissues.
The unbridled craziness of one species having several different names could not continue forever. The 18th International Botanical Congress assembled in 2011, in Melbourne, Australia decided that a fungus was not a plant, and renamed themselves “The International Code of Nomenclature for Algae, Fungi, and Plants.” More importantly, the Congress abolished longstanding provisions permitting separate names for the different morphologic forms of a pleomorphic fungal species (i.e., names for anamorphs and teleomorphs) [92]. The “One fungus = One name” rule, as it has come to be known, faces many practical obstacles to its quick implementation. For example, many fungi have never exhibit sexual reproduction in culture. Many other fungi cannot be cultured. A special pseudoclass of fungi, deuteromyctetes (spelled with a lowercase “d,” signifying its questionable validity as a true biologic class) has been created to hold these indeterminate organisms until definitive classes can be assigned. Currently, there are several thousand such fungi, sitting in a taxonomic limbo, until they can be placed into a definitive taxonomic class [46]. Still, the “one fungus = one name” rule is a step in the right direction, and we can expect that nonmorphologic (e.g., genetic) identifiers of fungal species will eventually lead to a coherent and logical fungal taxonomy.

Here is a small sampling of recent name changes in species or genus of infectious organisms:

- Aggregatibacter actinomycetemcomitans, formerly Actinobacillus actinomycetemcomitans
- Anaplasma phagocytophilum, formerly assigned two different species names: Ehrlichia phagocytophilum and Ehrlichia equi [93].
- Aonchotheca philippinensis, formerly Capillaria philippinensis
- Arcanobacterium haemolyticum, formerly Corynebacterium haemolyticum
- Arcanobacterium pyogenes, formerly Actinomyces pyogenes
- Bartonella quintana, formerly Rochalimaea quintana
- Brachyspira pilosicoli, formerly Serpulina pilosicoli
- Burkholderia mallei, formerly Pseudomonas mallei
- Cladophialophora bantiana, formerly Xylohypha bantiana
- Cystoisospora belli, formerly Isospora belli
- Elizabethkingia meningoseptica, formerly Chryseobacterium meningosepticum
- Encephalitozoon intestinalis, formerly Septata intestinalis
- Fluoribacter bozemanae, formerly Legionella bozemanae
- Gardnerella vaginalis, formerly Corynebacterium vaginalis, formerly Haemophilus vaginalis
- Helicobacter pylori, formerly Campylobacter pylori
- Klebsiella granulomatis, formerly Calymmatobacterium granulomatis, formerly Donovania granulomatis
- Malassezia furfur, formerly Pityrosporum ovale
Micromonas micros, formerly Peptostreptococcus micros formerly Parvimonas micros
- Mycolcadus corymbifera, formerly Absidia corymbifera
- Neorickettsia sennetsu, formerly Ehrlichia sennetsu
- Norovirus, formerly Norwalk virus (epidemic gastroenteritis)
- Pneumocystis jirovecii, formerly Pneumocystis carinii
- Rhodococcus equi, formerly Corynebacterium equi, formerly Bacillus Hoagii, formerly Corynebacterium purulentus, formerly Mycobacterium equi, formerly Mycobacterium restrictum, formerly Nocardia restricta, and formerly Proactinomyces restrictus.
- Rotavirus formerly known as gastroenteritis virus type B.
- Sarcocystis suihominis, formerly Isospora hominis
- Stenotrophomonas maltophilia, formerly Pseudomonas maltophilia
- Volutella cinereascens, formerly Psilonia cinereascens

Regional differences in nomenclature account for considerable confusion. For example, Enterobius vermicularis is called pinworm in the United States and threadworm in the United Kingdom; while strongyloides stercoralis is just the opposite (threadworm in the United States and pinworm in the United Kingdom). The only way to escape this trans-Atlantic confusion is to translate the common name of the organism back to its standard Latin binomial.

Taxonomic instability negatively impacts clinical practice. Changes in the standard names of a fungus, appearing in the ICBN, should trigger concurrent changes in the standard nomenclatures of medicine, such as the World Health Organization's International Classification of Disease, and the National Library of Medicine's Medical Subject Headings, and a variety of specialized disease nomenclatures. Some of these nomenclatures update infrequently. When disease nomenclatures lag behind official fungal taxonomy, errors in coding and reporting infectious fungal diseases will ensue [Glossary Dictionary, Nomenclature].

Section 8.6 Taxonomic stupidity

*I personally think we developed language because of our deep need to complain.*

Lily Tomlin

Nearly every medical science is a child compared with medical microbiology. Think a moment about the youthfulness of bioinformatics, genetics, and molecular biology. Medical subjects with ancient roots, such as physiology, embryology, histology, and cell biology, were relatively obscure until the 20th century. In the case of infectious illness, scientists were providing names to living organisms and to the biological processes of living organisms, for hundreds of years, often predating the invention of the microscope, and often invoking ancient and magical notions to explain invisible, malicious
entities. Consequently, biologists have expended a great deal of effort toward the expulsion of non-scientific terms from the vocabulary of modern microbiology.

**Class Protoctista**

A good classification is never complete until every member of the classification has a place in a class, every class has at least one member, and every member within a class has a defined relationship with every other member within the same class. Consequently, we avoid undefined classes with names such as “miscellaneous” or place-holding classes, named “not otherwise specified,” filled with objects waiting for their proper class assignments. Adhering to this last provision may be very difficult. When a classification is being constructed, it is common to have some objects whose properties are a mystery or objects that simply cannot be easily related to other objects. Taxonomists often have no choice but to put all their leftover objects into a miscellaneous class, until such time as additional information is obtained. The Latin term incertae sedis, meaning “of uncertain placement,” and indicating a problematic class, puts a veneer of classical authority on the practice [Glossary Prolematica, Unclassifiable objects].

In the classification of living organisms, 19th century taxonomists did not know quite what to do with the many different one-celled eukaryotes they were collecting. As a stop-gap measure, they invented the Kingdom Protozoa, the class of all one-celled animals, the parent class of all multicellular organisms. Kingdom protozoa was a pseudoclass, consisting of all manner of organisms that were not closely related to one another, and which contained organisms that should have been assigned to separately named classes of single-celled eukaryotic organisms [94]. Many decades passed before taxonomists caught up with the blunder, and reassigned individuals in class protozoa to proper classes of their own. Nonetheless, biologists are unwilling to abandon long-cherished terminology. Taxonomists who should know better have pleaded to retain obsolete and misleading plesionyms, such as “protist,” “protoctista,” and “protozoa” on the grounds that doing so will enhance communication and facilitate teaching [95]. They make a fair point, but surely the chief objective of science is to correct misconceptions, not perpetuate them. We have seen some evidence of progress. For example, the Society of Protozoologists, founded in 1947, has seen fit to update their name to Society of Protistologists, in 2005. It would be asking too much for them to change their name, once more, to the awkward but accurate “Society of single-celled Eukaryotic Organisms.” In this book, the term “protozoa” is avoided altogether.

**Informal classes of organisms that violate the rules of classification**

Class Anamniota sometimes appears in the literature, indicating the sister class to Class Amniota. In actuality, there is no legitimate Class Anamniota; there
are simply lots of anamniotes belonging to lots of distantly related classes. The source of the confusion came with the three subclasses of Class Tetrapoda: Class Amphibia, Class Sauropsida, and Class Synapsida. The Sauropsids and the Synapsids are the first classes of animals to lay their eggs on land or to retain eggs in gestating mother. To do so, the embryo acquired a set of protective extra-embryonic membranes (i.e., allantois, amnion, and chorion). If the Sauropsids (including future birds and reptiles), and synapsids (including future mammals) belong to Class Amniota, it would seem only fitting to presume that Class Amphibia, whose eggs lack an amnion, would be a subclass of Class Anamniota. This would be a mistake, insofar as none of the classes of animals other than the Sauropsids and Synapsids, and their descendants, have amnions; hence, the anamniotes do not constitute a sensible class of animals [Glossary Negative classifier].

We commonly encounter groupings of animals that have no logical place within a formal classification. While we are on the subject of amphibian classification, we may as well examine the term “herpetology,” it being the branch of zoology concerned with the study of amphibians and reptiles. Amphibians and reptiles belong to sister subclasses of Class Tetrapoda (i.e., Class Amphibia and Class Synapsida). The present-day descendants of these respective classes are only distantly related to one another. For example, Class Reptilia is a descendant of Class Sauropsida, but the pairing of present-day amphibians with present-day reptiles creates a grouping with a tenuous phylogenetic relationship. Furthermore, among the members of Class Reptilia are birds, which are not studied by herpetologists. In summary, the field of herpetology covers animals of two distantly related classes, but excludes certain subclasses of animals within its member classes (i.e., excludes birds). Herpetologists should choose one or two classes of animals to study, and not confuse the rest of us with a name that violates the laws of biological classification.

Gender assignment for asexuals

Biologists love assigning gender to any and every biological entity, whatever the consequences. When a mitotic cell divides asexually, the progeny are referred to as daughter cells. Whether the organism is a male or a female, it makes no difference. The product of cell division is a daughter cell. Similarly, Echinococcal cysts may harbor cysts within themselves, and these are referred to as daughter cysts.

Even abstractions are provided with a gender. When a class produces two subclasses, the two sexless subclasses become the sister classes of one another.

The problem is not confined to biology, and is not exclusively a foible of the English language. In French and Spanish, the uterus is assigned the male gender (preceded by “le” and “el,” respectively). In French and Spanish, the prostate is feminine (preceded by “la” in either language). Why do we do this to ourselves?

Class-specific terms applied to the wrong classes
As previously mentioned, Class Fungi were originally assigned as a subclass of Class Archaeplastida (plants), based on a few shared similarities (e.g., both live in soil and both grow as immobile, sessile multicolored structures). The misclassification of fungi as a class of plants has been hard to expunge. Universities, steeped in tradition, continue to assign their mycologists to the Department of Botany. Until earlier in this decade, the taxonomy of fungi was determined by the International Committee for BOTANICAL Nomenclature (ICBN). To this day, we find published taxonomies that identify fungi as types of flowers [96].

The language of biological science is peppered with taxonomically false terms. For example, the suffix “phyte” or “phyta” comes from the Greek “phyton” meaning plant. It is attached to all manner of nonplant organisms. As a case in point, heterokontophyta, the former name for the heterokonts, and still in common usage, is a single-celled eukaryote that is certainly not a plant.

Much of our terminological mischief harkens back to a time when it was common to divide all objects on earth into three classes: animal, vegetable, and mineral. Consequently, all of the nonmetazoan eukaryotes were thought of as vegetables or plants, and given names taken from the field of botany. So too the bacteria. Hence, the gut bacteria were called the human microflora. Mycelial growth was described as vegetative. The sporocarp of fungi continues to be called a “fruiting body.” The nearly meaningless term “fruiting body” is haphazardly applied to bacteria and slime molds, as well.

Just as we falsely apply strictly botanical nomenclature to nonbotanical terms, we also apply metazoan terms to nonmetazoan organisms. For example, the term “zoo” derives from the Greek “zoion,” meaning an animal. We find “zoo” or “zo” appearing as a prefix, infix, or suffix for organisms that are single-celled eukaryotes, fungi, and almost anything but animals.

Here is a list of confusing “zoo” terms, selected from this book:

- Amoebozoa (a one-celled eukaryote and not an animal)
- Apoikozoa (synonymous with Choanozoa, a sister class to animals, and not an animal)
- Bradyzoites (an encysted form of sporozoan, such as Toxoplasma gondii, and not belonging to any member of Class Animalia)
- Choanozoa (same as aforementioned Apoikozoa),
- Encephalitozoon (a member of Class Microsporidia, a descendant of Class Fungi, and not an animal)
- Enterocytozoon (another member of Class Microsporidia, a descendant of Class Fungi, and not an animal)
- Euglenozoa (a class of single-cell eukaryotes, and not an animal)
- Filozoa (an ancestral class for the metazoans, and hence not an animal)
- Holozoa (another ancestral class for the metazoans and hence, not an animal)
- Mesomycetozoea (a nonmetazoan opisthokont; hence, not an animal)
- Percolozoa (a descendant of Class Excavata, and not an animal)
– Protozoa (single-celled eukaryotes and hence, not animals)
– Sporozoan (synonymous with apicomplexan, single-celled eukaryotes that are not animals)
– Sporozoites (an infective, motile form of some sporozoans, and hence not an animal)
– Sulcozoa (a class of single-celled eukaryotes, and hence not an animal)
– Trichozoa (a subclass of Class Excavata, and hence not an animal)
– Trophozoite (a growth stage of some sporozoans, and hence not an animal)
– Zoopagomycota (a type of fungus, and hence not an animal)
– Zoospores (a taxonomically nonspecific term referring to a swimming spore, and not an animal)

Too many spores

The term spore (from the Greek “spora” meaning sowing) is used widely and indiscriminately in the biological literature to indicate an agent of microbial reproduction, often when an exact and unambiguous term is available. Hence, bacterial endospores, fungal conidia, and eukaryotic cysts are commonly lumped as “spores.” Within this very book, we have witnessed “spore” appearing as a prolific suffix, prefix, or infix of unrelated biological terms, including Autospores, Chrysosporium, Cladosporiosis, Cladosporium, Cryptosporidiidae, Cryptosporidiosis, Cryptosporidium, Cyclospora, Cystoisospora, Endospores, Haemosporida, Ichthyospora, Isospora, Micropolyspora, Microsporidea, Microsporidia, Microsporidiosis, Microsporidium, Microsporum, Oxysporum, Pityrosporum, Pleosporales, Pleosporomycetidae, Rhinosporidiosis, Rhinosporidium, Sarcosporidiosis, Scedosporium, Sporocyst, Sporothrix, Sporotrichosis, Sporozoan, Sporozoite, Streptosporangineae, Thermomonosporaceae, Tichosporonales, Zoospores, and Zygospore. It’s time to call for a moratorium on spores, which we shall not label as a “sporatorium.”

In addition, “spora” is the root for “sporadic” which extends the Greek meaning of “sowing” to conjure the notion of an aimless toss of seed, without any specific pattern. Hence, a sporadic disease has no known cause, and no discernible pattern of occurrence (e.g., neither genetic nor environmental, and without any particular geographic origin). The term “sporadic” is fraught with scientific ambiguity and should probably be abandoned altogether. To label a disease “sporadic” legitimizes and perpetuates the dubious notion that diseases can occur without cause (e.g., entirely by “chance”). Many of the diseases that were considered to be sporadic, decades ago, are now known to have specific causes. Would it not be more accurate to use the phrase “undetermined pathogenesis” in place of “sporadic,” for occurrences of a disease whose cause is currently unknown?

Squiggly things
Parasitic worms are called helminths. Class Platyhelminthes and Class Nematoda account for all the so-called helminthic diseases of humans. Readers should be warned that the term “worm” has no taxonomic meaning; soft, squiggly organisms colloquially known as “worms” are scattered throughout animal taxonomy, with no close relationship with one another. A small squirming organism referred to as a “worm” may be an insect larva (i.e., not a helminth), or it may be one of several unrelated classes of organisms. Class Acanthocephala includes the thorny-headed worms. Class Annelida (earthworms) descends from Class Lophotrochozoa, which includes molluscs. Acorn worms (Class Enteropneusta) are hemichordates whose closest phylogenetic relative are the echnoderms, which include sand dollars and starfish. Class Chaetognatha contains the predatory marine arrow worms. Class Lophotrochozoa contains the Nemertea, or ribbon worms. Class Nematoda (roundworms) and Class Annelida (ringed worms, including earthworms) are more closely related to spiders and clams, respectively, than either one is related to Class Platyhelminthes (flatworms).

Many so-called worms are actually the larval forms of animals whose adult stage bears no resemblance to worms. An example is Linguatula serrata (Class Crustacea), the agent causing tongue worm disease. The tongue worm is the larval stage of a crustacean. Likewise, the screwworm (Cochliomyia hominivorax) is actually a type of fly. It is called a screwworm because the disease is manifested by worm-like larvae growing on skin. Lastly, the ineptly named “ringworm” infections are not caused by worms or by any animals; they are fungal infections of the skin. The word “worm” may even refer to a marsupial joey (Class Mammalia), which is typically a smooth hairless slug-shaped organism the size of a jellybean.

The same form of objection can be applied to the word “fly.” The term “fly” should refer exclusively to member of Class Diptera (flies). As it happens, the term “fly” has been assigned, at one time or another, to just about any small flying insect, few of which are dipterans: butterflies (Class Lepidoptera), dragonflies (Class Palaeoptera), and mayflies (Class Palaeoptera). When a word is applied to morphologically similar, but phylogenetically unrelated organisms, what useful meaning could it convey?

Unnecessary ranks

In hierarchical biological nomenclatures, classes are given ranks. In early versions of the classification of living organisms, it was sufficient to divide the classification into a neat handful of divisions: Kingdom, Phylum, Class, Order, Family, Genus, and Species. Today, the list of divisions has nearly quadrupled. For example, Phylum has been split into the following divisions: Superphylum, Phylum, Subphylum, Infraphylum, and Microphylum. The other divisions are likewise split. The process whereby classes are split is somewhat arbitrary and subject to dispute among taxonomists [97].
Taxonomists referring to a class, without specifying its rank, will sometimes use the word “taxon.”

Most importantly, the complex taxonomic ranking system for living organisms does not carry over to the ranking systems that might be used for other scientific domains (e.g., classification of diseases, classification of genes, etc.) and creates an impediment for anyone wanting to bridge classifications held within diverse, but related, fields.

In this book, taxonomic complexity is drastically simplified by dropping named ranks and simply referring to every class as “Class.” When every class of organism were associated with the name of its one parent class, then it becomes possible to computationally trace the complete ancestral lineage for every class or species [98]. Likewise, knowing the direct parent class for every class and species permits us to find all the child classes (i.e., direct subclasses) for every class and, consequently, all the sibling classes for every child class.

Computer savvy biologists and bioinformaticians rely upon large taxonomic listings to trace the ancestry and to determine phylogenetic relationships among specific organisms and their classes. For example, a listing of species and classes of organisms that is used by bioinformaticians throughout the world is available at no cost from the European Bioinformatics Institute.

The taxonomy.dat, which is currently over 468 megabytes in length, can be downloaded via anonymous ftp at:

ftp://ftp.ebi.ac.uk/pub/databases/taxonomy/

Additional information on the taxonomy.dat file is found at:

http://www.ebi.ac.uk/msd-srv/docs/dbdoc/ref_taxonomy.html

A sample entry (one of hundreds of thousands in the file) is shown:

| ID      | 24 |
|---------|----|
| PARENT ID | 22 |
| RANK    | species |
| GC ID   | 11 |
| SCIENTIFIC NAME | Shewanella putrefaciens |
| SYNONYM | Alteromonas putrefaciens |
| SYNONYM | Pseudomonas putrefaciens |
| MISSPELLING | Shewanella putrifaciens |
| MISSPELLING | Alteromonas putrifaciens |

The sample entry (above) provides an ID number for the entry organism, and for its parent class. Since every organism and class has a parent, we can trace the taxonomic lineage of any organism or class by iterating through the parental
links [98]. For example, the following lineage, for Homo sapiens, was computed on the fly from the taxonomy.dat file:

Eukaryota: Opisthokonta: Metazoa: Eumetazoa: Bilateria: Deuterostomia: Chordata: Craniata: Vertebrata: Gnathostomata: Teleostomi: Euteleostomi: Sarcopterygii: Dipnotetrapodomorpha: Tetrapoda: Amniota: Mammalia: Theria: Eutheria: Boreoeutheria: Euarchontoglires: Primates: Haplorrhini: Simiiformes: Catarrhini: Hominoidea: Hominidae: Homininae: Homo: Homo sapiens.

Likewise, we can instantly compute the subclasses of any class we choose. For example, let's look at three classes and their computed subclasses:

Eumetazoa: Subclasses are Cnidaria, Ctenophora, and Bilateria
Fungi: Subclasses are Chytridiomycota, Microsporidia, environmental samples, unclassified Fungi, Fungi incertae sedis, Blastocladiomycota, Dikarya, Mixed fungal DNA libraries, Cryptomycota, Mucoromycota, and Zoopagomycota
Apicomplexa: Subclasses are unclassified Apicomplexa, environmental samples, Acanthoecida, Apicomplexa incertae sedis, and Conoidasida

In summary, modern taxonomists do not need to rely on class rankings. We only need to know the parent class for each class contained in a taxonomy. Every taxonomist and every bioinformaticians should have access to simple software that can compute the ancestral lineage, and the sister classes, for any given class of living organism. Very soon, scientists will have genomic sequences for representative species covering all the known classes of living organisms.

Section 8.7 Recurring sources of error

Many errors, of a truth, consist merely in the application the wrong names of things.

Baruch Spinoza (1632–77)

Alpha Proteobacteria—Readers should be careful not to confuse Bartonella with the similar-sounding Bordetella (Beta Proteobacteria).

Alpha Proteobacteria—Readers should be aware that brucellosis has been known by a great number of different names, including Mediterranean fever. Mediterranean fever, an arcane synonym for brucellosis, should not be confused with familial Mediterranean fever (a gene disorder characterized by fever and abdominal pain) or with Mediterranean anemia (a synonym for thalassemia).

Alpha Proteobacteria—Readers should be aware that Neorickettssia, despite its name, is not a type of Rickettsia (i.e., not a member of Class Rickettsiaceae).
Neorickettsia is a member of Class Anaplasmataceae; hence, the disease it causes is an ehrlichiosis.

Alpha Proteobacteria—Readers should not be confused by the term “scrub typhus” for infection by Orientia tsutsugamushi (alternately named Rickettsia tsutsugamushi). This disease is grouped as a “spotted fever,” not a form of typhus.

Gamma Proteobacteria—Organisms of Genus Cardiobacterium should not be confused with the similar-sounding Genus Corynebacterium (Class Actinobacteria).

Gamma Proteobacteria—The term “dysentery” (from the Latin “dys” and Greek “dus,” meaning bad, and the Greek “enterikos” meaning intestine) is often used to connote a specific disease, but dysentery is nonspecific term that can be applied to any enteric disorder associated with severe or bloody diarrhea. Because the group of diseases known as “dysentery” is the most frequent cause of childhood morbidity and mortality, it is important to use the term correctly. In developed countries, the term “dysentery” most often refers to salmonellosis, while in less developed countries, “dysentery” usually refers to shigellosis (also called bacillary dysentery, another misnomer) [99]. Other bacterial causes for dysentery are: Vibrio cholerae, Escherichia coli, Clostridium difficile, Salmonella, Campylobacter jejuni, and Yersinia enterocolitica. Viruses that cause dysentery include Rotavirus and Norwalk virus. The term “amoebic dysentery” is usually reserved for gastroenteritis caused by Entamoeba histolytica.

Gamma Proteobacteria—Granuloma venereum, caused by Klebsiella granulomatis, can be mistaken clinically with two other diseases that are characterized by genital ulcers: syphilis (Treponema pallidum Class Spirochaetae) and chancroid (Haemophilus ducreyi, Class Gamma Proteobacteria). Adding to the confusion, the syphilitic genital ulcer known as a chancre must be distinguished from chancroid. One last caveat. Granuloma venereum, caused by Klebsiella granulomatis, must not be confused with lymphogranuloma venereum, caused by Chlamydia trachomatis (Class Chlamydiae).

Gamma Proteobacteria—Readers should not confuse rhinoscleroma, caused by Klebsiella rhinoscleromatis (Class Gamma Proteobacteria), with rhinosporidiosis, caused by Rhinosporidium seeberi (Choanozoa).

Gamma Proteobacteria—Salmonella paratyphi and Salmonella typhimurium cause typhoid fever and paratyphoid fever, respectively. Neither of these diseases should be confused with typhus fevers, caused by Rickettsia typhi and Rickettsia prowazekii. Both diseases (typhoid and typhus) take their root from a Greek word meaning stupor, referring to the neurologic manifestations of the diseases.

Gamma Proteobacteria—Species of Genus Shigella cause Shigellosis, also known as bacillary dysentery. Despite its name, readers should not assume that the cause of bacillary dysentery is a member of Class Bacilli. The exclusive cause of bacillary dysentery are Shigella belonging to the Gamma Proteobacteria.
Gamma Proteobacteria—Shigella boydii, one of the causes of shigellosis, should not be confused with Pseudallescheria boydii, a fungus in Class Ascomycota, one of many fungal organisms associated with the skin infection maduromycosis.

Gamma Proteobacteria—Readers should not confuse Plesiomonas shigelloides, containing the species name “shigelloides,” with the genus name “Shigella” (vida supra).

Gamma Proteobacteria—Haemophilus influenzae causes pneumonitis, meningitis, and bacteremia, in infants and young children. Its species name, influenzae, was assigned when the bacteria was mistaken thought to be the cause of influenza. Influenza, also known as the flu, is caused exclusively by the influenza virus, a Group V orthomyxovirus.

Gamma Proteobacteria—Haemophilus parainfluenzae causes some cases of endocarditis. Despite its name, Haemophilus parainfluenzae is not the cause of the disease known as parainfluenza. Parainfluenza is a type of croup (laryngotracheobronchitis), and about 75% of the cases of croup are caused by the parainfluenza virus, a Group V virus.

Gamma Proteobacteria—Despite its name, Haemophilus parainfluenzae is not the cause of the disease known as parainfluenza. Parainfluenza is a type of croup (laryngotracheobronchitis), and about 75% of the cases of croup are caused by the parainfluenza virus, a Group V virus.

Gamma Proteobacteria—Haemophilus ducreyi is the cause of chancroid, a sexually transmitted disease. It must not be confused with Klebsiella granulomatus, in Class Enterobacteriaceae, the cause of granuloma inguinale.

Gamma Proteobacteria—Readers should not confuse Genus Acinetobacter (Gamma Proteobacteria) with Class Actinobacteria.

Spirochaetae—Rat-bite fever is caused by either Spirillum minus or by Streptobacillus moniliformis (Class Fusobacteria) [100]. Regardless of the causative organism, or the phylogenetic classes to which the organisms are assigned, the clinical symptoms are similar, as is the treatment.

Mollicutes—Erysipelothrix contains one infectious species; Erysipelothrix rhusiopathiae, the cause of erysipeloid, a type of cellulitis (subcutaneous infection). Students should not confuse erysipeloid with the similar-sounding disease, erysipelas. Both erysipeloid and erysipelas produce cellulitis. Erysipelas is more common and, potentially, a more serious disease than erysipeloid. Erysipelas is caused by members of Genus Streptococcus (Class Bacilli). Two additional similar-sounding skin conditions are erythrasma, characterized by brown scaly skin patches; caused by Corynebacterium minutissimum (Class Actinobacteria), and erythema infectiosum, caused by Parvovirus B19. All four skin conditions are associated with reddened skin, and all three diseases take their root from the Greek “erusi,” meaning red.

Class Bacilli plus Class Clostridia—The term “bacillary” is misleading. You might think that the adjective “bacillary” would be restricted to members of Class Bacilli, its subclasses, and Genus Bacillus. It seldom does. The word “bacillus” has its root in Latin, from “baculum” a rod or staff, so the name has been applied to the second term in the binomial name of bacteria that do not belong to Class Bacilli.
An example of a species with “bacilla” in its name that is not a member of Class Bacilli is Bartonella bacilliformis (the cause of verruga peruana). Examples of genera with “bacillus” in their name that are not members of Class Bacilli are: Actinobacillus and Streptobacillus. Genus Streptobacillus (Class Fusobacteria) is a terminological catastrophe, as it is not a sister genus to Streptococcus, and it is not a member of Class Bacilli.

The subclasses of Class Bacilli were assigned based on phylogeny, not on morphology. Therefore, there are members of Class Bacilli that are not rod-shaped (e.g., Genus Staphylococcus and Streptococcus).

Diseases containing the term “bacillary” are not caused by members of Class Bacilli. These include bacillary angiomatosis (caused by Bartonella quintana and Bartonella henselae) and bacillary dysentery (caused by four different Shigella species and by Yersinia enterocolitica).

Class Bacilli plus Class Clostridia—Listeria monocytogenes is the organism that causes listeriosis. Listeriosis should not be confused with the similar-sounding disease, leptospirosis (Spirochaetae) Spirochaetae.

Chlamydiae—Readers should not confuse trachoma with inclusion conjunctivitis, as each disease is caused by distinct variants of the same species (Chlamydia trachomatis). Trachoma is contracted by exposure to eye secretions from people with trachoma. Inclusion conjunctivitis is caused by ocular exposure to secretions from the sexually transmitted infection.

Chlamydiae—Chlamydia trachomatis may also cause lymphogranuloma venereum, a disease that usually presents as swollen lymph nodes in the groin. The lymph nodes often have draining abscesses. The disease is rare, with only a few hundred cases occurring in the United States each year. Lymphogranuloma venereum must not be confused with granuloma inguinale, also known as granuloma venereum, caused by the bacterium Klebsiella granulomatis.

Actinobacteria—Members of Class Actinobacteria tend to be filamentous, and this morphologic feature led to great confusion. In the past, these filamentous bacteria were mistaken for fungal hyphae, and many of the diseases caused by members of Class Actinobacteria are given fungal names (e.g., actinomycosis, mycetoma, and maduromycosis).

Actinobacteria—Readers should be aware of the highly confusing term, “diphtheroid,” from the Greek diphththera, meaning leather membrane, and commonly applied to all the nonpathogenic species within Genus Corynebacterium. As nonpathogens, the diphtheroids do not cause diphtheria. Diphtheria is caused Corynebacterium diphtheriae (i.e., a nondiphtheroid).

Actinobacteria—Readers should not confuse the bacterial genus Tropheryma with the similar-sounding term Taphrinomycotina, the fungal genus that includes Pneumocystis.

Actinobacteria—Actinomycosis (Greek “actino,” ray and “myco,” fungus), despite its misleading name, is a bacterial infection, not a fungal (i.e., mycotic) infection. Actinomycosis, also referred to as actinomycotic abscess, can be caused by any of several actinobacterial species.
Metamonada—It is important not to confuse trichomonas, caused by the metamonad Trichomonas vaginalis, with the similar-sounding name trachoma. Trachoma is a bacterial infection of the eyes caused by Chlamydia trachomatis.

Apicomplexa—The disease produced by any of the organisms belonging to Class Coccidia is known collectively as coccidiosis. This term is applied most often to coccidial infections in animals, excluding humans. Coccidiosis in humans must not be confused with the similar-sounding coccidioidomycosis (Ascomycota). Needless to say, Coccidia, the Apicomplexan subclass, should never be confused with conidio, the asexual fungal spore, with which it rhymes.

Heterokonta—Formerly known as Heterokontophyta. The roots “phyta,” “phyte,” and “phytic” all derive from the Greek “phyton” meaning plant. Despite its deceptive former name, the heterokonts are not plants.

Heterokonta—Oomycota, a “colorless” class of heterokonts, contains the organisms that produce late blight of potato (Phytophthora infestans), and sudden oak death (Phytophthora ramorum). Oomycota, despite its suffix (mycota, an alternative name for fungus), is not a member of Class Fungi.

Heterokonta—It is important to avoid confusing Blastocystis with three similar-appearing but unrelated terms: blastomycosis, blastocyst, and blastomycetica. Blastomycoses is a fungal disease (Ascomycota). Blastocyst is the fluid-filled embryonic body characteristic of animals. Blastomycetica appears in the name of a fungal infection “erosio interdigitalis blastomycetica.” This infection, despite what its name would imply, is a candidal infection of the web space between the third and fourth fingers of either hand. The infection was given its deceptive name in 1917, 5 years before the genus Candida was recognized [101]. As is often the case, the mistake stuck. All four terms come from the root word blastos (Greek for bud or embryo). Cystos (as in Blastocystis and blastocyst) is the Greek root meaning sac.

Amoebozoa—Do not confuse Entamoeba coli (abbreviation E. coli) with Escherichia coli (likewise abbreviated as E. coli). Both live in the colon, and both can be reported in stool specimens. Do not confuse Entamoeba (Class Amoebozoa) with Dientamoeba (Class Metamonada).

Amoebozoa—It is commonly agreed that the term “amoebiasis,” with no qualifiers in the name, refers exclusively to the intestinal infection by Entamoeba histolytica. Encephalitides caused by members of Class Amoebozoa (Acanthamoeba and Balamuthia) are named granulomatous amoebic encephalitis. Encephalitis caused by Naegleria fowleri (not an amoeba) is called primary amoebic meningoencephalitis, an accepted misnomer. Naegleria is a member of class Percolozoa. A better name for the Naeglerian disease would be primary percolozoan meningoencephalitis.

Archaeplastida—“Kleptoplast” should not be confused with the similar-sounding word, “kinetoplast.” A kleptoplast is a chloroplast that has been stolen by another organism. A kinetoplast, uniquely found in members of Class Kinetoplastida, is a clump of DNA composed of multiple copies of the mitochondrial genome, tucked inside a mitochondrion.
Nematoda—Astute readers will notice that the prefix “trich” appears often in connection with Class Nematoda: Trichostrongylus, Trichocephalida, Trichinellidae, Trichinella, and Trichuris. A wide assortment of organisms, diseases, and medical terms contain the root “trich” (pronounced trick) and produce similar-sounding terms (i.e., homonyms). If you want to avoid confusing one disease with another, it is best to “come to terms” with this “trichy” nomenclature. The suffix “trich” comes from the Greek “thrix,” meaning hair. Various unrelated organisms with a hair-like appendage are provided with the “trich” suffix. Likewise, medical conditions of the hair are provided the same suffix: trichosis is any pathologic condition of hair; trichilemmoma is a tumor of hair, trichobezoar is the medical term for hairball, and trichotillomania is compulsive hair pulling. Words that sound somewhat like “trich” include trachoma (caused by the bacteria, Chlamydia trachomatis) and trachea (the windpipe). In addition to Trichomonas, there are several unrelated “trich” organisms that cause disease in humans: Trichinella, Trichomonas, Trichomonad, and Trichophyton. Other “trich” diseases: Trichostrongylus trichinosis, trichuriasis, trichomoniasis, trichiasis (everted eyelashes that touch the cornea or conjunctiva, often a post-infectious condition).

Nematoda—When toxocara migrate through viscera, the condition is called visceral larva migrans. When toxocara migrate through an eye, the condition is called ocular larva migrans. When toxocara migrate through the skin, the condition is NOT called cutaneous larva migrans: this term is reserved for cutaneous manifestations of Ancylostoma braziliense.

Nematoda—Readers should not confuse “toxocara” with the similarly-sounding “toxoplasma” (Class Apicomplexa), a problem aggravated when clinicians use the abbreviated form “toxo,” when referring to “toxoplasmosis.”

Chelicerata—Most members of Class Chelicerata are noninfectious in humans. Only two genera of Class Chelicerata live in, or on, humans, and both genera belong to the subclass of arachnids named Class Acari, which includes mites and ticks. Readers should not confuse mites and ticks with insects. Insects are members of Class Hexapoda. In addition, Class Acari (in Class Chelicerata) should not be confused with the similar-sounding Class Ascaris (in Class Nematoda).

Hexapoda—Class Hemiptera are the so-called “true bugs.” They are distinguished from other insects by the shape of their mouth parts, which are shaped as a proboscis and covered by a labial sheath. The mouth parts of Class Hemiptera are designed for sucking. Class Hemiptera includes cicadas and aphids. The triatome species that are vectors for Trypanosoma cruzi (Euglenozoa) are members of Class Hemiptera.

Crustacea—One of the more confusing terms associated with pentastomiasis is “porocephaliasis,” named for a pentastome genus, Porocephalus. The genus “Porocephalus” and the infection “porocephaliasis” should not be confused with “porcephaly,” a rare developmental disorder in which cysts or cavities are found in the brains of infants.
Ascomycota—Readers should be alerted that the term “Candida” is a source of some taxonomic confusion: candida, in Latin, means white. Many organisms are white, and have taken “candida” as part of a binomial name. Though there is only one Genus Candida (the fungus), there are many species named candida, particularly in Kingdom Plantae. For example, there are three M. candida species: Mammilloydia candida, a cactus; Miltonia candida, an orchid; and Masdevallia candida, another orchid.

Ascomycota—Readers should remember not to confuse Microsporum with Microspora, a genus in Class Microsporaceae, a Chlorophyte. It is also important not to confuse fungi of Genus Microsporum with the fungi of Genus Microsporidium (Class Microsporidia).

Ascomycota—Readers should not assume that Lobo disease is caused by a member of Class Lobosea, a subclass of amoebozoans that includes Genus Acanthaemoeba. Lobo disease is caused by Lacazia loboï, an ascomycote fungus.

Ascomycota—Note that Piedraia hortae is not a member of genus Hortaea; being as a species of Genus Piedraia. Likewise, Hortaea werneckii does not share its genus with Piedraia hortae. The mycologists responsible for this nomenclature could not have been more confusing, if they tried.

Basidiomycota—Fungi of Genus Trichosporon, basidiomycotes causing white piedra, should not be confused with organisms of Genus Trichsporum, a name that includes both fungi in Class Ascomycota and plants in Class Gesneriaceae [102].

Microsporidia—It is important not to confuse microsporidiosis with cryptosporidiosis, an apicomplexan disease (Apicomplexa), that also produces diarrhea in immune-compromised patients.

Group I Viruses—Class Herpesviridae (Group I virus) should not be confused with Class Hepeviridae (Group IV virus).

Group II Viruses—Bocavirus, a Group II parvovirus, should not be confused with Bocas virus, a type of Coronavirus (Group IV).

Group IV Viruses—Hepevirus should not be confused with the orthographically similar “herpesvirus.” Also, readers should not confuse Class Hepeviridae (Hepatitis E virus) with Class Hepacivirus, a subclass of Class Flaviviridae that contains the Hepatitis C virus. Neither of these Group IV subclasses should be confused with Class Hepadnaviridae (Group VII).

Group IV Viruses—Readers should not confuse Rubella virus with the measles virus, Rubeola. Rubeola virus is a paramyxovirus (Group V), unrelated to Rubella virus.

Group V Viruses—One member of Class Arenaviridae, Lassa virus, the cause of Lassa fever, should not be confused with Lyssa virus, a member of Class Rhabdoviridae and the cause of rabies.

Group V and VI viruses—Readers should be careful not to confuse Class Deltaretrovirus (a class of Group VI retroviruses) with Class Deltavirus, a Group V single-strand RNA negative-strand virus containing Hepatitis delta virus.
Group VI Viruses—Readers should not confuse HTLV-III, a virus discovered in 2005, and which is not known at this time to produce disease in infected humans, with an early name (long since abandoned) that was assigned to the HIV virus.

Glossary

**Dictionary** A terminology or word list accompanied by a definition for each item.

**Hematoxylin and eosin** Abbreviation: H&E. The most common stain used in pathology laboratories. With H&E staining, the nuclei of cells are blue, and the cytoplasm is pink. Without staining, cells are colorless (except for those cells that are pigmented, such as melanocytes), and the anatomic parts of the cell (nucleus, cell membrane, nucleolus, brush borders, etc.) cannot be easily distinguished. The development of histologic staining techniques in the 19th century was among the most important advances in medical science.

**Negative classifier** A negative classifier is a feature whose absence is used to exclude an organism from a taxonomic class; it is the riskiest way to assign classes. A species may lack a particular feature because none of its ancestors ever had the feature, as might be the case in a valid lineage of organisms. An example is the Collembola, popularly known as springtails, a ubiquitous member of Class Hexapoda, and easily found under just about any rock. These organisms look like fleas (same size, same shape) and were formerly included among the true fleas (Class Siphonaptera). Like fleas, springtails are wingless, and it was assumed that springtails, like fleas, lost their wings somewhere in evolution's murky past. However, true fleas lost their wings when they became parasitic. Springtails never had wings, an important taxonomic distinction separating springtails from fleas. Today, springtails (Collembola) are not classed with fleas or with any member of Class Insecta. They belong to Class Entognatha, a separate subclass of Class Hexapoda. Alternately, taxonomists may be deceived by a feature whose absence is falsely conceived to be a fundamental property of a class of organisms. For example, Class Fungi was believed to have a characteristic absence of a flagellum. Based on the absence of a flagellum, the fungi were excluded from Class Opisthokonta and were put in Class Plantae, which they superficially resembled. However, the chytrids, recently shown to be a primitive member of Class Fungi, have a flagellum. This places fungi among the true descendants of Class Opisthokonta.

**Nomenclature** A nomenclature is a listing of terms that cover all of the concepts in a knowledge domain. A nomenclature is different from a dictionary for three reasons: (1) the nomenclature terms are not annotated with definitions, (2) nomenclature terms may be multiword, and (3) the terms in the nomenclature are limited to the scope of the selected knowledge domain. In addition, most nomenclatures group synonyms under a group code. For example, a food nomenclature might collect submarine, hoagie, po’ boy, grinder, hero, and torpedo under an alphanumeric code such as “F63958.” Nomenclatures simplify textual documents by uniting synonymous terms under a common code. Documents that have been coded with the same nomenclature can be integrated with other documents that have been similarly coded, and queries conducted over such documents will yield the same results, regardless of the term is entered (i.e., a search for either hoagie or po’ boy will retrieve the same information, if both terms have been annotated with the synonym code, “F63948”). Optimally,
the canonical concepts listed in the nomenclature are organized into a hierarchical classification [103, 104].

**Problematica** The term “problematica” is used by taxonomists to indicate a class of organism that defies robust classification [105]. The very existence of this term tells us that taxonomy is a delicate and tentative science. We must always be prepared to examine and test our current classification, and to make corrections wherever warranted.

**Proximate cause** Synonymous with the immediate cause. The proximate cause of a biological event is the closest action that can be held responsible for the cause of the event. For example, the rupture of a blood vessel in the lung may be the proximate cause of death, while an invasive lung cancer may have been the underlying cause of death. The erosion of a vessel by tumor cells was one of the sequence of events leading from the underlying cause of death to the proximate cause of death. The underlying cause of death satisfies the “but-for” condition. But for the lung cancer, the vessel would not have eroded, and blood would not have flooded the lung tissue. The proximate cause of death need not be a necessary condition resulting from the underlying cause of death. Had the vessel not ruptured, the individual may have died from an alternate proximate cause (e.g., metastasis, pneumonia).

**Root cause** The earliest event or condition that is known to set in motion a chain of additional events that can result in some specified result. The term “root cause” is preferable to another term “underlying cause” that is often applied to the same concept. Any of the events that precede a result could be construed as underlying causes. The term “root cause” conveys the idea of a first or earliest event in a multievent process.

Of course, we can never be certain what the earliest event is in any process. For example, infections from Naegleria fowleri result from exposure to free-living organisms in their natural habitat (pond and river water). The organism travels from the nose to the brain, where it causes a meningoencephalitis. It seems self-evident that Naegleria fowleri is the root cause of Naeglerian meningoencephalitis. Maybe not.

Because these organisms are widely found in water, it is presumed that millions of people are exposed to the organism, but only very few individuals develop meningoencephalitis. It is not known why most people are unaffected by the organism, while others develop a rapidly progressive meningoencephalitis. Perhaps the root cause of disease is a very specific deficiency in the host defense system, rendering a few individuals susceptible to infection with a ubiquitous organism. If so, the root cause shifts from the organism to the host.

Even in the simplest of cases, it is difficult to assign a root cause with any certainty. We never know if we’ve looked backwards far enough. Still, we do the best that we can, and we apply the term “root cause” with the understanding that we may need to modify our thinking, if evidence of an earlier event comes to light.

**Serotype** Subtypes of a species of bacteria or virus that differ in their surface antigens.

**Serovar** Same as serotype.

**Unclassifiable objects** Classifications create an hierarchical collection of classes, and their taxonomies assign each and every named object to its correct class. This means that a classification is not permitted to contain unclassified objects; a condition that puts fussy taxonomists in an untenable position. Suppose you have an object, and you simply do not know enough about the object to confidently assign it to a class. Or, suppose you have an object that seems to fit more than one class, and you can’t decide which class is the correct class. What do you do? Historically, scientists have resorted to creating a “miscellaneous,” “problematica,” or “incertae sedis” (uncertain placement) class into
which otherwise unclassifiable objects are given a temporary home, until more suitable accommodations can be provided [105].

Historically, the promiscuous application of “miscellaneous” classes has proven to be a huge impediment to the advancement of the biological sciences. In the case of the classification of living organisms, the class of protozoans stands as a case in point. Ernst Haeckel, a leading biological taxonomist in his time, created the Kingdom Protista (i.e., protozoans), in 1866, to accommodate a wide variety of simple organisms with superficial commonalities. Haeckel himself understood that the protists were a blended class that included unrelated organisms, but he believed that further study would resolve the confusion. In a sense, he was right, but the process took much longer than he had anticipated; occupying generations of taxonomists over the following 150 years. Today, the former members of Kingdom Protista have been reassigned to positions among the animals, plants, and fungi. In the meantime, therapeutic opportunities for eradicating the so-called protozoal infections, using class-targeted agents, have no doubt been missed [3]. For practical reasons, textbooks still use the term “protozoan,” but strictly speaking, Kingdom Protista no longer exists [95].

You may think that the creation of a class of living organisms, with no established scientific relation to the real world, was a rare and ancient event in the annals of biology, having little or no chance of being repeated. Not so. A special pseudoclass of fungi, deuteromycetes (spelled with a lowercase “d,” signifying its questionable validity as a true biologic class) has been created to hold fungi of indeterminate speciation. Currently, there are several thousand such fungi, sitting in a taxonomic limbo, waiting to be placed into a definitive taxonomic class [3, 46].

**Underlying cause** The event that initiated the sequence of events leading to some clinical outcome (e.g., disease). Death certificates require physicians to list the underlying cause of death. The World Health Organization, aware of the difficulties in choosing an underlying cause of death, and assigning a sequential list of the ensuing clinical consequences leading to the proximate cause of death, has issued reporting guidelines [106]. Instructions notwithstanding, death certificate data are notoriously inconsistent, giving rise to divergent methods of reporting the diseases that cause death [107–109].

Reluctantly, we must acknowledge that, in any biological system, we can seldom designate the underlying causes with any certitude. One event may lead to many other events, and events which we believe to be initiating may have their own predicative causes.

**Vector** An organism that moves a disease-causing organism from one host to another. Diseases spread by vectors include malaria, plague, leishmaniasis, African trypanosomiasis, relapsing fever, yellow fever, dengue fever and dengue hemorrhagic fever, hantavirus disease, West Nile encephalitis, Japanese encephalitis, Rift Valley fever, Venezuelan equine encephalitis, and chikungunya. All arboviruses have arthropod vectors, and there are about 100 known arboviruses that cause human disease [52]. One vector can carry more than one type of infectious organism. For example, a single species of Anopheles mosquito can transmit Dirofilaria immitis, O'nyong'nyong fever virus, Wuchereria bancrofti, and Brugia malayi. Obversely, one disease organism can be spread by more than one vector. For example, orbiviruses are spread by mosquitoes, midges, gnats, sandflies, and ticks.
References

[1] Jacomo V, Kelly PJ, Raoult D. Natural history of Bartonella infections (an exception to Koch's postulate). Clin Diagn Lab Immunol 2002;9:8–18.
[2] Woodgyer A. The curious adventures of Trichophyton equinum in the realm of cellular biology: a modern fairy tale. Med Mycol 2004;42:397–403.
[3] Berman JJ. Taxonomic guide to infectious diseases: understanding the biologic classes of pathogenic organisms. Cambridge, MA: Academic Press; 2012.
[4] Ren L-Q, Li X-J, Li G-S, Zhao Z-T, Sun B, Sun F. Coxsackievirus B3 infection and its mutation in Keshan disease. World J Gastroenterol 2004;10:3299–302.
[5] Wang SS. Big bone disease fades in China. Wall Street J 2011.
[6] Whipple GH. A hitherto undescribed disease characterized anatomically by deposits of fat and fatty acids in the intestinal and mesenteric lymphatic tissues. Bull Johns Hopkins Hosp 1907;18:382–93.
[7] Relman DA, Schmidt TM, MacDermott RP, Falkow S. Identification of the uncultured bacillus of Whipple's disease. N Engl J Med 1992;327:293–301.
[8] Marth T, Roux M, von Herbay A, Meuer SC, Feurle GE. Persistent reduction of complement receptor 3 alpha-chain expressing mononuclear blood cells and transient inhibitory serum factors in Whipple's disease. Clin Immunol Immunopathol 1994;72:217–26.
[9] Iverson SA, Ostdiek S, Prasai S, Engelthaler DM, Kretschmer M, Fowle N, et al. Notes from the field: cluster of acute flaccid myelitis in five pediatric patients—Maricopa County, Arizona, 2016. MMWR—Morb Mortal Wkly Rep 2017;66:758–60.
[10] Schoenborn L, Abdollahi H, Tee W, Dyall-Smith M, Janssen PH. A Member of the Delta Subgroup of Proteobacteria from a pyogenic liver abscess is a typical sulfate reducer of the genus Desulfovibrio. J Clin Microbiol 2001;39:787–90.
[11] Janda JM, Abbott SL. 16S rRNA gene sequencing for bacterial identification in the diagnostic laboratory: pluses, perils, and pitfalls. J Clin Microbiol 2007;45:2761–4.
[12] Woo PC, Lau SK, Teng JL, Tse H, Yuen KY. Then and now: use of 16S rDNA gene sequencing for bacterial identification and discovery of novel bacteria in clinical microbiology laboratories. Clin Microbiol Infect 2008;14:908–34.
[13] Barlett DL, Steele JB. Monsanto's Harvest of Fear. Vanity Fair; 2008.
[14] Srinivasan R, Karaoz U, Volegov M, MacKichan J, Kato-Maeda M, Miller S, et al. Use of 16S rRNA gene for identification of a broad range of clinically relevant bacterial pathogens. PLoS One 2015;10:e0117617.
[15] Wang Q, Garrity GM, Tiedje JM, Cole JR. Naive Bayesian classifier for rapid assignment of RNA sequences into the new bacterial taxonomy. Appl Environ Microbiol 2007;73:526–5267.
[16] Simmons G, Glynn SA, Komaroff AL, Mikovits JA, Tobler LH, Hackett J, et al. Failure to confirm XMRV/MLVs in the blood of patients with chronic fatigue syndrome: a multi-laboratory study. Science 2011;334:814–7.
[17] Inglis TJ. Principia aetiologica: taking causality beyond Koch's postulates. J Med Microbiol 2007;56:1419–22.
[18] Forterre P. The two ages of the RNA world, and the transition to the DNA world: a story of viruses and cells. Biochimie 2005;87:793–803.
[19] Prusiner SB. Novel proteinaceous infectious particles cause scrapie. Science 1982;216:136–44.
[20] Aguzzi A, Heikenwalder M. Pathogenesis of prion diseases: current status and future outlook. Nat Rev Microbiol 2006;4:765–75.
[21] Michelitsch MD, Weissman JS. A census of glutamine/asparagine-rich regions: implications for their conserved function and the prediction of novel prions. PNAS 2000;97:11910–5.

[22] Asante EA, Linehan JM, Smidak M, Tomlinson A, Grimshaw A, et al. Inherited prion disease a117v is not simply a proteinopathy but produces prions transmissible to transgenic mice expressing homologous prion protein. PLoS Pathog 2013;9:e1003643.

[23] Watts JC, Prusiner S. Mouse models for studying the formation and propagation of prions. J Biol Chem 2014;289:19841–9.

[24] Bernardi L, Cupidi C, Bruni AC. Pathogenic mechanisms of the prion protein gene mutations: a review and speculative hypotheses for pathogenic potential of the pro39leu mutation in the associated ftd-like phenotype. J Neurol Neurosci 2017;8:208.

[25] Kabani M, Melki R. Yeast prions assembly and propagation: contributions of the prion and non-prion moieties and the nature of assemblies. Prion 2011;5:277–84.

[26] Saleem F, Bjorndahl TC, Ladner CL, Perez-Pineiro R, Ametaj BN, Wishart DS. Lipopolysaccharide induced conversion of recombinant prion protein. Prion 2014;8:221–32.

[27] Supattapone S. Prion protein conversion in vitro. J Mol Med 2004;82:348–56.

[28] Castle AR, Gill AC. Physiological functions of the cellular prion protein. Front Mol Biosci 2017;4:19.

[29] Schmitz M, Zafar S, Silva CJ, Zerr I. Behavioral abnormalities in prion protein knockout mice and the potential relevance of PrPC for the cytoskeleton. Prion 2014;8:381–6.

[30] Safar J. Molecular pathogenesis of sporadic prion disease in man. Prion 2012;6:108–15.

[31] Ayers JI, Giasson BI, Borchelt DR. Prion-like spreading in tauopathies. Biol Psychiatry 2018;83:337–46.

[32] Alpers MP. The epidemiology of kuru: monitoring the epidemic from its peak to its end. Philos Trans R Soc B 2008;363:3707–10.

[33] Gambetti P, Cali I, Notari S, Kong Q, Zou WQ, Surewicz WK. Molecular biology and pathology of prion strains in sporadic human prion diseases. Acta Neuropathol 2011;121:79–90.

[34] Prusiner SB, Woerman AL, Mordes DA, Watts JC, Rampersaud R, Berry DB, et al. Evidence for alpha-synuclein prions causing multiple system atrophy in humans with parkinsonism. Proc Natl Acad Sci U S A 2015;112:E5308–17.

[35] Jucker M, Walker LC. Self-propagation of pathogenic protein aggregates in neurodegenerative diseases. Nature 2013;501:45–51.

[36] Kane MD, Lipinski WJ, Callahan MJ, Bian F, Durham RA, Schwarz RD, et al. Evidence for seeding of beta-amyloid by intracerebral infusion of Alzheimer brain extracts in beta-amyloid precursor protein-transgenic mice. J Neurosci 2000;20:3606–11.

[37] Nizhnikov AA, Antonets KS, Bondarev SA, Inge-Vechtomov SG, Derkatch IL. Prions, amyloids, and RNA: pieces of a puzzle. Prion 2016;10:182–206.

[38] Craig J. Complex diseases: research and applications. Nat Educ 2008;1:1.

[39] Loria K. One of the largest human experiments in history was conducted on unsuspecting residents of San Francisco. Business Insider 2015;.

[40] Silberman JD, Sogin ML, Leipe DD, Clark CG. Human parasite finds taxonomic home. Nature 1996;380:398.

[41] Amin OM. Seasonal prevalence of intestinal parasites in the United States during 2000. Am J Trop Med Hyg 2002;66:799–803.

[42] Sekas G, Hutson WR. Misrepresentation of academic accomplishments by applicants for gastroenterology fellowships. Ann Intern Med 1995;123:38–41.

[43] Samuelson J. Why metronidazole is active against both bacteria and parasites. Antimicrob Agents Chemother 1999;3:1533–41.
[44] Inamadar AC, Palit A. The genus Malassezia and human disease. Indian J Dermatol Venereol Leprol 2003;69:265–70.
[45] de Mauri A, Chiarinotti D, Andreoni S, Molinari GL, Conti N, De Leo M. Leclercia Adecarboxylyata and catheter-related bacteremia: review of the literature and outcome of catheters and patients. J Med Microbiol 2013;
[46] Guarro J, Gene J, Stichgel AM. Developments in fungal taxonomy. Clin Microbiol Rev 1999;12:454–500.
[47] Pounder JI, Simmon KE, Barton CA, Hohmann SL, Brandt ME, Petti CA. Discovering potential pathogens among fungi identified as nonsporulating molds. J Clin Microbiol 2007;45:568–71.
[48] Garrison FH. History of medicine. Philadelphia: WB Saunders; 1921.
[49] Baron EJ, Allen SD. Should clinical laboratories adopt new taxonomic changes? If so, when? Clin Infect Dis 1993;16:S449–50.
[50] Committee on A Framework for Developing a New Taxonomy of Disease, Board on Life Sciences, Division on Earth and Life Studies, National Research Council of the National Academies. Toward precision medicine: building a knowledge network for biomedical research and a new taxonomy of disease. Washington, DC: The National Academies Press; 2011.
[51] The state of world health. Chapter 1 in World Health Report 1996. World Health Organization. Available from: http://www./whr/1996/en/index.html; 1996.
[52] Lemon SM, Sparling PF, Hamburg MA, Relman DA, Choffnes ER, Mack A. Vector-borne diseases: understanding the environmental, human health, and ecological connections, workshop summary. Institute of Medicine (US) Forum on Microbial Threats. Washington (DC): National Academies Press (US); 2008.
[53] Fan L, Lee SY, Koay E, Harkensee C. Plasmodium knowlesi infection: a diagnostic challenge. BMJ Case Rep 2013;2013:.
[54] Caboche S, Audebert C, David HD. High-throughput sequencing, a versatile weapon to support genome-based diagnosis in infectious diseases: applications to clinical bacteriology. Pathogens 2014;3:258–79.
[55] Zoll J, Snelders E, Verweij PE, Melchers WJ. Next-generation sequencing in the mycology lab. Curr Fungal Infect Rep 2016;10:37–42.
[56] Zimmer C. In a first, test of DNA finds root of illness. The New York Times; 2014.
[57] Massana R, Guillou L, Diez B, Pedros-Alio C. Unveiling the organisms behind novel eukaryotic ribosomal DNA sequences from the ocean. Appl Environ Microbiol 2002;68:4554–8.
[58] Stoeck T, Fowle WH, Epstein SS. Methodology of protistan discovery: from rRNA detection to quality scanning electron microscope images. Appl Environ Microbiol 2003;69:6856–63.
[59] Romero EC, Billerbeck AEC, Lando VS, Camargo ED, Souza CC, Yasuda PH. Detection of leptospira DNA in patients with aseptic meningitis by PCR. J Clin Microbiol 1998;36:1453–5.
[60] Sainani K. Error: what biomedical computing can learn from its mistakes. Biomed Comput Rev 2011;Fall:12–9.
[61] Sainani K. Meet the skeptics: why some doubt biomedical models, and what it takes to win them over. Biomed Comput Rev 2012;.
[62] Unreliable research: Trouble at the lab. The Economist; 2013.
[63] Kolata G. Cancer fight: unclear tests for new drug. The New York Times; 2010.
[64] Baker M. Reproducibility crisis: blame it on the antibodies. Nature 2015;521:274–6.
[65] Ioannidis JP. Is molecular profiling ready for use in clinical decision making? Oncologist 2007;12:301–11.
[66] Ioannidis JP. Why most published research findings are false. PLoS Med 2005;2:e124.
[67] Ioannidis JP. Some main problems eroding the credibility and relevance of randomized trials. Bull NYU Hosp Jt Dis 2008;66:135–9.

[68] Ioannidis JP. Microarrays and molecular research: noise discovery? Lancet 2005;365:454–5.

[69] Ioannidis JP, Panagiotou OA. Comparison of effect sizes associated with biomarkers reported in highly cited individual articles and in subsequent meta-analyses. JAMA 2011;305:2200–10.

[70] Ioannidis JPA, Panagiotou OA. Comparison of effect sizes associated with biomarkers reported in highly cited individual articles and in subsequent meta-analyses. JAMA 2011;305:2200–10.

[71] Ioannidis JP. Excess significance bias in the literature on brain volume abnormalities. Arch Gen Psychiatry 2011;68:773–80.

[72] Pocock SJ, Collier TJ, Dandreo KJ, de Stavola BL, Goldman MB, Kalish LA, et al. Issues in the reporting of epidemiological studies: a survey of recent practice. BMJ 2004;329:883.

[73] Misconduct in science: an array of errors. The Economist; 2011.

[74] Begley S. In cancer science, many ‘discoveries’ don’t hold up. Reuters 2012;.

[75] Abu-Asab MS, Chaouchi M, Alesci S, Galli S, Laassri M, Cheema AK, et al. Biomarkers in the age of omics: time for a systems biology approach. OMICS 2011;15:105–12.

[76] Moyer VA, on behalf of the U.S. Preventive Services Task Force. Screening for prostate cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2011;.

[77] How science goes wrong. The Economist; 2013.

[78] Gayathri D, Rashmi BS. Development of celiac disease: pathogenesis and strategies to control: a molecular approach. J Nutr Food Sci 2014;4:310.

[79] Bouziat R, Hinterleitner R, Brown JJ, Stencel-Baerenwald JE, Ikizler M, Mayassi T, et al. Reovirus infection triggers inflammatory responses to dietary antigens and development of celiac disease. Science 2017;356:44–50.

[80] Heiligenhaus A, Kasper M, Grajewski R. hla-b27 positive acute anterior uveitis: a translational perspective. Klin Monatsbl Augenheilkd 2017;234:652–6.

[81] Chen B, Li J, He C, Li D, Tong W, Zou Y, et al. Role of HLA-B27 in the pathogenesis of ankylosing spondylitis. Mol Med Rep 2017;15:1943–51.

[82] Resnikoff S, Pascolini D, Etyaale D, Kocur I, Pararajasegaram R, Pokharel GP, et al. Global data on visual impairment in the year 2002. Bull World Health Org 2004;82:844–51.

[83] Slatko BE, Taylor MJ, Foster JM. The Wolbachia endosymbiont as an anti-filarial nematode target. Symbiosis 2010;51:55–65.

[84] Johnson TP, Tyagi R, Lee PR, Lee MH, Johnson KR, Kowalak J, et al. Nodding syndrome may be an autoimmune reaction to the parasitic worm Onchocerca volvulus. Sci Transl Med 2017;9:377.

[85] Liu Y, Chiba M, Inaba Y, Kondo M. Keshan disease—a review from the aspect of history and etiology. Nihon Eiseigaku Zasshi 2001;56:641–8.

[86] Badorff C, Lee GH, Knowlton KU. Enteroviral cardiomyopathy: bad news for the dystrophin-glycoprotein complex. Herz 2000;25:227–32.

[87] The Alzheimer’s Disease Anti-inflammatory Prevention Trial Research Group. Results of a follow-up study to the randomized Alzheimer’s Disease Anti-inflammatory Prevention Trial (ADAPT). Alzheimers Dement 2013;9:714–23.

[88] Singhrao SK, Harding A, Poole S, Kesavalu L, Crean S. Porphyromonas gingivalis periodontal infection and its putative links with Alzheimer’s disease. Mediat Inflamm 2015;2015:137357.
[89] Dominy SS, Lynch C, Ermini F, Benedyk M, Marczyk A, Konradi A, et al. Porphyromonas gingivalis in Alzheimer’s disease brains: evidence for disease causation and treatment with small-molecule inhibitors. Sci Adv 2019;.

[90] Vellas B, Carrie I, Gillette-Guyonnet S, Touchon J, Dantoine T, Dartiges JF, et al. MAFT study: a multidomain approach for preventing alzheimer's disease: design and baseline data. J Prev Alzheimers Dis 2014;1:13–22.

[91] Cavalier-Smith T. The phagotrophic origin of eukaryotes and phylogenetic classification of Protozoa. Int J Syst Evol Microbiol 2002;52(Pt 2):297–354.

[92] Braun U. The impacts of the discontinuation of dual nomenclature of pleomorphic fungi: the trivial facts, problems, and strategies. IMA Fungus 2012;3:81–6.

[93] Malik A, Janeel MN, Sohail S, Mir S. Human granulocytic anaplasmosis affecting the myocardium. J Gen Intern Med 2005;20:958.

[94] Scamardella JM. Not plants or animals: a brief history of the origin of Kingdoms Protozoa, Protista and Proctostista. Int Microbiol 1999;2:207–16.

[95] Schlegel M, Hulsmann N. Protists: a textbook example for a paraphyletic taxon. Org Divers Evol 2007;7:166–72.

[96] Suggested Upper Merged Ontology (SUMO). The OntologyPortal Available from: http://www.ontologyportal.org/; viewed August 14, 2012.

[97] Adl SM, Simpson AGB, Farmer MA, Anderson RA, Anderson OR, Barta JR, et al. The new higher level classification of eukaryotes with emphasis on the taxonomy of protists. J Eukaryot Microbiol 2005;52:399–451.

[98] Berman JJ. Methods in medical informatics: fundamentals of healthcare programming in perl, python, and ruby. Boca Raton: Chapman and Hall; 2010.

[99] Traa BS, Walker CL, Munos M, Black RE. Antibiotics for the treatment of dysentery in children. Int J Epidemiol 2010;39(suppl_1):70–4.

[100] Khatchadourian K, Ovetchkine P, Minodier P, Lamarre V, Lebel MH, Tapiero B. The rise of the rats: a growing paediatric issue. Paediatr Child Health 2010;15:131–4.

[101] Schlager E, Ashack K, Khchemoune A. Erosio interdigitalis blastomycetica: a review of interdigital candidiasis. Dermatol Online J 2018;24:1.

[102] Restrepo A, De Uribe L. Isolation of fungi belonging to the genera Geotrichum and Trichosporum from human dermal lesions. Mycopathologia 1976;59:3–9.

[103] Berman JJ. Tumor classification: molecular analysis meets Aristotle. BMC Cancer 2004;4:10.

[104] Berman JJ. Tumor taxonomy for the developmental lineage classification of neoplasms. BMC Cancer 2004;4:88.

[105] Jenner RA, Littlewood TJ. Problematika old and new. Philos Trans R Soc B 2008;363:1503–12.

[106] U.S. Vital Statistics System: major activities and developments, 1950–95. Centers for Disease Control and Prevention, National Center for Health Statistics; 1997.

[107] Ashworth TG. Inadequacy of death certification: proposal for change. J Clin Pathol 1991;44:265.

[108] Kircher T, Anderson RE. Cause of death: proper completion of the death certificate. JAMA 1987;258:349–52.

[109] Berman JJ. Rare diseases and orphan drugs: keys to understanding and treating common diseases. Cambridge, MD: Academic Press; 2014.