One of the major forces, if not the major force, that propelled the evolution and growth of microbiology as a scientific discipline has been and remains the effort to understand and to alleviate disease related to the incursion of “foreign” microorganisms into humans, domestic animals, and crops. The concern about disease has been a real presence in all of recorded history; long before the microbial and viral role in infection was discerned, Girolamo Fracastoro (1478–1553)—forgotten or, at best, neglected—described contagion as an infection that was transmitted from one individual to another. Indeed, he listed three forms of contagion—contact, fomites, and airborne—omitting only disease agents carried by insect vectors but postulating a form of seed or “germ” as the vehicle responsible for transmission. Parenthetically, Fracastoro coined the term “sифилис” in a poem describing the clinical manifestations of this disease.

The 19th century could be described as the age of microbial discovery with the recognition, isolation, and detailed description of many of the bacteria responsible for the scourges that plagued humans and their food supplies for the course of recorded history. As a microbiologist, I find the temptation to list all of the giants of bacteriology and the geniuses such as Louis Pasteur and Robert Koch almost irresistible.

My task, however, is to remind my colleagues in immunology and readers of this journal that the concerns of the original scientists active in all aspects of medical microbiology were not focused on the responsible microbial entity alone but rather on the causal relationship between that entity and the host as far as so-called pathogenic agents were concerned. Edward Jenner’s use of the vaccinia virus to protect against smallpox adumbrated the efforts of Louis Pasteur to use attenuated strains of bacteria and the rabies virus to protect animals and humans with vaccination, a term retained in recognition of Jenner’s great contribution. Koch attempted to attain similar success with the ill-fated administration of tuberculin. These are just a few instances to demonstrate the total awareness of all the individuals engaged in microbiological research of the role of the host—the patient and the healthy contact, often assumed to be immune following a previous experience with the same microorganism. Pasteur was not satisfied with his practical successes but attempted to explain the mechanism of the protection afforded by vaccination or immunity with his “exhaustion hypothesis,” which suggested that resistance to disease was intimately involved with the disappearance of nutrients from the body consumed by the infectious agent during its initial encounter with the host organism.

Elie Metchnikoff (1845–1916) was the first scientist to recognize the significant role of the professional phagocytes in the host’s response to microbial challenges. This was first observed with phagocyte-like cells in the larvae of sea stars challenged with rose thorns introduced by Metchnikoff. His quasi-intuitive application of this observation to the defense mechanisms of higher animals and humans is a striking illustration of the cosmopolitan interests of the 19th-century investigators and the benefits of a broad rather than a narrow approach to the subjects under investigation. Metchnikoff’s emphasis on cellular immunity as the sole purveyor of host defenses exaggerated this particular arm of immunity and met with neglect until its more recent revival in a modified fashion integrated into the larger perception of the host immune response. Nevertheless, the concern for understanding the host response to microbial challenges and the demonstration of neutrophil and macrophage phagocytosis of microorganisms were the initial steps in the explanation of cellular immunity.

At the same time that Metchnikoff described phagocytosis, other bacteriologists became intrigued with the serological responses of mammals and humans to microbial challenges. Nuttall demonstrated in 1888 that some bacteria were killed by defibrinated animal blood, a finding to be followed the following year by Buchner’s demonstration that serum was bactericidal, a property readily abolished by heating at 55°C for 1 h and called “alexine” by Buchner. Jules Bordet refined these observations in 1893 while studying the Pfeiffer phenomenon, the bacteriolysis of Vibrio cholerae when the bacterium is introduced into the peritoneum of guinea pigs immunized with killed cultures of the bacterium. Bordet showed that the alexine of Buchner, “complement” in today’s terminology created by Ehrlich, was required for the lytic activity preceded by the sensitizing action of Bordet’s “substance sensibilatrice” (antibody), the result of immunization with the particular bacterium. Bordet also noted that the vibrios clumped when exposed to the serum, leading Gruber and Durham to explore the phenomenon of agglutination. Interestingly, Bordet followed his work with vibrios with immunizing animals with the erythrocytes of other species and showed that they were lysed just like the bacteria in the presence of specific antibodies and complement.

While the efforts with bacteria were in progress, Emil Behring and S. Kitasato, the latter credited with the actual isolation of Clostridium tetani, demonstrated that animals immunized with sublethal doses of toxin produced sera that neutralized the toxin and could protect normal animals from usually lethal doses of toxin. Indeed, similar results were achieved with snare venom and plant toxins, leading investigators to explore the chemical and physical attributes of what we now call the antigen-antibody interactions.

Another important step in the evolution of immunity ascribable to microbiological efforts was the demonstration by several investigators at the turn of this century that the presence of immune serum was needed for the phagocytosis of...
streplococci, the process of opsonification described by Wright and Douglas in 1903 and confirmed further by Neufeld and Rimpau in 1904 and 1905. These observations advanced the perception of humoral immunity since phagocytosis was enhanced in the presence of antibodies, complement, toxins, and other microbial products. Therapeutic approaches have been based on these considerations ever since, albeit modified as the complexities of the host-parasite interaction became evident.

Even the problem of hypersensitivity had its origins in observations accompanying use of microorganisms and viruses. Jenner's description of the exaggerated reaction resulting from a second injection of vaccinia or Koch's discovery of the tuberculin reaction in addition to studies with nonmicrobial antigens led to the recognition of immediate and delayed hypersensitivities, with anaphylaxis being the worst example of the former, and of its transferability with the sera of immunized individuals. Investigators were justifiably impressed with the specificity of the immune response especially in view of the seemingly unlimited array of antigens and their specific antibodies, the nature of each being totally unknown. Many different efforts emerged to define the properties of antigens and antibodies and to integrate that knowledge into an appreciation of the biology of immunity. Numerous investigators have played significant roles in the discoveries of today's concepts of immunology, many of whom considered themselves microbiologists or fell back on the microorganisms as ideal objects for the proof of new hypotheses.

It may be a microbiologist's prejudice, but the most profound influence on the emerging concepts of immunology was exercised by Paul Ehrlich (1854–1915). Besides the application of aniline dyes for the visualization of microorganisms including mycobacteria and his work with finding appropriate drugs for protozoan diseases and syphilis, he defined the quantitation of antitoxin by using the plant toxins abrin and ricin and initiated the standardization of diphtheria antitoxin, a boon to the children of the world at the turn of the century. Ehrlich was intrigued by immune specificity and worked hard to find a theoretical basis to explain these reactions within his view of biological processes. His “side chain” theory addressed the generation of antibodies by special cells endowed with side chains that would capture antigens, structures he called “receptors.” He suggested that the binding of the antigen to the receptor led to the production of more side chains, which, liberated into the blood, would act as antibodies. He asserted that the antigen-antibody reaction was chemical in nature and visualized the specificity of the reaction as a key (antigen) fitting into a lock (antibody). As usual, many of his colleagues attacked this hypothesis. Later, modifications were advanced, aspects of it expanded, but on the whole his explanation of receptors on cell surfaces and their basic role in the process of living cannot be denied.

Perhaps in keeping with Ehrlich's concept, Obermayer and Pick, and especially Landsteiner, modified numerous soluble proteins by adding nitro groups or reacting functional groups with iodine to produce antibodies totally specific for these small substitutions, leading Landsteiner to coin the term “happen” to describe the specificity-determining configurations. In the 1920s, Heidelberger and Avery initiated the analysis of naturally occurring antigens beginning with the polysaccharide capsules of pneumococci, demonstrating that the antigenic differences resided in the arrangements of various carbohydrate moieties. These first steps led to the serological identification of bacterial species and variants within species, opening the approaches to work with blood group substances and the many presently recognized antigens of the HLA system and elucidating the differences and similarities of animal and plant constituents. Thus, the investigations of microbial differences, the host’s reactivity to harmful members of the microbial world, and the host’s tolerance and in many cases the symbiosis of the normal microbiota with animal and plant surfaces and structures provided the scientific foundation of immunology as an independent discipline.

Nevertheless, our collective ignorance makes it desirable, perhaps necessary, that the two sciences remain intimately interactive. The contributions and discoveries in each field have repercussions in the other and in disciplines such as biochemistry and molecular biology, derived to an appreciable degree from microbiology. The initial, understandable concern that scientists and especially physicians expressed for the alleviation or at least palliation of human disease now embraces many other living and inanimate matters, especially as our sights now include space dwellings and explorations. The lines that delineate scientific disciplines are losing the distinctiveness so apparent at the close of the 19th century; as we enter the second century of the American Society for Microbiology, one can only hope that this discipline will continue to generate approaches that expand the human understanding of nature and eventually of the humans themselves.

The views expressed in this Commentary do not necessarily reflect the views of the journal or of ASM.