Edwin L. Cooper *Editor*

Advances in Comparative Immunology

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Preface

Punch's almanac for 1882: 'Man is but a worm', published in Punch Magazine on 6 December 1881. The satirical cartoon shows how Darwin has evolved from chaos, over earthworms to respectable gentleman.

The first version of *Comparative Immunology* (1976) was an integral part of the early full summation of the field. We included for the first time 16 chapters which treated the immune systems of various phyla in depth: (1) the immune system, (2) phylogeny of the immune response, (3) nature of antigens, (4) phagocytosis, (5) quasi-immune recognition and primordial cell-mediated immunity, (6) primordial cell-mediated immunity, (7) the machinery of the immune system, (8) development of transplantation immunity, (9) characteristics of transplantation immunity, (10) genetic control and transplantation immunobiology, (11) invertebrate humoral immunity, (12) antibody synthesis, (13) the immunoglobulins, (14) activities of immune cells, (15) immunosuppression, and (16) epilogue.

That was the leading edge of our knowledge in 1976. There is a different approach in this book, some 42 years later. This assumes that readers are now educated enough to obviate the need to explicate intricacies of the immune response in great detail. That detail was an essential approach for the first edition – not so for the first revision. After all, many mechanisms are now sufficiently understood. Instead this revision has another approach: a focus on unique models, groups, exotic species – no need to spend time *ad nauseam* explaining antigen-antibody reactions in mice! The successors are animal species perhaps more interesting and exotic. Rather more exciting – the response in bats! After all, bats are carriers of various infections, so an analysis of their immune reactions would seem to be more novel. The study of their other physiological adaptations such as echolocation would be more exciting and new! And what about bigger, non-flying mammals – the elephant, promising clues to the scourge of cancer and dampening, we hope significantly, the urge to extinguish them permanently in their native habitats!

The 1976 edition dealt with humoral immunity in 4 phyla within a single 29-page chapter: echinoderms, mollusks, annelids, and arthropods. The book you hold now disperses these phyla into separate chapters that focus on different functions. Therefore, readers of this new edition can expect to find numerous characteristics of immune phenomena in separate animal taxa being presented in depth. This is evidence that the field has advanced immeasurably since the first edition.

The emphasis now is on function, a veritable *jardin zoologique*, not technique. Moreover, methods and materials must often be modified for phyla that have distinct characteristics. For example, to perform a skin allograft on a fish, we transplant scales and watch the degeneration of melanophores as an indication that the graft is destroyed by the host immune system. In contrast, the equivalent skin graft in a mouse would require suturing or more drastic methods, then watching the healing process including signs of cicatrix formation, hemostasis, and ultimately rejection. Independently of technique, the principle is rejection of *non-self*, and the acceptance of *self*, whether fish scales or mouse skin. Another example of the widening scope of comparative immunology is single cell organisms. In 1976, knowledge of the prokaryotic immune response was nascent, as studies of restriction enzymes to cut viral DNA were just ramping up. Thanks to the discovery/addition of CRISPR (very simply, editing of disorganized nucleic acid) to the toolkits of prokaryotes and immunologists, the explication of *self/not self* and immune reactions at the molecular level should make significant strides forward.

Part 1 of this book looks at the immune system in taxa from prokaryotes to urochordates, all of them invertebrates. The overarching first chapter summarizes the evolution of immunity. This segues into discussions of amoebae, corals, flatworms, and roundworms. Annelids, arthropods, and mollusks are covered in three, two, and two chapters respectively. (To spread these three phyla into seven chapters would have been unthinkable in the first edition; too little was known!) Echinoderm immunology introduces us to the deuterostomes. Urochordates, which include tunicates, are a suitable bookend; they are among the most "primitive" of the chordates.

Part 2 covers cephalochordates up to and including mammals. The cephalochordates include branchiostomes (lancelets or amphioxus), fishes (cartilaginous and bony), reptiles, and birds (with focus on ostriches). This section ends with chapters that consider immunity in bats and elephants, followed by the phylogeny of nasopharynx lymphoid tissue.

Part 3 considers certain broader implications and vulnerabilities due to worldwide climate change, cancer, therapy, and the quest for more diverse food sources. Immune responses in poikilotherms and ectotherms are vulnerable to temperature change making them sources of information that senior comparative immunologists always knew – internal temperature will affect the outcome and reproducibility of trials – a factor of less concern in experimental homeothermic species. The continued search for food sources may turn us to additional edible invertebrates, perhaps more plentiful and less polluting. Variations in immunity within a species and between species are the topic of the chapter on ecoimmunology. Toxicity and disease are explored in earthworms, bivalves, and frogs. The clinical use of maggots in biotherapy is described. The last chapter links cancer and evolution, connecting to evidence for neoplasia in bivalve mollusks seen before in this part.

With such impressive advances in comparative immunology since the first edition of this book, who can predict what the third edition will cover? Surely the maturation of this field within the umbrella of immunology, combined with bright researchers adapting sound techniques, will lead to further basic and applied knowledge.

Acknowledgments and Reminiscences

Rita Beck

It is a pleasure to acknowledge the collaboration of Rita Beck, Publishing Editor at Springer. Rita found an earlier attempt to revise *Comparative Immunology* and realized that no further writing had been initiated. Prompted by a friendly suggestion—why not continue revision?—a productive, cordial, and extremely helpful collaboration was launched, bringing the revision to fruition. I thank Rita for her inestimable help during the writing of this edition and her patience during its revision. We established a realistic due date to coincide with the next International Congress of International Society of Developmental & Comparative Immunology (ISDCI) in June 2018 in Santa Fe, New Mexico. One of our authors, Irene Salinas, is the organizer.

Michael Suzuki

Another person—friend and former PhD student at UCLA—has played an extremely vital role in bringing my revised comparative immunology book to completion. Michael Suzuki knows the field and did much to move forward early experiments of leukocyte biology in earthworms, especially their role in killing foreign cells. Long ago, I had been impressed by Michael's intellect, sense of humor, and taste. Relatively free from teaching undergraduate biology at community colleges in the Los Angeles area, Michael became available part time just when I was desperately in need of a computer expert, unlike myself, a Luddite! In addition to his computer skills, Michael is well read and cultivated and possesses a refined taste in wine, is a capable editor, and always ready to laugh at the vagaries of whatever! Well read and not just religiously devoted to the *New York Times*, Michael moves fluidly between baroque and classical!

Donald Buth

I thank Professor Donald Buth, Department of Ecology and Evolutionary Biology, University of California, Los Angeles (UCLA), for checking the classifications, especially of fishes. Professor Buth is interested in phylogenetic systematics, ecology and evolution in extreme environments, and the evolutionary history of fish; he was recently accorded recognition by his academic senate.

Deepak Devakumar
I would like to acknowledge the work of Deepak Devakumar, Production Editor, Springer, for facilitating the production process. He helped coordinate the transformation of the manuscript into a printed book ready for sale.

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Helene Cooper
Helene, my wife of nearly half a century, has been incredibly effective and efficient at managing our domestic and cultural life in such a way that I never experience any negative surprises with respect to work or creative activity. She is an axle rod on which our familial wheel turns. And if that weren't enough, Helene is and has been supremely supportive, always available, helpful, and dependable. She was the first and only editorial assistant for the journal *Developmental and Comparative Immunology* (DCI). DCI, founded in 1970, was a unique journal devoted to the development and evolution of the immune system. Helene and I were equally excited during four sabbatical leaves in four different countries: Sweden, Switzerland, Egypt, and Italy (generously supported by the Guggenheim, Eleanor Roosevelt, Fulbright, and Humboldt foundations and of course UCLA) or as volunteers on Earthwatch teams aiding other investigators or digging around in archeological pits searching for shards and clues to ancient civilizations or inviting friends and colleagues for long weekends to our farm that has been in the family since 1800 in the Auvergne region of France. Well-being has been and will always be essential manna for a life of creativity. Our children, Astrid and Amaury, and now grandsons Theodore and Adrien Cooper, are thriving and already questioning, alongside their father/grandfather, the differences between frogs and earthworms. Hope lives on!

Career Path
During a long and productive career that has been most enjoyable and exciting, I have had the chance to travel, always searching for ways to explain comparative immunology to those who attended my lectures. Some of my colleagues who remain friends opened their homes and universities to me. Travels have included at least twenty-five countries, four year-long sabbaticals in four different countries supported partially by prestigious foundations, Guggenheim, Eleanor Roosevelt, and Fulbright, as well as the Bologna Institute for Advanced Studies. In addition, the Agency for International Development opened my eyes in 1966 to the culture of Mexico and the Spanish language and gave me the chance to contribute to the basic blueprint for the now ten University of California campus programs that are part of the collaboration between the university and Mexican institutions known as UC MEXUS. After receiving a diploma in Spanish, I became more Mexican, publishing one of my first papers on graft rejection responses in a South American legless amphibian, a relative of frogs and salamanders. I continued my study of French by marrying Helene and in 1976 was invited to present a lecture at the Collège de

France, In addition, I accepted an invitation from Professor Jean Dausset to publish a major review in French in the popular science magazine *La Recherche*.

It is impossible to mention everyone who has earned my appreciation in the writing of this book, for which I would run the risk of omission. I have now joined, to a limited extent, the digital age and suggest that interested colleagues search Google or PubMed to find a variety of publications consisting most recently of reviews and, occasionally, experimental papers. Generous research funds were provided by National Science Foundation, National Institutes of Health, and the American Cancer Society in support of my research in comparative immunology. As my publications increased, there was a corresponding decrease in national funding, which did not dampen my enthusiasm or productivity. As the old adage has it, “I will either find a way, or make one” (supposedly said by Hannibal in 218 BC when his plan to cross the Alps via elephants was challenged).

It was not always easy to win the intense competition for funds since comparative immunology was not mainstream in the late 1960s; still, it was important enough to maintain funding for some of us still embued with questions that could be answered and useful after experimenting with plants and animals (leading to the production of pharmaceuticals). I interpreted this as an obscure hint that a new tactic that could provide support was needed! Why not increase the importance of comparative immunology by making it better understood, thus augmenting its visibility? Aha! Start a much needed journal! Founding a journal, like any project, whether a book or invention was feasible if a unique proposal could be presented to a publisher. Several disappointments greeted my proposal until finally, and seemingly spontaneously, came a positive response in 1976: Pergamon Press, under the guidance of Robert Miranda, offered a contract to publish a journal, which I called *Developmental and Comparative Immunology* to be inclusive. I nervously signed the contract at the Federation meetings in nearby Anaheim, appointing my wife Helene the first and only administrative assistant for 18 years to assist in this international effort. With some minimal fanfare but discreet determination, Volume 1 was published in 1977 with two hastily formed but enthusiastic advisory and editorial boards, lending a measure of prestige!

Some aspects of the journal in the midst of substantial visibility were not usual. DCI was at first a “cut-and-paste” journal, produced like an international quilt (all sorts of fonts!)—but it was published nonetheless, extending the reach of DCI. DCI opened the giant doors of the publishing empire of Robert Maxwell, a CEO with a keen eye for up-and-coming publications. On his 65th birthday and the 10th anniversary of DCI, we, meaning all of his several hundred editors, gathered for a celebration in Oxford, England. Sessions during the day were devoted to the realities of publishing, the advent of computers, and sneak peeks at what publishing was about, including scientific journals. Evenings featured elegant black-tie-and-tail events! Bubbles and exquisite cuisine rounded things off.

DCI matured, opened many more doors, and provided the necessary and continuous visibility so essential for any idea as it might relate to biomedicine. But alas, it matured up to a point, when it came time to make some changes after more than 15 years, when I passed the torch and other chief editors took up the reins. Having published my own papers and organized and published symposia, I gladly stepped down and gave impetus for national societies under the aegis of DCI, Japan's strong and influential JADCI, for example, is now a flourishing model.

Moreover, certain findings by studies of comparative immunology gave birth to other disciplines and journals, for example, the immune systems of animals and plants, harnessing the resources of the ocean. The idea was to promote the renaissance of ancient medical remedies, paying special attention to the beneficial substances derived from the sea that could be developed into medicinal products! What about bee venom acupuncture, born from the observation of humoral immune system products? And bees are just one of many examples. Finally, tribute was paid to the earthworm, a source of food in other cultures whose humoral immune system had progressed to the point where an agent was isolated from its serum like fluid to prevent blood clots. The innovations kept coming!

One of the important spinoffs from my duties as DCI editor emerged as an incredible windfall while I was lecturing in Japan. Professor Nobuo Yamaguchi was a long-time friend in comparative immunology who was interested in launching, under Oxford University Press, a journal devoted to complementary medicine to fit this growing need to expand aspects of medical practice. For centuries, humans subsisted on natural products derived from plants and animals, before the advent of pharmaceutical houses, and the rapid advance of medical science. To my surprise, I was offered the editor-in-chief position. After a few hours of personal deliberation, I accepted the offer, which provided manna to fuel the emerging discipline of complementary and alternative medicine (Cooper EL, Yamaguchi N (Eds). Complementary and alternative approaches to biomedicine. Advances in experimental medicine and biology. vol. 546. New York: Kluwer Academic/Plenum Pubs 2004). The journal *Evidence-Based Complementary and Alternative Medicine* (eCAM) is published by Hindawi, is open access, and, like DCI, earlier afforded me new opportunities to engage in an activity that gives me great pleasure—writing.

The spectre of starting a new organization provided a windfall of enthusiasm so essential during the birth of a cohesive, dedicated group. eCAM, like DCI and the aforementioned book, began with a bang. Here is a sampling of scholarly contributions as per Scopus, which are direct evidence of enthusiasm: Gibellini L, Marcello P, Milena N, Montagna JP, De Biasi S, Roat E, Bertoncelli L, Cooper EL, Cossarizza A (2011) Quercetin and cancer chemoprevention. *Evid Based Complement Alternat Med*. 2011:591356. doi: 10.1093/ecam/neq053; Cooper EL, Yao D (2012) Diving for drugs: Tunicate anticancer compounds. *Drug Discov Today* 17:636-648; Cooper EL, Balamurugan M, Huang C-Y, Tsao CR, Heredia J, Tommaseo-Ponzetta M, Paoletti MG (2012) Earthworms dilong: Ancient, inexpensive, noncontroversial models may help clarify approaches to integrated medicine emphasizing neuroimmune systems. *Evid Based Complement Alternat Med*. 2012:164152. doi: 10.1155/2012/164152; Cooper EL, Hirabayashi K (2013) Origin of innate immune responses: revelation of food and medicinal applications. *J Tradit Complement Med* 3:204-212; Mackler AM, Heber D, Cooper EL (2013) Pomegranate: Its health and biomedical potential. *Evid Based Complement Alternat Med*. 2013:903457. doi: 10.1155/2013/903457; Huang C-Y, Cooper EL, Fang-Yeu Poh C, Kuo WW, Chen T-S, Sherman R (2014) Special invertebrate models and integrative medical applications: Regulations, mechanisms, and therapies. *Evid Based Complement Alternat Med*. 2014:843961. doi: 10.1155/2014/843961.

Advances in Comparative Immunology Introduction

Why Study Comparative Immunology?

This is the first revised textbook to offer a comprehensive review of recent and exciting advances in comparative immunology. The book presents an evolutionary approach to cellular and humoral immunity and reveals the immune system as ubiquitous and necessary for all animals to survive. Many textbooks are available on immunology, but often they are oriented solely toward medicine or allied professions. This textbook of comparative immunology is a unique beginning text for those advanced students of biology, zoology, immunology, and other disciplines who are interested in more biological or comparative approaches to the analysis of immune competence.

This book provides us with an overview of immune reactions—a possible stepping stone to graduate study in comparative immunology. Specialists, often with a mammalian orientation, can use the text as an introduction to a wealth of other vertebrates and invertebrates and a source of new and meaningful facts pertinent to immunology. Despite this orientation, the book would even be appropriate for medical, dental, and nursing students. Thus, comparative immunology is important to anyone who understands and appreciates the fundamental aspects of immunology and biology and who can grasp significant breakthroughs in immunology when viewed in phylogenetic perspective. Since the first edition, progress in the field has been outstanding!

Immunologists will quickly recognize many fruitful approaches to understanding immunity. To aid the reader, much illustrative material and many references to original works and reviews are given. This expanding information reveals that analyses need not be restricted to rabbits or guinea pigs, since the invertebrates, fishes, amphibians, reptiles, and certainly birds are excellent species for deciphering the basic mechanisms of immune reactions. It should be remembered that cellular immunity, undergoing rapid refinement and extended breadth, had deep historical roots in observations on invertebrate cellular immunity. For this reason a good deal of attention is devoted to specific cellular immunity in invertebrates. The apparent absence of circulating immunoglobulins, but the presence of a complicated and efficient humoral immune system, in invertebrates should offer fertile ground for speculating on the nature of those pressures that may have led to the evolution of antibody synthesis in vertebrates.

2018: Evaluating the Impact of Comparative Immunology

Actually, comparative immunology may succeed even further by some productive and essential “mimicry.” Comparative neurobiologists are now questioning their approaches in the special issue of *Science* called “Challenges in Neuroscience” (Yartsev 2017). They pose the question of whether a comparative approach is important in exploring the nervous system. In essence, their proposal suggests a recognition of and focus on a handful of animal models to explore particular questions—more narrow analysis. Here are several of their suggestions: Utilize the frog *Rana pipiens* as ideal for a strategy to clarify synaptic transmission, or investigate the squid, horseshoe crab, and sea hare *Aplysia* to understand respectively action potentials, retinal physiology, and learning associated with neural memory. Back to immunology: *R. pipiens* can offer extended clues due to the metamorphosis from tadpole to adult frog, setting in motion organogenesis, especially bone marrow, which is the source of immune stem cells.

I would suggest a similar discussion with respect to both the invertebrates and vertebrates in mind—offering more numerous models that can be whittled down to fewer numbers with a focus on the additional, more ecological problem of food supplies and terrestrial and aquatic species as sources of life-saving drugs. Possible models are plentiful even after judicious and practical selection.

The study of immune systems in disparate phyla is also a way to quantify the biological effects of global climate change. Food webs are among the most significant phenomena affected by planetary warming. A population decline in one member species could be disastrous for the remainder of the web. Likewise, a significant increase in the individuals of another species “invading” an extant web might lead to disruption. It is extremely conceivable that the dysfunction or competent function of a species’ immune system could be a factor in population collapse or explosion, respectively. For example, temperature change will likely alter the mix of pathogens present in a particular habitat. The ability of species’ immune systems to cope with a disruption in any pathogens surrounding them could in turn impact the species’ survival.

And it is not disputable that humans and mice are the organisms in which the immune system has been most deeply investigated. The unquestioning extrapolation of these findings to other animal species, including invertebrates and poikilothermic ones, entails risks. Yet it is these nonmammalian species that dominate among animals in food webs. As Yartsev noted, “In the absence of comparative studies, an entire field may be led astray by observations that are either species specific or misinterpreted in the absence of comparative data.” He adds later, “… the comparative approach serves as an extremely powerful tool to assess the validity of universal principles on a case-by-case basis. In the absence of the comparative approach, many discoveries may not have occurred, would have reached the wrong conclusions, or would have taken far longer to be unveiled.” Thus the comprehension of nonmammalian immune systems, which may be a large factor in the survival of food web members, will likely be unachievable by the simple extension of what is known about humans and rodents.

Research into temperature changes and the immune system in poikilotherms began years ago. Cellular immunity in Antarctic sea urchins reflected signs of stress with a 4 °C rise in temperature (Branco et al. 2012). Many marine organisms must adjust to acidification as well as warming. Expression of immunity-related genes was altered by lowering the pH in the mussel *Mytilus chilensis* (Castillo 2017). The effectiveness of the insect immune system may be heightened by heat shock (Wojda 2016), but this is different from the chronic temperature rises that are occurring now. Immune competence declined in two species of freshwater fish of the Iberian Peninsula (Jesus et al. 2017). Hibernation and other survival strategies by poikilothermic animals (Storey and Storey 2017) depend heavily on ambient temperatures, which are likely to increase by global warming.

Distinct Periods in Conceptualizing Comparative Immunology

As suggested by Michael Suzuki, PhD, former graduate student, this book required something more than an ordinary preface of just two pages. After careful examination, the discipline of comparative immunology has in fact a long history, even as far back as early indications and records of concern by observers of disease onset. What is left in Egyptian tombs as evidence of war between humans and infectious disease? Aulus Cornelius Celsus recorded evidence of inflammation in mummies in his encyclopedia compiled in the Roman era. The early twentieth century revealed compelling evidence of inflammation, which we surely know today as the beginning that "jump starts" one component of the innate immune response.

This first revision of *Comparative Immunology* is an exciting contribution. Boyhood observations (e.g., ants on a well-worn trail always attack nonmembers) have been transformed into important real-world concepts (e.g., ants recognize *self/nonself*, a cardinal principle of immune competence). Early hunches are now channeled into tangible events. As a discipline, comparative immunology is an offshoot of the parent field, immunology, and is an amalgam of immunology and zoology. Comparative immunology has gained wide acceptance in the biological sciences. All animals from protozoans to humans have solved the threat of extinction by evolving an immune-defense strategy that ensures the capacity to react against foreign, *nonself* microorganisms and cancers that disturb the homeostatic *self*. Invertebrate-type innate immune responses evolved first, and they characterize the metazoans. These rapid natural responses act immediately and are often essential for the occurrence of slower, more specific, adaptive vertebrate-type immune responses. As components of the innate immune system, there is an emphasis on several major steps in the evolutionary process: (1) recognition, (2) the phagocytic cell, and (3) the natural killer cell. We now know that some invertebrate and vertebrate mediators are homologous.

The zoological inheritance received by comparative immunology is evident from the astute recognition by the organization of the American Society of Zoologists (ASZ) (now the Society for Integrative & Comparative Biology) in 1975. The ASZ always exerted a strong influence, and reinforced the will and ensuing success, which was official and provided essential support for establishing a fledgling group; I experienced this first-hand while creating the first organized group. Innate immune systems have been successfully defending invertebrates and plants against microbial infections since time immemorial. The germline-encoded receptors of innate systems are relatively limited in diversity and able to make only coarse distinctions between closely related structures. Nevertheless, they can recognize certain chemical features shared by groups of microorganisms (e.g., pattern recognition receptors) but not by the host, such as lipopolysaccharide of Gram-negative bacterial cell walls. This capability enables innate immunity to detect the presence of an infection, if not the precise cause—perhaps considered a biological, not a structural, distinction.

Because of its evolutionary success, innate immunity is no longer considered primarily a stopgap measure, a temporary expedient for host defense; it is ubiquitous and omnipresent. There seems to be an absence of genetic-recombination mechanisms to generate specificity or "memory" because first and second exposures to a microbial substance elicit similar responses; yet there are exceptions. Acquired immunity first appeared in vertebrates. When they evolved, beginning with fish, thymus-controlled T cells appeared, as did bone-marrow-derived B cells (first found in anuran amphibians with long bones, as mentioned earlier in connection with metamorphosis). These were the precursors of the plasma cells that synthesize and secrete antibodies. Confirming the concept of *self/nonself*, invertebrates possess *natural, nonadaptive, innate, nonclonal, nonanticipatory* immune responses, whereas vertebrates possess *acquired, adaptive, induced, clonal, and anticipatory* responses. The essence is survival.

Thus, *Comparative Immunology*, one of many contributions to immunology appearing around 1976, provided real evidence, not guesswork, constituting the basis for a legitimate discipline. That survey added strong and palpable support for further advances, reaching out to scattered hints of observations that belonged to the ancestral parentage of animals. Through persistent local initiatives at many levels and in many cultures, there accumulated consistent evidence for the ubiquitous phenomenon of immunity. Immune competence is everywhere, globally, and has thrived, providing and giving back its fruits of understanding. As it happens, a cross-fertilization of many disciplines need not threaten the original views that were chiefly derived from mammals and, therefore, human oriented, essential but not universally pertinent.

Retrospective Look at Comparative Immunology

Egyptians' Discovery of Inflammation in Ancient Humans

The earliest surviving records of immune phenomena describe ailments in humans. For instance, inflammation is noted in an Egyptian papyrus of 3000 BC. (Weissman 1990). Bacterial DNA isolated from an Egyptian infant mummy demonstrates that bacteremia and likely septicemia affected that child (Zink et al. 2000). Parasitic infection by *Ascaris* spp. and related helminths were found in 1200 CE mummies of the Guanche people of the Canary Islands (Jaeger et al. 2016). Egyptian mummies exhibited signs of malaria, and symptoms of this parasitic disease were described by Hippocrates among some of his Greek contemporaries (Nerlich 2016).

Some progress in the war against infectious agents affecting humans was made during later centuries, before these agents were identified and methods invented to assay immune responses. For instance, smallpox inoculation is mentioned in a Chinese text of the sixteenth century, written long before the nature of viruses became known. Benefits from such intellectual "low hanging fruits" were finite, and modern advances in understanding human immunity have required tools to observe and comprehend what people were fighting against. Mass production of microscopes and chemicals, invention of chambers for cell and tissue incubation, centrifugation, and usable radioisotopes are only a few of the influential technical approaches that have allowed the dissection of emerging immune responses. Techniques that could reveal how human immunity fights disease were eventually adapted and elucidated the immune systems of other animals, providing ever greater clarity in lower animals in the early to mid-twentieth century, and these efforts continue today.

Advent of the Modern Era: Élie Metchnikoff

Since the time of Élie Metchnikoff, there has been a steady, but most of the time informal, approach to invertebrate immunity (Cooper et al. 2002). Yet more than 20 years later after the discovery of simple phagocytosis, his views were rewarded and recognized by the Nobel Prize in Physiology or Medicine in 1908. For the cellular arm of the immune system his contribution is far-reaching; over the years the implications have been extensive (Cooper 2008). Rather than dismissing his views entirely, the cellular arm of the immune system continued to enlarge, so overarching that it permeated every facet of the immune response, except for activities specific to B cells. The essence of comparative immunology has been pervasive.

Twice in the history of twentieth- and twenty-first-century immunology, the Nobel Prize in Physiology or Medicine has been based on simple basic aspects of inflammation. (The second was Jules A. Hoffman in 2011 for the intricacies of receptor activity that drive immune responses.) Moreover, the experimental subjects have been animal models other than mice, again invertebrates, specifically insects. This lent credence to the advisable use of all species as sources of interrelated phenomena. Metchnikoff spearheaded this significant approach by identifying phagocytosis in *Daphnia*, the water flea. Peering through the flea's translucent body wall, our eminent Russian zoologist from Odessa, enjoying the beach in Sicily, reasoned that white mobile cells (leukocytes) slowly and deliberately encircled the foreign body, rendering this alien cell inactive and preventing death.

The prescience of this observation did much to link aspects of protection to ubiquitous leukocytes or white cells, sensitive to uninvited intrusion and providing the first line of the body's defense to foreign invasion: the militaristic analogy! Thus was born the essence of innate immunity, later declared constant in all living species. Metchnikoff, somewhat like Darwin, became a ubiquitous name associated with the essence of biology in the nineteenth century. There were glimmers of hard science that attempted to invade or break the intellectually stubborn doors of a naturalist's views. Although some have supported Darwin's influence on the development of comparative immunology, this has become evident only in recent years (Cooper 1982, 2008; Cooper et al. 2002).

Darwin was born in 1809 and died in 1882. The young Darwin was well traveled and the quintessential observer in the wild. Metchnikoff, born in 1845, was less the adventurer, more a microbiologist, who died in 1916. They were a generation apart and apparently never met in person. Yet the aura of what they had discovered was surely "in the air," creating an atmosphere whose influence was most probably felt internationally. For each achievement, in summary, there was an element of simplicity despite the end product/result of shared similarities. Although they overlapped substantially in age, there are no records showing mutual influence on each other nor on the fields to which they contributed so vastly. One was the exploring naturalist who traveled extensively, the other staying close to his laboratory to make his discoveries. The universal act of phagocytosis, its ubiquity, laid the foundation for its acceptance as universal—no complicated reagents necessary to assert its pervasive influence. A similar prescient simplicity characterized them both.

Leo Loeb: *The Biological Basis of Individuality* – Emergence of Self/Nonself

Early in my career, as a junior faculty member, I accepted this Loeb book as a most treasured gift from Prof. Nicholas Cohen, the second postdoctoral fellow of W.H. Hildemann. Nick and I overlapped in many ways—our choice and subsequent abandonment of a first PhD research problem: the development of limb regeneration in urodele amphibians. On a page of this gift Nick wrote, "***Let us never forget individuality***."

The Prussian-born physician Leo Loeb contributed the early appearance of the basis for *self/nonself* concepts as expressed in his 1945 *The Biological Basis of Individuality*. (This represented the beginning of crucial and important tomes and treatises in the field, which focus on *self/nonself* and mutually related variations.) Whether it was absolute prescience on the part of Loeb to anticipate *self/nonself*, or it was so obvious that the duality emerged, after a good deal of thought and publication, that there were inherent differences among all individuals, is unknown. Early on, what was crucial to comparative immunology was a recognition that this individuality was characteristic of all species. To add support to this emerging doctrine, Loeb not only perceived or anticipated the concept of *self/nonself* but recognized early on that any differences or likenesses were clearly demonstrable by simple experiments involving the transplantation of grafts in as many animal species as possible. What was revealed was the essence of *self/nonself*. To support his view that all living creatures possess the capacity to show differences when confronted with unlike tissues, Loeb established the field of transplantation immunity, whose basis was the early recognition of *self/nonself*, only later to be accepted by the founders of transplantation biology including Burnet and Brent.

As a favorite animal model, somehow earthworms became the choice of many colleagues close to Loeb who would become the experts providing the confirmatory evidence when transplantation immunology in invertebrates was first discovered (Cooper et al. 1992). To confirm the universality of this kind of response, the recognition of individuality differentials (later known as self), Loeb the inquiring scientist hastened to include other creatures where easily transplanted tissues could be made, thereby revealing the existence of individuality differentials. Quoting at length from Loeb (1946): "The lumbricidae differ from the planarians in a considerably greater fixity of their organs and presumably in a correspondingly greater specificity and fixity of the substances on which the differences between organs depend (organ differentials, a predecessor of the *self / not self* concept). While the organs have not yet become entirely rigid, still the differentiation between head and tail parts is more fixed than in planarians [see chapter by Oviedo]…

"In accordance with this change in the organs we find a greater differentiation in the organismal differentials, as is indicated in the transplantation experiments on lumbricidae which have been carried out especially by Korschelt and his associates, Joest, Rutloff, Leypoldt, Harms, Rabes, and more recently by Mutscheller. The earlier of these experiments antedated the majority of the investigations on coelenterates and planarians. At that time attention was focused on problems which have since" been couched in different terms. Every effort made by Loeb emphasized the individuality of all beings regardless of level of evolution expressed as distinctions between *self* and *nonself* that characterized that individuality. To lend credence to universality, various models explored the unique character of the experimental species. As will be seen later, many of the models in this period were analyzed later, beginning in the 1970s as the parent field of immunology became better understood. Still we must recognize that even among mammals, like the laboratory mouse, information was woefully inadequate with respect to components of the immune system and what each component did when confronted with the demand of the animal to defend itself against that which was foreign, again expressing individuality differentials, later becoming self/nonself.

For example, several researchers working in the 1920s devoted enormous attention to the fate of transplants between different species of earthworms. Only in the 1970s did investigators see that the observation of earlier scientists was immune capability, expressed as the *biological basis of individuality*. However, the 1970s workers were equipped with functioning stronger evidence that specifically defined differentials, i.e., *self/nonself*. The *self/nonself* model remains solid and was only questioned many years later. In the 1990s the view that danger in an organism could act as a *nonself* stimulus arose, offering more testable opportunities for further research (Matzinger 2002a, b).

1960–1980

First appearance of clonal selection; *self* versus *nonself*; integrity of body; ontogeny and phylogeny of immune system; phylogeny separately; defense reactions in invertebrates; Cushing and Campbell, *Principles of Immunology* (1957), whose chapter 12 has an early mention of comparative immunology).

Immunology was beginning to show some resemblance to what we know today as comparative immunology. As a growing field, it was turning toward analysis and considerations of mechanisms. However, as we see from today's vantage point, mechanisms were really scant, since technology was undeveloped, and the application of technology to questions rarely yielded meaningful analyses and conclusions. Naturally, as an emerging experimental science, advancement of the parent discipline required animal models. The first two acceptable models were the laboratory mouse and rat. Rabbits were also employed as the discipline grew. Eventually other warm-blooded animals, such as chickens, guinea pigs, and hamsters, were sometimes added to the necessary experimental mix of animal models. Immunology concerned with human problems naturally searched for relevant animal models and posed questions that could be answered, thereby opening windows and doors, perhaps advantageous, as would be seen later, what were somewhat unproductive exercises. These early forays into the science revealed little, yet they stimulated researchers' desire to open yet more doors and windows. Once these were opened, what would become the emphasis?

Enter an emerging group of biologists *qua* zoologists (not yet comparative immunologists!) familiar with other animals as incredible sources of relevant immune characteristics. This was further hampered again by a lack of sufficient immune information to establish universal traits among many animal species. These new fledgling immunologists were often not viewed as such by the existing mammalian immunologists, who were locked in imperceptibly with their furry and homeothermic creatures. Still, their value as former microbiologists, now focused on the immunology of infectious diseases, was a source of consolidation and bridge building, capable of straddling the divide less strenuously than the uncomfortable hard-core microbiologists. After all, they were and are more open to the beauties of the living world, able to escape from a firmly closed mindset focused narrowly but understandably on humans. This essential anthropocentricity offers little in our search for the universality of the basics, which include widespread mechanisms of survival; after all, at best survival meant preserving certain warm-blooded creatures and barnyard birds as sources of food. In this book, it is the immune system that we analyze for common denominators, thus opening doors for our entrance into the wide array of animal species to the exclusion of plants—although equipped to guard against disease and ensure survival, their mechanisms are different.

I worked driven by affection and dedicated to the cause of the first version of *Comparative Immunology*, published in **1976**. This was done through multiple invitations actually, one for *Comparative Immunology* via a comparative endocrinologist, Prof Howard Bern of the University of California, Berkeley. The decade of the **1970s** represented an important watershed. Doors opened and my ideas, whose seeds lay dormant to some extent in the 1960s, suddenly burst forth. This was an important period for laying the groundwork of comparative immunology. For me, it began with the award of a Guggenheim Fellowship for studies on comparative immunology at the Karolinska Institute Sweden in **1970**. This period saw the launch of dedicated efforts to understand the evolution of the immune system. It seemed reasonable to think and to imagine that protection against infectious microbes was a property of all creatures, humans included.

Burnet wrote *Immunological Surveillance* in 1970, where he revealed the possibility that immune systems evolved to protect against mutated cells, including cancer cells; two textbooks on comparative immunology, one by Cooper, another by Marchalonis, appeared; nomenclature that is still in use today was laid down; Volume 1, Number 1 of the journal *Developmental and Comparative Immunology* was published in January 1977; books on animal models of comparative and developmental aspects of immunity and disease appeared; volume 4 of *Contemporary Topics* was commissioned (part of a series). Thus, the 1970s were especially productive—different names, but universality among animal groups and problems of disease were important topics.

This was immunology's turning point, a crucial period devoted to comparative immunology. In **1974** I edited *Contemporary Topics in Immunobiology* (Cooper 1974). The fourth volume in this outstanding series presented modern approaches to cellular and humoral immunity and examined relationships between invertebrate and vertebrate immune capacity. Noted scientists, including Nobel Laureate Macfarlane Burnet, discussed the novel theory of immunologic surveillance—an explanation of how cells distinguish between *self* and *nonself*—and related it to cancer biology. Also included were studies of graft rejection in earthworms, as well as in hydras and other marine invertebrates. The work looked at several insect immune defenses and described leukocytes derived from the octopus white body. (By the way, it would be interesting to see how the immune system of the octopus surpasses that of many other animals, considering the complexity of the octopus nervous system and the fact that octopuses have the capacity to show emotion, as demonstrated in some studies.) Finally, this book describes events in phagocytosis and presents a notable but contentious view—tumors in *Drosophila* ***and, perhaps, in some other invertebrates***.

My **1976** book, *Comparative Immunology*, was part of the *Foundations of Immunology* series by Prentice Hall, which included at least five other volumes. This series of monographs was intended to provide readers of diverse backgrounds with an authoritative and clear statement concerning aspects of immunology. This book contained 16 chapters with such diverse topics that were intentionally basic, seeking clarity for a diverse audience. It covered the immune system, phylogeny of the immune response, nature of antigens, phagocytosis, quasi-immune recognition, primordial cell-mediated immunity, the machinery of the immune system, development of transplantation immunity, characteristics of transplantation immunity, genetic control and transplantation immunobiology, invertebrate humoral immunity, antibody synthesis, the immunoglobulins, activities of immune cells, immunosuppression, an epilogue that treated two pertinent topics for adaptive immunity, and, finally, the impact of immunology.

The year **1976** also saw the publication of another book called *Comparative Immunology*, edited by John J. Marchalonis. This book was similar to the one by E.L. Cooper except for a focus on authors, of whom many agreed on certain characteristics. This contrasted with Cooper's emphasis on animal models. Thus Marchalonis's book was more universal with respect to subjects and experts in the field, which counted up to almost 25 comparative immunologists! The Marchalonis book was perhaps easier to read and covered the subject of comparative immunology in more depth if for no other reason than its breadth (740 pages long) compared to Cooper's (338 pages). Both were and still are valuable, but a comparison of the two with each other revealed that their style and content were not so even.

Enter a different twist to the topic of comparative immunology, a tertiary book, *Comparative Immunobiology*, by Margaret Manning and Rodney Turner. Compared to the two previously mentioned texts, this book contained approximately 180 pages, small and compact, written by two colleagues, and based upon their experiences teaching the subject to students in the last year of a biology sequence. This book was aimed primarily at students who wanted to understand how the immune system works, especially aspects of comparative and evolutionary biology, but who weren't planning on specializing in immunology. Manning and Turner expressed the hope that their book would introduce the phylogeny of immunity to students already knowledgeable in other aspects of immunology.

The year **1977** was a good one, soon after *Comparative Immunology*, when J.J. Marchalonis published his *Immunity in Evolution*. "Evolution of the vertebrate complex immune system has shown no morphological changes apparent from fossil evidence. But comparative studies of immunity in invertebrate species reveal an extraordinary evolution of cellular and molecular mechanisms capable of differentiating *self* from *non self*. In this thorough review, Marchalonis introduced readers to the evolutionary background of immunity and showed how this approach can illuminate this phenomenon in more familiar eutherian mammals." These, of course, are in contrast to monotreme and marsupial mammals, lesser known exotic species, typically Australian.

Although some invertebrates appear capable of immune-like responses (this was proven in the 2000s), only in vertebrates does highly specific biochemical recognition of foreign substances occur. As we would see some 30 years later, this seeming gap or even pessimism with respect to invertebrate responses was due to a lack of strong evidence. Marchalonis traced the evolution of cellular and humoral immunity from the versatile system of cyclostome fishes through the elaborations introduced by subsequent evolving vertebrate groups. Modification of the ancestral immunoglobulin IgM into a variety of Ig types received detailed attention. The emergence of T and B lymphocytes and cooperative interactions were revealed in detail. Marchalonis provided background on evolution and biochemistry so that readers unfamiliar with one or more aspects of this review could follow along with relative ease. Numerous illustrations summarized data, showed evolutionary development, or explained genetic hypotheses. Immunologists, evolutionary biologists, and readers interested in molecular evolution would and will still find frequent use for this book!

1980–Present

The period opening the **1980**s was ripe with a concern for the concept of *self/nonself* discrimination. *Self/nonself* discrimination; *Contemporary Topics in Immunobiology*, volume 9, 1980; cellular recognition reactions in invertebrates; 1st Congress of Developmental and Comparative Immunology held in Aberdeen, Scotland in 1980;

proceedings of that congress were published as *Aspects of Developmental and Comparative Immunology*, J.B. Solomon (ed); two influential books by Jan Klein; Sigel and Cohen (eds), *The Reticuloendothelial System,* volume 3: *Phylogeny and Ontogeny*, published in 1982.

Already *self/nonself* was riding high on more and more confirming evidence, strengthening this view that had firm roots that had been published as early as the late nineteenth century. J.J. Marchalonis and Nicholas Cohen (with MG Hanna, Jr) edited *Contemporary Topics in Immunobiology*, volume 9, 1980. As a special tribute they dedicated the volume to Sir Frank Macfarlane Burnet, who "first used the phrase '*self/non self* discrimination' in 1940. His concepts have provided a challenge to two generations of immunologists….It is with great pleasure that we dedicate this volume to Sir Mac on the occasion of his 80th birthday" (M.G. Hanna, Jr.). Very briefly, at that time there was demonstrable concern for considering cellular recognition reactions in invertebrates: (1) Do invertebrates show specificity in the recognition of antigen? (2) What is the molecular basis for this interaction? (3) Does a phylogenetic lineage of immunoreactive complexity exist, which eventually leads to the complex vertebrate immune response?

The 1980s were also an especially fertile time for expansion in several directions and were characterized by enormity, as illustrated by the two monumental treatises of Jan Klein, plus the volume edited by Sigel and Cohen, *The Reticuloendothelial System*, volume 3. Jan first published *Immunology: The Science of Self/Non-self Discrimination* in **1982**. The content was provocative, but it is the organization that stands alone in structure and deserves some explanation. Rather than organizing the text into four "nonprovocative" sections, for example, Introduction, and so forth, Jan published an unusual set of sections, each of which described aspects of *self/nonself* recognition. Here is his unique presentation. He opened this composition, his book, as his symphony, by confessing that he knew very little about immunology! In my opinion this is not true. His knowledge was as extensive as that of any of us who dared to approach mid-nineteenth-century immunology since what we know now hardly resembles the early days of *self/nonself*. For each of those designations, there are infinitesimal splinterings into various markers, signals, stimuli and receptors, that it boggles the mind to think how far and fast we went from individuality differentials to our present state, past the reigning dogma in the late nineteenth century. Later in the decade, Jan Klein introduced us to another way of looking at the essence of the immune system. This time, *Natural History of the Major Histocompatibility Complex* was published some six years after the "symphonic" look at the immune system. Actually this second book echoed what was enunciated in the book *The Biological Basis of Individuality* by Leo Loeb.

A third member of the club of large sequels (tomes) to the Loeb book is the book edited by Cohen and Sigel, *The Reticuloendothelial System* (Cohen and Sigel 1982). There are at least ten volumes in this series on the reticuloendothelial system; the Cohen and Sigel book is volume 3, *Phylogeny and Ontogeny*, and was published in 1982. (One partner in this series, the Reticuloendothelial Society, renamed itself the Society for Leukocyte Biology in 1984.) The tome's 21 chapters and 740+ pages included most of the invertebrate and vertebrate phyla covered in the present book, but no mention was made of nematodes. Perhaps the explosion of research in *C. elegans* over the intervening decades provided a motivation to investigate the immunology of roundworms. The preface by Cohen and Sigel mentions a driver of the diversity of animals studied in the current book: “a wealth of new, often unique, models with which to study immunological problems that are not restricted to mammals.”

The 1990s were also a busy and productive period. *Immunologie Animale*, published in 1990 by Flammarion (Paris), includes 15 chapters on comparative immunology, for example, invertebrates, fish, and so forth. The period also saw the resurrection of Metchnikoff. Other figures or topics included AI Tauber, *Metchnikoff, and the origins of immunology: metaphor to theory* (1991); earthworms alone; primordial immunity—foundation for vertebrates; developmental immunology; evolution and phylogenesis of immune reactions; comparative histophysiology; modulators of immune responses; publication of *New Directions in Invertebrate Immunology* in 1996, edited by K. Söderhäll, S. Iwanaga, and G.R. Vasta; this book from SOS Publications has more extension to invertebrates of concepts well studied in mammals, including clotting cascades in horseshoe crabs, lectins in insects, and pheromones in ciliate protozoa.

Leslie Brent, professor emeritus of immunology, St Mary’s Hospital Transplant Unit, Paddington, London, published the book *History of Transplantation Immunology* over which there was considerable excitement since the second chapter was devoted to the immunological basis of allograft rejection. He opens that chapter with a statement from Sir Peter Medawar (1957): “… the immunology of transplantation not merely for its bearing on cancer research or the repair of radiation damage, but it offers one of the few negotiable pathways into the central regions of biology, where immunology, genetics, embryology and the rest of them lose their identities in problems that bear upon biology as a whole.”

The early years of the field focused on various contributions. Of much interest to comparative immunologists, in the middle of that second chapter, Brent immediately poses the following question: Are invertebrates capable of allograft reactivity? Then comes the explosion: For here enter statements expressing skepticism that they are capable, despite the fact that a variety of invertebrate groups supported the idea, with observations in sponges, coelenterates, sea anemones, coral, and worms. Organisms from echinoderms to insects all possess the following immunologically competent characteristics: (1) selective reactivity, (2) cytotoxic or antagonistic reactions following sensitization, (3) inducible memory, and (4) selective altered reactivity on secondary contact—criteria with which most immunologists would concur. The debate moved to comparing Hildemann and Cooper vis-à-vis the mammalian transplantation contingent. The discussion was devoted then to a defense of graft rejection in earthworms and other invertebrates. Not all immunobiologists agreed with the notion, yet Cooper, Rinkevic, Uhlenbruck, and Valembois published “a stout defense” in 1992 in the *Scandinavian Journal of Immunology*. This lively discussion ended on a somewhat sad note with the untimely death of Hildemann, who had been a staunch promoter and advocate of what his post doc Cooper had been doing, inspiring other people.

Subsequent years saw a continued proliferation of books dealing with the panorama of animal evolution and immunity and the appearance of the journal *Trends in Innate Immunity* (Karger), a blurring of the clear border between innate and adaptive immunity (Cooper 2012), publication of "Adaptive Immunity from Prokaryotes to Eukaryotes: Broader Inclusions Due to Less Exclusivity?" in *Recent Advances in Immunology to Target Cancer, Inflammation and Infections*, edited by J. Kanwar , the discovery of B and T lymphocytes that have some properties of innate immunity and natural killer cells with antigen-specific immune memory.

Self/nonself is an important hypothesis that has guided research in immunology. It is closely connected to adaptive immunity (restricted to vertebrates) and innate immunity (found in vertebrates and invertebrates). *Self/nonself* is now being challenged, and investigators are turning to the danger hypothesis to guide and open new areas of research. Emerging information suggests that genes involved in the development of cancer are present in *Drosophila* and *C. elegans*. Short lifespan may not rule out the presence of genes that are related to the development of cancer (Cooper 2010).

The self/nonself theory has dominated immunology since the 1950s. In the 1990s, Matzinger and her colleagues suggested a new, competing theory, called the danger theory. This theory has received mixed responses, both enthusiasm and criticism. Here we assess the danger theory vis-à-vis recent experimental data on innate immunity, transplantation, cancers, and tolerance to foreign entities and try to determine more clearly whether danger is well defined (Pradeu and Cooper 2012).

Adaptive immunity is now being deconstructed to encompass less stringent rules, including initiation and actual effector activity. Expanding the repertoire of invertebrate innate immunity has greatly facilitated the search for what actually constitutes ***innate*** and ***adaptive***. Strict definitions become *blurred*, casting a skeptical eye on the use of rigid definitions of *innate* and *adaptive immunity* (Kvell et al. 2007). Immunology has experienced remarkable growth. Immutable tenets deserve a brief mention. First, there must be strict divisions between ***adaptive*** and ***innate*** immunity. *Second*, to raise these two views allows for extended inclusions, reveals the essential merits of innate immunity, and acknowledges inclusive invertebrate characteristics. We can even include features of adaptive responses especially to ***danger*** (Pradeu and Cooper 2012). To facilitate this emerging reality means recognizing hazy characteristics that fade into each other, that ***blur***; they are neither black nor white but a "clear gray"—reminiscent of impressionist paintings (Cooper 2010, 2012).

What Hath Comparative Immunology Wrought?

Knowing how the immune system works is lifesaving, now requiring less analysis. Comparative immunology knocked on the hermetically sealed door and opened it, revealing an incalculable cornucopia of biomedical importance and relevance: it has clarified innate immunity, recognized cancer which still has a limited acceptance in lower animals, identified sources of less polluting food, and called for respecting and humanely treating all species. Thus, comparative immunology is no longer esoteric, no longer buried in the earth, but is now out in the open with its relevance and benefits for all to see and enjoy!

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Part I

From Prokaryotes to Urochordates

Evolution of Immunity

Kurt Buchmann

History

It has been estimated that Earth appeared around 4600 million years ago (MYA), and organic molecules of increasing complexity were subsequently established in the surface layers. Primitive anaerobic life forms may have seen light soon after, around 3700 MYA (Hassenkam et al. 2017), and the advent of photosynthesis (2400 MYA) created the basis for an even more intense expansion of diversity. Ever since this early history of Earth, basic organic molecules and primitive organisms have been exposed to infection and parasitism. From the very start of these interactions mechanisms to protect the integrity of the molecules and organisms must have been present, securing their subsequent survival and development. RNA molecules can be interpreted as the first parasites of DNA, and molecular mechanisms for the release and processing of RNA may have appeared to regulate their binding. These became important tools when the first simple microorganisms appeared and were attacked by plasmids and virus. Protective molecular mechanisms including the use of restriction enzymes and clustered regularly interspaced short palindromic repeats protected bacteria against plasmids and irrelevant or harmful genes (Dunin-Horkawicz et al. 2014). The first unicellular organisms needed a wider array of cellular tools to recognize food and secure its uptake. Active contact with other organisms required methods to resist invasion by foreign pathogens, including viruses, bacteria, or even other protozoans.

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