Paul's Fundamental Immunology

EIGHTH EDITION

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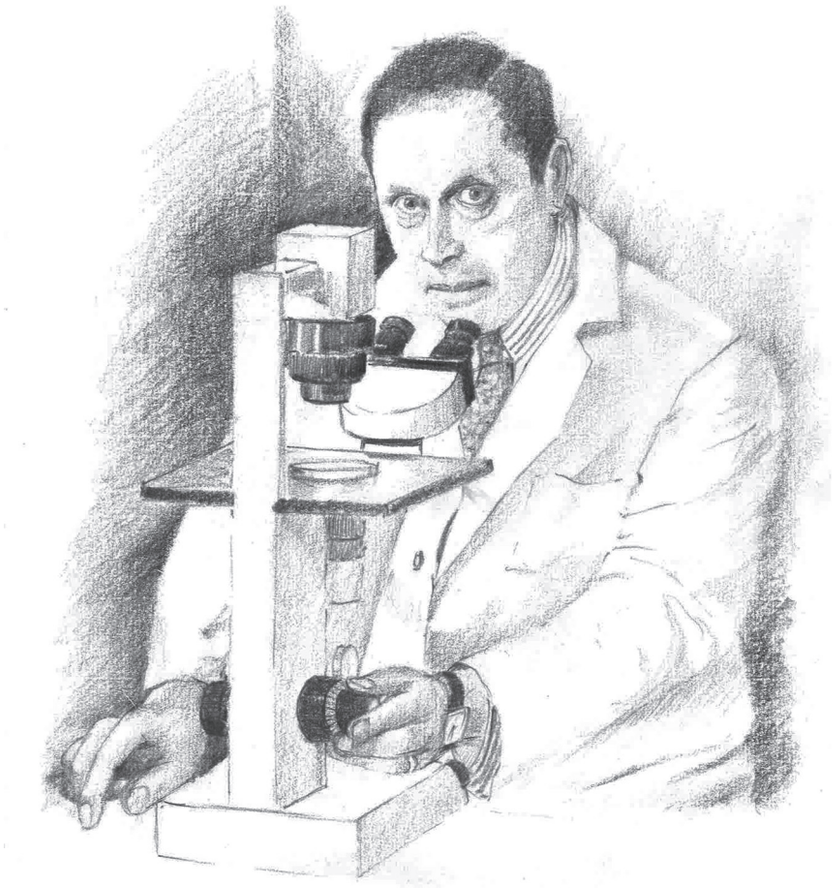

William Paul at the microscope, drawing by Louis Du Pasquier

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FOREWORD

WILLIAN E. PAUL: AN IMMUNOLOGIST'S IMMUNOLOGIST

William Erwin Paul was born in 1936 in Brooklyn, the son of an immigrant father and a mother who was the daughter of immigrants, as part of the Jewish diaspora that came in a great wave to the United States in the early part of the last century and produced many of our greatest scientists. While his father Jack ran a car repair shop, his mother Sylvia came from a family that included a number of prominent scientists, including one older cousin on his mother's side of the family, who was a Professor of Neurology at Harvard. As a bright kid, Bill skipped two grades in high school and entered Brooklyn College at 16, where he majored in chemistry and premed studies. He notes that it was free and of high quality. He then attended the State University of New York's Downstate Medical School, also in Brooklyn, where he had his first taste of research working in the lab of George Talbot, studying growth hormone activity in rats. He also had the good fortune to marry Marilyn Heller during that time, an important source of support and advice for the rest of his life. He then left Brooklyn for an internship and residency in Boston at Boston University's Massachusetts Memorial Hospital. There he also turned to research in the lab of Alan Cohen, working on the biology of fibrils and their contribution to Alzheimer and other diseases. A pivotal moment came when he applied for a very competitive NIH clinical fellowship, since the alternative was likely being drafted into the army. Fortunately, he was awarded the fellowship and so in 1960 he and Marilyn moved to Bethesda, the main NIH campus, where they had their first child, Jonathan.

Here he worked with Bill Odell and Jack Wilbur on the first antibody-based assay for thyroid-stimulating hormone, which was the most sensitive assay available for detecting abnormalities of the thyroid. The subsequent paper received over 500 citations, quite an accomplishment for a newcomer who also had patient-care responsibilities. Bill also describes this time at NIH as quite exciting, and many of the brightest MDs at that time were gravitating toward a research stint at the NIH as an alternative to the doctor draft. This trend would accelerate dramatically as the Vietnam War ramped up, so much so that for the whole era through 1972, the "yellow berets" as they were called, included many famous scientists of later years, contributing to a veritable golden age of science at NIH. Yet, after 2 years at NIH, Bill moved on to NYU to work with Baruj Benacerraf, then a rising star in immunology; he'd hoped to work with Henry Kunkel at Rockefeller University but that laboratory had no open positions. Bill had been fascinated with the mysteries of immunology since college, when he happened on the work of Michael Heidelberger, who strove to introduce precise quantitation to the study

William (Bill) Paul in 1982, around the time that Mark Davis worked with him at NIH. Bill is shown with one of his mentors, Baruj Benacerraf (mentioned in the Foreword), and James Wyngaarden, the director of the NIH from 1982 to 1989. Bill was presenting the G. Burroughs Mider Lecture, inaugurated in 1968 in honor of the first NIH director of laboratories and clinics. The title of Bill's lecture was "Living with Lymphocytes. B Lymphocytes and How They Grow."

of antibody responses and specificity. By coincidence, Heidelberger, who lived to the ripe old age of 104, was doing a second postretirement stint next door to Bill's lab and they frequently interacted. In the Benacerraf group, Bill became immersed in the mysteries of the burgeoning field of cellular immunology, far removed from immunoglobulin chemistry, the pursuit of which would guide the rest of his career.

In 1968, Bill moved back to the NIH when Benacerraf was recruited to NIH to head the Laboratory of Immunology. Soon after they had arrived, however, Benacerraf was offered a Chaired Professorship at Harvard, and decided to go there. He asked Bill to go with him but Bill was ready for independence at this point, and decided to stay at NIH, probably remembering his exciting days there earlier. When a prominent immunologist declined to replace Benacerraf, the job of lab chief, essentially the department chair in other academic settings, was open; with Benacerraf's strong support, Bill was selected for this position, and would remain as lab chief for the rest of his life. While some NIH lab chiefs chose to devote all the resources of a laboratory to their own interests, Bill was much more egalitarian, more in the line of a modern academic department, where faculty-level scientists were independent, and had their own small groups of postdocs and technical staff (PhD students would only come later in a program with Oxford University developed by Michael Lenardo). The 1970s was a time of turmoil but also great insights in the field of cellular immunology. The importance of the MHC

loci was being defined, first by Benacerraf and McDevitt, but also by Rosenthal/Shevach and Zinkernagel/Doherty who showed that the true function of the MHC proteins is to provide a context for T cell antigen recognition. Thymic selection was also being defined by Bevan and Zinkernagel and others. Then in the mid-1970s, recombinant DNA became mainstream and utterly transformed almost all of biology, especially immunology. Susumu Tonegawa, then at the Basel Institute for Immunology, showed the first evidence of DNA rearrangement in the formation of immunoglobulin genes, followed quickly by Phillip Leder at NIH, and Leroy Hood at Caltech, and others, in a flurry of remarkable papers. These studies resolved the most age-old questions about antibody diversity, class switching, membrane-bound and secreted forms of antibodies, and affinity maturation in rapid succession in just 4 years. As a graduate student at Caltech, I was in the thick of isolating and characterizing mouse Ig heavy chain genes in the Hood lab at the time, working with fellow PhD student Phillip Early. We were helped enormously by the arrival of Tom Maniatis and his group, who brought a wealth of recombinant DNA expertise from Cold Spring Harbor and Harvard, and developed many more key methods at Caltech.

Norman Davidson and Tom started what was essentially a recombinant DNA club, with regular meetings to disseminate the emerging technology. Tom later wrote the recombinant DNA "bible" of that era (*Molecular Cloning*, CSH press 1982) and started a summer course at Cold Spring Harbor on recombinant DNA methodologies that I was later honored to be part of. Phil and I were lucky to be included in the "club" and benefited enormously from what we learned, so much so that we ended up scooping Tonegawa's lab on several fundamental aspects of heavy chain genes. As I neared the end of my PhD in 1979, a crisis loomed as my then girlfriend and now spouse, Yueh-hsiu Chien, had finished up work in Norman Davidson's lab and taken a job at NIH, using her newly minted recombinant DNA skills to clone endocrine system genes. I asked Mitch Kronenberg, a fellow student in the Hood lab and the only one of us broadly knowledgeable about immunology beyond antibodies, if he could recommend a postdoctoral mentor at NIH. Mitch immediately said, "Bill Paul, he's really smart," or words to that effect. At that time immunology was clearly divided between the antibody people—biochemists and molecular biologists who studied the relatively straightforward world of antibodies—and cellular immunologists who did much more mysterious things like putting the thymus of one mouse into another mouse, and who discovered the phenomenon of MHC restriction despite having no idea of how it worked molecularly. Very weird but strangely wonderful stuff, to someone like myself who had only worked on, and thought about, molecules (mostly DNA and RNA). I then visited Bill and his department (AKA "Laboratory of Immunology") and was struck and fascinated that his group almost exclusively worked in this exotic area of cellular immunology. Originally I thought that I learning about this world would expand my immunological horizons, but encouraged by Bill, I also applied for postdoctoral fellowships. This was great advice and something that I encourage all of my postdoctoral applicants to do, since it forces one to think critically about what to study in a new environment. In my case this discipline worked exceptionally well, because I realized that the antibody gene work was reaching an end—the major questions had been answered or nearly so, and thus it was important to think about what might come next. One obvious route that many took was to study transcriptional regulation of whatever gene you had in hand, but that didn't excite me. Another possibility was to identify the recombinases that mediate V-D-J joining, but this brought two problems to my mind: (1) they would be very hard to clone because they would be very rare transcripts, since they would need to be tightly controlled to avoid deleterious rearrangements, and (2) they were probably related to topoisomerases which was a popular field at the time, but I never could understand the lectures. But even in ruling out that option, I asked myself, if I did want to clone these recombinases, how could it be done? Here I drew on my knowledge of nucleic acid reassociation kinetics and RNA handling that I had learned about earlier in the lab of Eric Davidson. If T and B cells shared most of their gene expression, I could subtract the T and B transcriptomes from each other to perhaps identify the rare T- or B-specific gene products. This strategy could result in the cloning of all sorts of genes that were required for B and T cell function. So, I wrote up these wild speculations into my grant proposal and submitted them to the proper authorities, finished up my work in the Hood lab, and made it out to NIH in the fall of 1980. I told Bill at some point about this idea, and he asked a few pertinent questions, as always, but also suggested that I might work on some projects that he was interested in.

When I told him that I preferred to work on my idea, Bill was totally supportive and introduced me to Jin Kim and Richard Asofsky who had various mouse B and T cell tumor lines that they could grow for me. I gratefully accepted, since at that time I had never grown any mammalian cell lines. From these cells I was able to purify cytoplasmic RNA from several B and T cell lines and by the end of 1980 I did my first subtractions of labeled B or T cell cDNAs with RNA from the other cell type. I found that very reproducibly, 98% of the cDNA of T cells would hybridize with RNA from B cells, and vice versa. Thus, purifying B or T cell-specific probes would result in a ~50-fold enrichment for these sequences, enabling even rare genes (most of them) to be detectable. This was even better than I could have hoped for and excited all of us. I think it had immediate appeal to Bill and other immunologists because it was standard practice at the time to absorb complex antisera with unwanted antigens, to obtain antibodies for specific target antigens. In contrast, molecular biologists tended to be dismissive, because they never appreciated (or even understood in many cases) DNA or RNA reassociation kinetics, considering it to be a relic of molecular biology in the precloning age, now past. Fashion is a surprisingly major influence, even in science, although it's clear that progress often comes from resisting this impulse. In any event the subtraction project progressed quite well, and was clearly working, when we found that the just recently cloned Thy-1 gene (by a former Hood lab colleague Jack Silver) was present in our T cell-specific collection, and we also helped Lee Hood and his group identify the location of class II E^k in their MHC

cosmid clones. As this was going on, Bill told me something astonishing, which was that he didn't understand enough about the technical aspects of my work to be competent to supervise me, and that I should consider myself independent and he wouldn't put his name on my papers. In addition, he wanted me to stay in the LI and join the faculty.

He assigned to me a fantastic technician, Ellen Nielsen (now Bernstein), and encouraged two postdocs, David Cohen and then Steve Hedrick, to work with me, as they were eager to learn recombinant DNA technologies. It was also very helpful that Tom Sargent, a graduate school buddy who had also gone to NIH, shared with me a neat trick for making subtracted cDNA libraries. David Cohen used this procedure to make our B-subtracted T-specific library, later used by Steve and I to extract the first T cell receptor (TCR) gene. However, Bill's support wasn't entirely on faith, as much later Tasuku Honjo told me that Bill had asked him if what I was doing made any sense. Luckily, Honjo had done some DNA reassociation analysis himself earlier to define deletion as part of immunoglobulin heavy chain switching, and so he wasn't as prejudiced about the value of this methodology as most other molecular biologists. Bill was true to his word, and when my little group actually produced the first TCR clone (TCR beta) in July 1983 among our T cell-specific genes, he was incredibly supportive, even though by then I had accepted an offer from Hugh McDevitt at Stanford to join the newly reconstituted Department of Medical Microbiology (now Microbiology and Immunology). Bill was enormously generous to not insist on even a co-authorship on what would be the hottest papers in immunology at the time, but it shows the lengths he went to for the advancement of others' careers. As a famous and experienced immunologist in 1983, Bill knew that if his name were on the papers that he would reap most of the credit for this seminal discovery. He also declined an NIH-sponsored trip to China that year, suggesting me as a substitute, which I accepted, even though I had just arrived at Stanford and was setting up the lab with Chien, who volunteered to help (since she knew I would need all I could get!). It was a curious trip, since China had only recently opened to the West and the people were very poor, and the immunology in the country was largely focused on monoclonal antibodies.

The greatest value for me was that this trip was timed to end just as the International Congress of Immunology was set to begin in Kyoto Japan. I never would have gone to that meeting if it were not a convenient hop from Shanghai to Kyoto. Unfortunately, I didn't know that one needed a visa to enter at that time, and so I spent hours in the airport chatting with the immigration authorities about why I had arrived without a visa. I volunteered Dr. Honjo as a character witness, and while I don't know if they ever contacted him, the authorities eventually let me officially enter the country. At the meeting, I received a fresh infusion of data from my NIH lab. Steve and Ellen had been working away sequencing our new TCR genes, including some we isolated from a thymocyte library kindly provided by Christoph Benoist. And so I approached Harvey Cantor, who was chairing the session on T cell recognition, and asked if I could present our data. Somehow he said yes, and later I found myself in front of over 5000 immunologists telling them we had solved a puzzle that had frustrated the field for years. Definitive earlier work on the TCR heterodimer by Jim Allison, Ellis Reinherz, and Kappler and Marrack, presaged our work, but nothing was as tangible, or empowering, as a gene clone, in this case TCRb from mice. Our work was published in the following year, along with the unexpected human TCRb clone from Tak Mak, and later a paper from Susumu Tonegawa, to whom I had naively given my subtraction protocol. Later in 1984 both my group and Tonegewa's published on the TCRα gene, essentially launching the modern era of T cell biology.

Meanwhile Bill was working away to define a novel cytokine activity that Maureen Howard in his group had identified, initially identified as a novel B cell growth factor (Howard and Paul JEM 1982). This turned out to be IL-4, which was later shown to be crucial for driving the differentiation of the Th2 subset and for the switch to IgE by B cells (Paul and R Seder 1994). The identification of this important factor is perhaps Bill's greatest scientific achievement, and was the subject of many subsequent studies.

Bill also increasingly became a statesman of Immunology. In the early 1980s, he was elected to the governing council of the American Association of Immunologists, the major immunology society, and then its President from 1986 to 1987. During this time he also was the founding editor of the *Annual Reviews of Immunology* in 1983, where he served for 31 years.

Somehow he also found the time to edit an advanced text with up-to-date chapters written by experts in the various areas of immunology (*Fundamental Immunology* 1984). This book has been extremely valuable for graduate students and researchers in the field and went through seven editions in Bill's lifetime. This eighth edition, ably helmed by Martin Flajnik, is a small token of our esteem.

Also very important, in the AIDS crisis that began in late 1980s, there was increasing anger in the gay community at what was perceived as a lack of urgency on the part of NIH and the government. This created a crisis of trust that was corroding support for basic research, and someone of stature was needed to calm the waters. Bill was the natural choice, not because he had ever worked on HIV, but because of his ability to listen and render thoughtful responses to frustrated and angry people. Thus he agreed to become the first head of the NIH Office of AIDS research in 1994, to coordinate funding decisions and to liaise with the public. In this role he was very successful, and in this capacity helped usher in the life-saving protease inhibitors, which revoked the death sentence for HIV-infected individuals. Yet, in this capacity, Bill saw that an effective vaccine was also required, and that the basic science of HIV infection was needed to move the understanding of vaccines forward. Thus, he thought that what was needed was to establish a dedicated vaccine research center at NIH. After vetting this idea with colleagues he went to the White House with Anthony Fauci and others in 1997 to pitch the proposal directly to President Bill Clinton. Clinton was persuaded and, with subsequent congressional approval, this became a reality in just a short time. Thus the Dale and Betty Bumpers Vaccine Research Center open its doors in 2000,

with a mission to both explore the science of vaccination and to manufacture vaccines and conduct early clinical trials. In these missions, the VRC has been very successful, developing effective vaccines for Ebola and RSV, and most recently led the first trials of the SARS-CoV-2 vaccine from Moderna. With these major accomplishments, Bill stepped down from his role at the Office of AIDS Research in 1997 and was able to devote more time to his own research and other pursuits.

In summarizing a remarkable life like Bill's, it seems clear that while his scientific achievements were remarkable, what really stands out was his concern for the field of immunology and humanity in general, as well as his unparalleled selflessness. While almost all of the attention in science deals with the achievements of individuals, talented people curious about the rules governing the natural world—in earlier times Newton, Darwin, and Einstein—all worked essentially alone to achieve their stunning insights. Modern science, on the other hand, is a team sport with single-author papers a rarity from physics to biology; multiple to dozens of authors are individuals, and are needed to achieve a recognizable advance in that field. Still, scientists are typically individualistic loners and thus are attracted to these icons of the past. We are typically not "joiners" or "followers" but take pride in thinking for ourselves and taking the path "less traveled." Yet, while singular visions and pioneering efforts are as important as ever, it is also critical to recognize that individuals can flourish scientifically with the support of a strong team and community, so that the vision of an individual or group can actually be realized. William Erwin Paul (1936-2015) recognized this reality long before most of us, and while pursuing his own scientific interests, he very successfully devoted more and more of his efforts to creating a supportive scientific community, both in his own department (the Laboratory of Immunology at NIH) but also more broadly at the NIH and in the entire country. This enabled many young immunologists he mentored, including this one, to achieve much more than they could have normally. Most scientists take on community-building activities only under duress, especially B.T. (before tenure). Their mission is to build up an important body of work as quickly as possible, and indeed, this is what they are rewarded for. I have an interesting thought experiment, which asks, "what would your colleagues think if you were second author on the 10 greatest papers in biology? The correct answer is "loser!". This common attitude is destructive to collaborations and the supporting scientific community—we need each other, but many factors work against this and to some extent we can entrap ourselves into how science was done long ago. Here again, we have Bill Paul as an example of science in the modern age, encouraging young scientists to do their best in his role as chief of the LI, always ready with sage advice, and not concerned with credit for himself. It's a wonderful example to us all, and a remarkable legacy.

Mark M. Davis

ACKNOWLEDGMENT

William Paul's wife Marilyn is acknowledged for providing the Paul family history and editing of the Foreword.

PREFACE

This is the eighth edition of *Fundamental Immunology* (now called *Paul's Fundamental Immunology*), a decade since the previous edition was compiled and the first edition after the untimely death of Bill Paul in 2015. As Dr. Paul wrote in the preface of the last edition: "*Fundamental Immunology has the goal of aiding in the education of a new generation of immunologists who can both probe more deeply into the organizing principles of the immune system and can translate this new information into effective treatments and preventatives that will extend and enlarge on the record of immunologic science in bettering the lot of humankind.*" We agree wholeheartedly with this sentiment but would add that seminal features in immunology such as the generation of antigen receptor diversity, germinal center reactions, antigen processing, lymphocyte development and migration, among many others, are fascinating in their own right, regardless of the therapeutic potential.

In this eighth edition, we go into some detail in the Introduction (Chapter 1) to familiarize readers with the topics covered in each of the following 49 chapters. The classical areas in immunology included in previous editions were all updated with the latest captivating discoveries in basic and translational immunology. Furthermore, in this edition there are new topics included that have come to the fore in the last decade including innate lymphocytes, maternal-fetal immunity, programmed cell death, interactions with microbiota, evolution of immunity, and neuroimmunology.

In the preface to the last edition Dr. Paul also wrote: "*The continued need for progress in immunology is clear. The epidemic of human immunodeficiency virus roars on. Glimmers of hope from vaccine trials have led to a redoubling of effort, and the struggle to design effective vaccines for the great infectious scourges goes on, with encouraging results but no breakthroughs yet. Highly effective therapeutic vaccines for cancers still elude us, but some immunologic therapies for cancer have met with encouraging results.*" Encouraging results indeed! The amazing progress we have witnessed in the last decade in cancer immunotherapy with checkpoint inhibitors and CAR-T cells has been revolutionary, to state the obvious. Permutations of these therapies, in combination with new strategies on how to manipulate the tumor microenvironment to render tumors susceptible to T cell/NK cell destruction, will be the goals for the next 10 years. Regarding vaccines, we were privileged to observe the taming of a viral pandemic with the first use of mRNA vaccines, in combination with approaches to activate the innate immune system and manipulate the structure of the immunogen. We predict that in the next decade, in addition to continued progress in cancer immunotherapy and vaccine development, our asymptotic knowledge on basic immunology will result in breakthroughs in treatment of autoimmunity and transplantation.

In a final nod to Dr. Paul, he wrote, "*I repeat a word of caution that has been in the Preface to each edition. Immunology is moving very fast. Each of the chapters is written by an expert in the field, but in some areas there may be differences of opinion expressed by equally accomplished authors. I ask the reader to take note of the differences and to follow developments in the field.*" Such differences of opinion are to be expected in any rapidly moving field, yet disagreements and frank discussions are *actually required* for a field to continue to progress. It is our hope that readers of this edition will not only come away with an appreciation of immunology, but also become privy to the controversies and areas that still befuddle us.

We would like to thank each of the authors for their contributions to this eighth volume of *Paul's Fundamental Immunology*. We appreciate the efforts to assemble their chapters amid a global pandemic, while the authors were trying to sustain their lab structure, and many were actually examining various aspects of immunity to COVID-19. It was a pleasure for us to edit each chapter, as we learned a great deal about every topic. We especially are grateful to those authors who stepped up late in the game (you know who you are!) when we recruited you to contribute to chapters that were essential for the volume. Special thanks to Mark Davis, who in addition to writing the chapter on T cell receptors with Yueh-Hsieh Chien wrote the foreword as a dedication to William Paul, one of his mentors.

Finally, we thank Wolters Kluwer for taking on the responsibility for publishing this new edition of *Fundamental Immunology*, with special recognition of Ariel S. Winter, Christopher Rodgers, and Ramkumar Soundararajan, who worked with us tirelessly to plan this volume, interact with all of the authors, and shape each chapter into its final form. This edition would not have been possible without their support.

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