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Acceptance of the Howland Award

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This is truly a happy occasion for me. I am most appreciative to be a recipient of the Howland Award. The time allotted for my response permits only a very brief word of thanks. Wilson remarked when asked how long it took him to prepare a speech that it depended upon the length of the speech. If time was unlimited he could be ready instantly; if the time available was short, it might take more than a fortnight. Since I have but 5 minutes to speak and it would have taken too long to prepare such a short speech I will just say thanks.

I want first to reflect thankfully on my mentor, Irvine McQuarrie, that great pediatrician and teacher of pediatric teachers. In 1958 Dr. McQuarrie was a recipient of the Howland award, the highest honor of the American Pediatric Society to recognize contributions to the welfare of children. McQuarrie was a people watcher par excellence and taught by example the art of watching people, selecting the right ones, and encouraging each to develop in his or her own way to reach full academic or professional potential. I learned from McQuarrie that to make the fostering of academicians work well the technique required a capacity to encourage, encourage, encourage, and wait, wait, wait. Patience is required in the development of men and women as scholars because each develops at his or her own pace.

McQuarrie tried to teach me to search out Experiments of Nature. He linked the concept of nature's experiments to the earlier contributions of William Harvey, Osler, and Garrod. Thanks much to McQuarrie this powerful approach for penetrating the unknown has now been highly developed and extends throughout modern medicine. In my brief scientific life I have seen it especially well developed in Minnesota and at the Thorndike Memorial laboratories in Boston.

I also wish at this time to express my appreciation to the many teachers of science who influenced me in my early years. Berry Campbell, my thesis mentor viewed anatomy in the broadest perspective, ranging from neuroanatomic and neurophysiologic development to hematopathology and to locomotion of the hagfishes. He always stressed the developmental perspective. He showed me firsthand the power of this developmental approach, and this in turn made me a sitting duck for McQuarrie's challenge for me to cast my lot with pediatrics. Hal Downey and Fred Kolouch taught me experimental and clinical hematology, also in the developmental perspective. Kolouch, the young scientist at Minnesota, who did classical experiments that identified the antibody-producing cells as plasma cells, willed me the cells of the immunological system when he turned his attention to surgery. He later turned to psychiatry and in both fields was an impressive innovator. But I thank him for leaving the lymphocytes and plasma cells to me.

Chuck Evans and Robert Green taught me virology; Glick and Koltoff taught me chemistry; and Vince Kelley, McQuarrie, and Mildred Ziegler helped me with my initial experiments in biochemistry.

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Maclyn McCarthy and Henry Kunkel at the Rockefeller Institute gave me good examples of how to design and execute a proper experiment and how to create a properly disciplined laboratory environment. Lewis Thomas and the late Al Stetson showed me how much fun there is in science. They each shared with me the great happiness of discovery in science and the deep satisfaction of a truly critical analysis. I thank each of my teachers sincerely—they left their mark.

Next, I want to say thanks to my students at all levels. Already nearly 300 of the students who studied with me for extended periods hold professorships, department chairmanships, associate professorships, or equivalent positions in industry or public health departments around the world. These are the scholars who cut their scientific eye teeth in my laboratory and developed their scientific disciplines in interactions with me. They now, of course, spawn their own intellectual children and already a few intellectual grandchildren who in turn I count as my intellectual grandchildren and great grandchildren. It is, indeed, a wonderful big family, and in them all I take great pride. I am sure that long ago those who know me well realized that my language, like that of other mentors, often must be translated. Sometimes when I have said I, I really have meant we, or when I have said we, I have meant they. Our students at all levels are especially valuable to us and to science when they point out the reality of the Emperor's new clothes when he is not wearing them. And *this* particular emperor has often been endowed with such fine new apparel.

Yes my students have been most valuable teachers, they have kept me abreast of what is going on and the information and orientation they have given me has helped me stay scientifically young. It is every true that the youngsters must teach, so that their more senior teachers will be able to teach effectively.

I wear on my lapel today what I was told is a VIP pin. This pin of course symbolizes a mouse. Nothing could be more appropriate for this occasion since the lowly inbred laboratory mouse has been a great teacher of immunologists in general, for the past 65 years. My debt to the mouse as a teacher has been particularly great. But for me this symbol could have been a chicken, a lamprey, a hagfish, a shark, a skate, a ray, a lungfish, or even some amphibian or reptilian form. When difficult issues are viewed in both ontogenetic (pediatric) and phylogenetic perspective they are often revealed in a penetrating light.

But my greatest teachers of all have been my patients, who as children or adults with serious medical problems have so often presented the opportunity to interpret exciting and revealing experiments of nature. These experiments of nature have often been temporally poised so that my colleagues, students, and I might interpret them profitably. Experiments of nature have, indeed, often become a lynch pin capable of holding together accelerating surges in the scientific revolution in medicine. It is for this reason that I have always tried very hard to keep my head, hands, and feet in my clinics and on the wards, even when time would allow only my head and my feet, but not always my hands, to be in my laboratory.

It is those questions raised at the bedside which can be taken

to the laboratory bench that permit important and useful answers to be derived at a critical time. So generated, the new information can flow quickly and profitably from the bench back to the bedside.

Agammaglobulinemia is one very good example. This disease discovered by Ogden Bruton, bisected the microbial universe, and also bisected the lymphoid systems into T and B cells or humoral and cell-mediated forms of immunity. The disturbed immunological defenses of such children also bisected the universe of immunopathogenetic mechanisms and even bisected the viral universe. Study of agammaglobulinemic patients offered the possibility to immediately disprove the plasma cell theory of antibody production on which we were working. Of course, since we found that agammablobulinemic patients lacked plasma cells, our observations were in keeping with the hypothesis that was guiding our analyses.

The patients with primary immunodeficiencies have also often been the critical testing grounds for our new theories as they have developed. For example, the theories of the importance of thymus function, and the concept that the bone marrow contained the stem cells, the postulated cells of origin of all of the forms of immunocompetent and hematopoietic cells could be fairly tested, respectively, on patients with DiGeorge athymic syndrome or patients with severe combined immunodeficiency. Thus, thymus transplantation and bone marrow transplantation in DiGeorge athymic syndrome and in severe combined immunodeficiency, respectively, became the launching pads for a new era of cellular engineering.

Experiments of nature do not become less important as our technologies harden. No, the tools of molecular biology, molecular genetics, biochemistry, and modern cell biology simply make experiments of nature a bit easier to recognize, more certain to be defined, and more likely to be analyzed definitively.

AIDS is a new and demanding teacher. This teacher, like some I seem to remember from high school, is an awful presence in our midst. This of course is the lethal manifestation of a very complex retrovirus infection. The specter of this awful sexual plague, like nuclear power, has appropriately emphasized our vulnerability as a society and our mortality as individuals and even our gross inadequacy as scientists. This teacher has taught us once again to be humble and has emphasized that humility and audacity are both essential for effective scientific inquiry. It is certain that the very fragile thread of our immunological function contains the essence of our individuality and this in turn may be responsible for cohesion in our social fabric.

Solutions to AIDS are being found, and determinate solutions will hopefully soon turn up to stem this frightening plague. In gaining these solutions we will certainly have to learn new fundamental truths and expand greatly our immunological, virological, and molecular genetic understandings. In achieving these solutions we will, I believe, address not only the challenge represented by the plague of AIDS but perhaps also the still poorly understood mystery of immunological tolerance of pregnancy. With the understanding to be thus derived we may even finally begin to define the nature of immunosurveillance against cancers and also surveillance against virus-infected cells. We will understand better the biological role of cellular and viral oncogenes and will develop new approaches to treatment of virus infections in general. We will design and develop truly new approaches to effective immunization. Immunologically we long ago showed we can beat nature's capacity for immunization when we learned to immunize in clinically useful form against tetanus toxoid and when smallpox was eliminated from the globe. We will of course have to beat nature again with the HIV virus because no one infected by the virus seems to develop an immunity naturally.

And finally, I say thanks to you my peers in clinical investigation and in pediatric research. We are each very special teachers of one another. We experience great excitement when, as part of our yearly rites of spring, we come together to bring new discoveries and analyses to one another. We like to "show and tell" to each other what we have seen and learned during the year. In so doing, we naturally await the highest honor one scientist can pay to another—namely the offering of his criticism. Criticism implies that the critic cares—that he or she cares enough to understand what has been said or shown and understands enough to be able to focus a truly critical comment or question. Criticism also implies that the critic recognizes the inadequacy of "the one"—anyone—everyone. Criticism also implies that the critic wants to help and thus in his way contribute to the development of the discipline and discourse.

Yes, I appreciate all of you, and each of you. I appreciate deeply what you stand for, and all that you mean by your presence here today. I thank you for this great honor—The Howland Award.