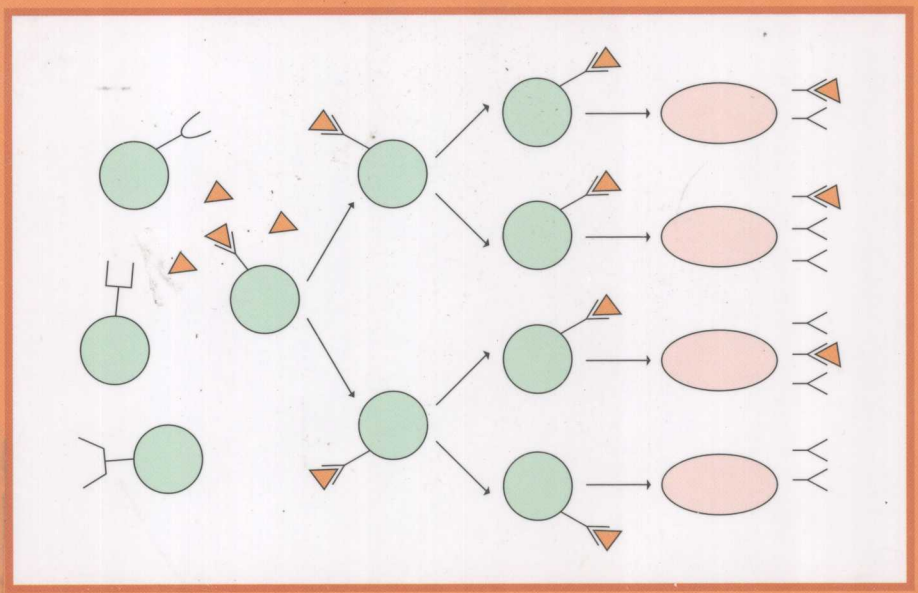
A History of Modern Immunology

The Path Toward Understanding



ZOLTAN A. NAGY

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A History of Modern Immunology

Dedication

In memory of my friends
Rodney Langman and
György Fehèr

Introductory Words About Science, Scientists, and Immunology

Before we set out to follow through the events of a very exciting era in the history of immunology, I feel I owe the reader at least an attempt to define what science, and more specifically, immunology is all about.

There are several different ways to define science, but if we want to grasp its essence, the following simple statement is adequate: Science is an intellectually driven, often experimental activity, whose goal is to gain insight into the works of the universe.

Hence ideally a scientist is a person, who is blessed (or damned) with a restless mind, and an overdose of curiosity, which properties literally force him/her to keep asking all those What?, Why?, and How? questions that down-to-earth people only ask in their childhood. Not that scientists would be more infantile than others, but their extremely critical mind makes them reject all answers that they have been given by others. It is thus not surprising that the greatest reward for scientists is the moment, when their hard work and good fortune permit them a glimpse into a new facet of reality, be it even a tiny little one that has not been seen by anyone else before. Such rare moments set them into a state of euphoria that cannot be achieved by any other way, for example, by a tenure position at a famous university or even by a Nobel Prize (although these may also be good to have).

Unfortunately, this little sketch I have just drawn of science and its players deviates grossly from the picture that the mass media prefer to convey to the public. According to media representation, science is a very logical and very dry (i.e., boring) undertaking with the final goal of donating a significant benefit to mankind. The problem with this perception is that it confounds science with its potential utility. Undoubtedly, usefulness is an important aspect, and nobody is more aware of it than scientists themselves, particularly when they try to apply for a research grant. Nevertheless, the driver and the final goal of science is understanding and not utility.

For example, physicists, when they started to study nuclear fission hoped for a new insight into the structure of matter, and certainly did not intend to build nuclear power stations, let alone atomic bombs. The sad fact, however, that finally they were the ones to point out that nuclear fission can be used for a bomb, and indeed they participated in the construction of the bomb cast a dark and long-lasting shadow over the public image of science. This example also reveals that, although utility is a side-effect rather than the goal of science, it can sometimes change the life of mankind significantly, and in an often unforeseeable direction. This is why science is usually considered to be

dangerous by the public. However, the statement that science itself is a purely mental pursuit remains valid, danger arising only from its uncontrolled applications. The important thing to keep in mind is that all qualities human beings can enjoy nowadays, beyond the ones given by nature, have resulted from either science or arts (and not from money, as most would think at the dawn of the third millennium).

Of course, the media, in order to avoid inconsistency with the picture they painted of science, also try their best in creating a false image of scientists. Accordingly, scientists who are selected to appear in public must look very stern and serious (although they can still be somewhat handsome), they must emanate unusual mental power, and their behavior must resemble that of a high priest in ancient Egypt. Admittedly, some colleagues like to use this image as a respectable disguise, but most scientists are not like this. Indeed, they are just like other people: they can be aggressive or timid, egomaniac or humble, dictatoristic or self-enslaving, careeristic or modest, political or naïve, business-like or puristic, conformistic or anarchistic, opportunistic or revolutionary, but they all have one thing in common: their inability to stop asking questions and seeking answers.

Let us turn now to immunology that, based on the foregoing discussion, is easily defined as the particular branch of life sciences, whose aim is to understand how the immune system functions. This definition has always been valid, even at times when the immune system existed solely as an assumption, and immunology appeared to be equal to vaccination, or antibodies, or serological reactions, and it will remain valid until the last piece of stone is placed into the wall of the knowledge tower of the immune system.

As the title of this book indicates, I shall attempt to summarize here the major events in the construction of the immunology tower during a period roughly corresponding to the last third of the twentieth century. There were several reasons for choosing this period. First, this era followed immediately the so-called 'immunological revolution', and was thus the time when most questions about the biology of the immune system were raised and also found their answers. Second, because I had the privilege to be an immunologist in this period, I shared all the excitement associated with it, and can thus convey its events to the reader on the basis of personal experience. Finally, the time that has elapsed since then provides one with the wisdom of hindsight, as well as sufficient distance to cool down and look back with sharper, more critical eyes.

Although the book was originally planned to summarize the history of immunology from about 1970 onward, I realized that the story would remain 'hanging mid-air' without at least a short résumé of the preceding 10–15 years, when most knowledge was generated on which modern immunology has been based. Furthermore, the language spoken by immunologists also originated from this time. Therefore, the highlights of this fruitful era are included, for the sake of non-immunologists, as a 'pre-history'. The science then generated can now be found in every immunology textbook, and the detailed history of this era is well covered in Arthur Silverstein's book.[1]

To return to the metaphor used above, I should point out that the immunology tower has not been built of uniform bricks, but rather of individually carved stones of different shapes and sizes, similarly to the Inca buildings in Matshupitshu and Sachsahuayman. But unlike the Inca buildings, the construction of the immunology tower has not been led by a chief architect, and thus every single stone reflects the idea of its mason about the best fit. Consequently, many (or perhaps most) of the stones would not fit. Nevertheless, ideas and data that have, in retrospect, turned out to be misfits will also be included here, because nothing illustrates better the development of a cognitive process than the errors made on the way. Not to mention that the omission of errors and inclusion of only the highlights would have reduced the book to an 'executive summary'. Nonetheless, this book is not meant to be a complete historical account of all immunological research conducted during the last third of the twentieth century. To keep a better focus, I will only cover topics that appeared most central for our understanding, corresponding largely to what was considered 'mainstream' immunology at that time.

Another, perhaps unusual feature of this book is that it will not only deal with science, but also with the personalities of scientists. I have always found it a great injustice to remember only the names of scientists in conjunction with their contributions, and not their personality, although the latter was often more interesting than the former. This applies all the more to immunology that has abounded in interesting, colorful personalities. In an attempt to correct this injustice at least to some extent, I included short comments or anecdotes about many of the participants of the immunology game. More often than not, these comments just represent snapshots that have, for inexplicable reasons, remained stuck in my memory. At this place, I apologize to those colleagues, who may not agree with their snapshots. My only excuse is my good intention to preserve at least a fragmentary image of their personalities, without becoming either insulting or flattering.

Also, to render the text more 'palatable', whenever it comes to personal experience or views, I will pass on the narrative to an imaginary 'Doctor G' (who is the author in singular first person, in analogy to 'K' in Franz Kafka's 'Castle'). This arrangement permits a clear distinction between objective and subjective/interpretative passages, and also a more direct colloquial style for the latter.

The language of the book is kept intentionally simple, to facilitate understanding of the complicated scientific content. In the referencing, I did not strive for completeness, but selected primary publications that first described a key discovery important for understanding of the topic discussed.

Despite all efforts for clarity and simplification, an appropriate background will be mandatory for full comprehension of the text, and thus the readership for whom I would recommend this book is, on the first place, research and clinical immunologists, as well as students and teachers of immunology. Novices in any of the covered subdisciplines may make particularly good use of the book, as

they could get the complete background information of the respective area, with all key discoveries, references and interpretations by a short reading. For the same reason, the book may be useful for research managers in the pharma and biotech industry, who are running or planning to run immunology projects. Of course, immunology aficionados with a biomedical background are also welcome, in general all those, whose interest – beyond merely gathering chronologically ordered information – is in the process of how our understanding of the immune system has evolved.

At this place I would like to express my deep thanks to many colleagues, who helped me along the way. I am most indebted to Melvin Cohn for his following the development of the manuscript with interest and providing invaluable comments, references and encouragement. I thank Arthur Silverstein for reviewing the manuscript and commenting on it from the perspective of the historian. I owe a debt to Hugh McDevitt for reviewing part of the manuscript and giving valuable advice. Finally I thank Christophe Benoist, Zlatko Dembic, Donald Forsdyke, Robert Huber, Robert Kerbel, Paul Lehmann, Sebastian Meier-Ewert, Hans-Georg Rammensee, Thomas Revesz, Edward Rosloniec, and Ronald Schwartz for their help in refreshing my memories and providing references.

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Part I

Pre-history with Far-reaching Consequences

Chapter 1

The Immunological Revolution

Those who received their biomedical education around 1960 could not even have suspected that one of the most significant revolutions in life-sciences was taking place at that time: the transformation of serology-centered immunology into immunobiology. Students could not have possibly been informed about this, as the university textbooks at that time were only allowed to contain solid, well-established facts of science, notably those that had survived at least a decade without being refuted. Thus little wonder that the students missed out the birth of immunobiology. As a matter of fact, immunology at that time was not considered as a science in its own right, it usually occupied a single chapter in the students' microbiology textbook, describing at most vaccination, antibodies, serological reactions, and the use of antibodies for typing of bacteria. The most sophisticated piece of science included was the description of how to render antisera 'monospecific' by sequential absorption. Concerning the possible nature and origin of antibodies, a single laconic statement was made, namely that they were localized in the gamma-globulin fraction of serum, implying cautiously that not all gamma-globulins were necessarily antibodies. Indeed, the bulk of gamma-globulins was thought to represent 'normal' serum proteins that were probably produced in the liver (by the motto that substances of unknown nature and origin are best to be blamed on the liver; nota bene, even old, conservative textbooks could contain not all that solid facts!). Naturally, nothing about the cellular basis of immunity passed the inclusion criteria, since the first discoveries in this direction were at most a couple of years old. It is not surprising that the biologically interested student, after reading through the chapter, might have concluded: 'All this may well be very useful, but rather boring.'

Consequently, chances were meagre that creative students would have decided to join immunology research, the few exceptions were those who attained the new knowledge by self-education.

At this point, the reader may wonder why self-evident questions, such as the cellular origin of immunity, were not addressed long before 1960. The explanation lies in what one could rightly call a historical artefact. Namely, immunology in the preceding 50 years had dealt only with antibodies, and immunologists had been convinced that clarifying the nature of antibodies and of their interaction with antigen would answer all outstanding scientific questions. In accordance with this notion, the approach to immunology was predominantly chemical,

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