A History of Modern Immunology
The Path Toward Understanding

Zoltan A. Nagy
Dedication

In memory of my friends
Rodney Langman and
György Fehér
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.
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.

REFERENCE

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,
biological concepts hardly having a chance to penetrate the field. Therefore, the designation of this era by historians as the ‘dark ages of immunology’ is not quite unfounded, although important contributions were also made at this time, in particular to serology. The prevailing paradigm blindfolded immunologists so strongly that new facts, not accounted for by the effect of antibodies, were needed to change their mind.

The earliest ‘heretical’ phenomenon was delayed-type (or tuberculin-type) hypersensitivity (DTH; its history is amply described). It had been known for some 50 years that *Mycobacterium tuberculosis*, when administered intradermally in small amounts, caused a local inflammatory reaction, which was also widely used as a reliable diagnostic marker for previous infection. Although it was noted that the reaction developed in the absence of circulating antibodies against the bacteria, it was easier to ‘sweep it under the carpet’ by postulating that it represented a local, non-immunological reaction against toxic bacterial products. But this proposition became untenable some 20–30 years later, when it was demonstrated that DTH could also be induced with a variety of simple proteins. Soon became the immunological nature of the reaction also evident, and the finding that it could be passively transferred with blood cells of sensitized donors to naïve recipients marked the birth of cellular immunology.

Studies on the mechanism of skin-graft rejection were even more revealing. Thanks mostly to Peter Medawar and his group, the immunological nature of graft rejection was proven quickly and beyond any doubt, and it was also observed that the majority of cells infiltrating the graft were lymphocytes, providing the first hint to an immunological role for this abundant but thus far functionless blood cell population. Further, it was shown that graft rejection was not accompanied by antibody formation against donor erythrocytes, and that the immunizing antigens were on donor leukocytes. Finally, the demonstration by Mitchison and Billingham et al. that transplantation immunity could be adoptively transferred with cells but not with the serum of sensitized donors placed graft rejection into the category of cellular immunity together with DTH. Thus, here were two, well-established immunological phenomena that had nothing to do with antibodies.

A major eye-opener was also the discovery of immunological tolerance that could not be explained by the then-fashionable instructive models of antibody production (the latter proposed that antigen would instruct, or even serve as a template for antibody synthesis). Finally, the accumulation of new evidence alerted immunologists to wake up from their ‘sleeping beauty slumber’, and start asking all those questions that would have been due long ago. These were the most important preparatory steps to what is usually referred to as ‘the immunological revolution’.

### 1.1 THE CLONAL SELECTION THEORY

If immunologists were asked to name one single event that marks the beginning of the immunological revolution, most of us would vote for the appearance of ‘The Clonal Selection Theory of Acquired Immunity’ by Macfarlane Burnet.
in 1959. This theory provided, for the first time, a biology-based conceptual framework for the development of immune responses, and its main theses have remained valid to date, so it has rightly become the alphabet of immunological thinking, and it is now ‘in the blood’ of every immunologist.

Of course, the clonal selection theory did not come ‘out of the blue’, it was indeed preceded by two major selectional hypotheses, namely the side-chain theory\textsuperscript{11,12} of Paul Ehrlich in 1897, and the natural selection theory\textsuperscript{13} by Niels Jerne in 1955 (the gap in between was filled with instructional theories of the ‘dark ages’). Common to all three concepts is the basic postulate that antibodies are natural components of the body, produced at a slow, constant rate, independent of antigen challenge (a sharp demarcation from the instructionists’ view). The role of antigen is then to select and bind to the appropriate specific antibody (out of a mixture of many), and this triggers the production of large amounts of the same antibody. The distinctive features of the three theories lie in the assumed place of selection and the subsequent events.

Ehrlich placed the antibodies as ‘side-chains’ onto the surface of cells. In his view, a single cell possesses many different side-chains, but only those binding antigen will be overproduced and shed into the blood. In contrast, Jerne’s natural antibodies were assumed to circulate in the blood, and the ones binding antigen would then be transported to specialized cells capable of producing the very same antibody. How this transport and the subsequent triggering of specific antibody production would occur have remained unexplained.

Burnet’s concept that also incorporated new knowledge about protein synthesis was the one to hit the nail on the head. Burnet realized that neither antigen nor antibody could carry specific information to a cell to induce antibody formation, what they could do at most is to signal a pre-programmed machinery for protein synthesis. Thus he placed the natural antibody of Jerne back onto the cell surface as a receptor, similarly to Ehrlich. And here came the stroke of genius: he postulated that each specific antibody receptor was only expressed on a single cell and its descendants, i.e., a cell clone. This statement implied that cells of each clone had been programmed to produce one single antibody specificity. Specific binding of antigen would trigger only the cells of the relevant clone to expand (proliferate) and differentiate into antibody-secreting cells (Fig. 1.1).

Besides being essentially correct, Burnet’s theory offers several advantages. First, it allows the body to run several different immune responses simultaneously, a definitive advantage in a pathogen-ridden world. Furthermore, the postulated clonal expansion accounts nicely for the observed continued antibody production after elimination of the antigen, as well as for the enhanced antibody response upon repeated immunization (‘booster effect’). To explain the improved quality of antibodies after booster (‘affinity maturation’), Burnet invoked minor somatic mutations in the antibody-encoding gene, an aspect that was further elaborated by Lederberg.\textsuperscript{14} The newly discovered phenomenon of self-tolerance could also be explained by the deletion of self-reactive clones early in ontogeny.
From the experimentalists’ point of view, the most attractive aspect of the theory was that many of its postulates were testable. For example, with the development of the new immunofluorescence technique, it became easy to demonstrate that the precursors of antibody-forming cells (now B cells) indeed carried immunoglobulin receptors on their surface. Indirect evidence also accumulated to support the one-cell-one-antibody thesis. First, each B cell was shown to express antibodies of a single molecular species, i.e., the same heavy and light chain class of immunoglobulin, and in animals heterozygous for immunoglobulin allotypes (allelic variants of immunoglobulin) either one or the other allotype but not both. The latter finding has indicated that mechanisms must exist in the lymphocyte that inactivate the immunoglobulin gene in one of the two parental chromosomes (‘allelic exclusion’), pointing again in the direction of lymphocyte monospecificity. Second, using radiolabeled antigens, specific antigen binding was demonstrated to only very small fractions of lymphocytes, suggesting clonality of their antigen receptors. Third, the use of heavily radioactive antigens permitted selective killing of antigen-binding cells by local radiation, and the remaining cell population was shown to be incapable of responding to the same antigen, whereas it responded to other antigens normally. The latter, so called ‘antigen-suicide’ experiments provided the strongest indirect evidence for the clonality of immune response. But the final evidence came from the discovery of monoclonal antibodies, whose very existence would be impossible, if lymphocytes were not monospecific. The proposal that clonal deletion should
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be a mechanism of immunological tolerance was also proven experimentally, some 30 years later.19–21

Besides his theoretical contributions, Burnet had another important achievement, namely, that he managed by his knowledge and personal charisma to turn the Walter and Eliza Hall Institute in Melbourne into one of the most prominent immunological sites of the world, a Mecca of immunologists, for many years to come. It was thus more than deserved that Macfarlane Burnet was awarded with the Nobel Prize (together with Peter Medawar), even though he received the prize for the discovery of immunological tolerance that he did not really discover himself.

No concept has ever existed in science without inciting opposing views, and thus clonal selection had its opponents too. Of the numerous arguments brought up against it, the funniest one is the so-called ‘elephant–tadpole paradox’. It goes as follows: The clonal selection theory implies that a large animal with a vast number of lymphocytes must have many more clones than a small animal, and consequently, an elephant should be much better protected against infections than a tadpole, which is not only absurd but is also not observed in reality. Even funnier is that this argument could not be refuted, and thus the paradox had stayed with us until its explanation almost 30 years later.22 Fortunately, tadpoles were meanwhile investigated, and found to have a sufficiently large antibody repertoire,23 so we need not worry too much about them.

1.2 THE BIRTH OF B AND T LYMPHOCYTES

Perhaps the most obvious sign for the one-sided thinking in the ‘dark ages’ was that nobody asked the question: What cells are responsible for the immune response? It was taken for granted that upon immunization, highly sophisticated, specific antibodies arose in the body, whose chemical structure and specificity were worth the scientific pursuit, but the cellular origin of these highly rated substances did not raise curiosity in anybody.

The first important step toward clarification of the cellular basis for immunity was taken as late as in 1956, when Bruce Glick and his colleagues reported that the removal of bursa of Fabricius (a curious little gland-like organ on the dorsal site of the cloaca) from chicken embryos resulted later in a failure to produce antibodies.24 Unfortunately, not a single immunologist took notice of his results for several years. The reason was that he published this epoch-making finding in Poultry Science, a journal highly unlikely to be found in the library of immunological institutions. The finding was then seized upon by several groups, and the chicken became the favorite animal model in immunology for a while. The details were soon worked out: bursectomy shortly before hatching has been shown to result in either a complete loss of antibodies or only IgM antibodies were made,25 whereas cell-mediated immunity (e.g., delayed-type hypersensitivity, allograft rejection, graft versus host reaction) remained unaltered.26 Bursectomy combined with irradiation caused, in addition,
total agammaglobulinemia, but cell-mediated immunity was only minimally affected. The time point of bursectomy appeared important: bursectomy performed on day-old chicks or later led only to partial unresponsiveness to antigens and the serum gamma-globulin level also tended to normalize with age. Thus it appeared that precursors of antibody-forming cells left the bursa already in the late embryonic life, at first the IgM-producing cells. The cellular basis for the functional deficiency was shown to be a complete absence of the antibody-forming cell lineage (surface immunoglobulin-positive cells, plasmoblasts, preplasmocytes, plasma cells), and a loss of germinal centers and periellipsoidal lymphoid tissue in the peripheral lymphoid organs (i.e., spleen). The transfer of histocompatible bursa cells into bursectomized, irradiated chicken led to the restoration of all these deficiencies. Taken together, these results have indicated that the bursa serves as a ‘nursery school’ for early precursors of a distinct lymphoid cell lineage that eventually develops into antibody-forming plasma cells. This lineage of lymphoid cells was then termed bursa-derived lymphocytes.

Of course, this discovery launched a chase for the mammalian equivalent of the bursa of Fabricius, which was more difficult to find, as a discrete organ for this purpose is not available in mammals. On the basis of experimental data, two organs could compete for the bursa-equivalent title, namely the bone marrow and the fetal liver. Finally, the bone marrow won the race, and because its initial is also ‘B’, the subset of lymphocytes responsible for antibody production could be termed B lymphocytes (or B cells), to the great relief of nomenclature committees.

A few years later, one of the giants of the ‘Australian school’, Jacques Miller started a quest for an immunological role of the thymus, another mysterious organ that had been held for an endocrine gland, but it seemed to be comprised of lymphoreticular tissue. At that time, the thymus was considered to be immunologically inert, because, first, no plasma cells and germinal centers were found there after antigenic stimulation, and second, adult thymectomy had no effect on antibody response. Miller might have thought, brilliant as he has been, that the thymus, similarly to the bursa of Fabricius, might be an originator of immunocompetent cells in embryonic life. And he was right, as he was also later in so many instances. To test this hypothesis he performed neonatal thymectomy in mice, and found a severe depletion of lymphocytes and a loss of cellular immunity in the mature animals. He published his observations as a one-and-a-half-page-long preliminary communication in *Lancet*, and this modest paper marked the birth of a new cell lineage. Later similar deficiencies were reported in the chicken after neonatal thymectomy. The new cell lineage responsible for cellular immunity was therefore termed thymus-dependent, or T lymphocytes (or T cells, for short).

The bursa/bone marrow and thymus were then coined the ‘central lymphoid organs’ to emphasize their decisive role in the ontogeny of lymphocytes, whereas the sites where the functionally mature lymphocytes migrate...
The spleen and lymph nodes, were referred to as ‘peripheral lymphoid organs’ or simply ‘the periphery’.

Later on it was demonstrated that the two lymphoid cell lineages not only differ in their development and function, but are also distinguishable by cell surface markers. The pioneering work on lymphocyte markers was done by Martin Raff, a Canadian neurobiologist (and former star quarterback football player for McGill University) upon his sabbatical leave at Mitchison’s famous laboratory at the Department of Zoology, University College, London. He showed that B cells expressed readily detectable amounts of immunoglobulin (Ig) on their surface, and thus, surface Ig could be considered as a B cell marker, although not a distinguishing one, because it was unclear at that time, whether T cells also expressed Ig in small amounts or failed to express it altogether. The first marker that enabled a clear distinction between T and B cells was the ‘theta’ alloantigen, a nerve cell antigen that Raff found to be expressed also on the cell membrane of T cells, but not of B cells. The theta antigen exists in two allelic forms in mice, a rare allotype (later termed Thy-1.1) in strain AKR and a frequent one (Thy-1.2) in all other known mouse strains. Thus, immunization of AKR mice with thymocytes of other strains (e.g., CBA or C3H that are identical at major histocompatibility loci with AKR) resulted in a Thy-1.2-specific alloantibody (or anti-Thy1.1 in the opposite strain combination), which turned out to be an extremely useful tool in T-cell studies. Martin Raff’s contributions also affected his own life, in that he has never returned to Canada, he remained in England permanently. What he did return to, however, was neurobiology, at least this can be assumed, because he disappeared after a while from the hectic show-stage of immunology.

The identification of B and T lymphocytes was perhaps the most important discovery in the history of immunobiology. Yet, the fathers of T and B cells have never been considered for a Nobel Prize. The ways of the Nobel Committee are sometimes inscrutable.

### 1.3 T-B CELL COLLABORATION

By the early 1960s, immunologists had a good reason to be satisfied with themselves: they seem to have finally found, in the dualistic build-up of the immune system, an appropriate model to answer many longstanding questions. In fact, all known immunological phenomena (except allergy) could now be ascribed to either T-cell-mediated cellular or B-cell-dependent humoral immunity. Since the T and B cell lineages not only performed different tasks, but also followed distinct developmental pathways, it was logical to view them as separate systems that functioned completely independent of one another. Therefore, the first demonstration of a cross-talk between them created more annoyance than happiness in the immunological community.

The trouble had started earlier, with a mysterious finding by Benacerraf and Gell. These authors studied the minimal antigenic requirements of a
DTH response by adopting Landsteiner’s classical experimental system, i.e., using a small chemical compound (hapten) coupled to an immunogenic protein (carrier). It had been well established that immunization with a hapten-carrier conjugate yielded antibodies exquisitely specific for the hapten, irrespective of what carrier it was coupled to. Benacerraf and Gell found, however, that this rule was not applicable to DTH: here, the response induced by, for example, hapten ‘X’ coupled to carrier ‘A’ could only be elicited with the same, ‘X-A’ conjugate, but not with the same hapten ‘X’ coupled to another carrier, e.g., protein ‘B’. This finding, termed ‘carrier effect’ incited wild speculations, of which still the most logical was the one proposed by the same authors, namely, that the combining site involved in DTH was larger than that of an antibody to encompass, in addition to the hapten, also part of the carrier protein. But eventually all speculations succumbed to Mitchison’s findings demonstrating that indeed two different cell types participated in the responses to hapten–protein conjugates, namely, an effector cell recognizing the hapten and a ‘helper’ cell recognizing the carrier.

Subsequently, Claman and colleagues observed a synergy between thymus and bone marrow cell populations in antibody production. But it was again Jacques Miller together with his student Graham Mitchell, who firmly established the helper role of T cells in the production of IgG antibodies by B cells, in two ground-breaking papers in the *Journal of Experimental Medicine*.

Although at a scientific meeting in 1968, Miller was accused of overcomplicating immunology, later on, most immunologists had to admit that what they had viewed as a nuisance turned out to be the birth of a new, exciting concept: the regulation of immune responses by cell to cell interactions. This concept opened up a fury of research activity that almost overdominated immunology in the subsequent 25 years. As we will see later, this research produced many important pieces of data but also some problematic ones.

### 1.4 THE STRUCTURE OF IMMUNOGLOBULINS

It was an interesting coincidence that the 60-year-old quest for the structure of antibodies and the nature of their interaction with antigen was crowned with success exactly during the period of the immunological revolution. This enabled a happy union of old established immunochemistry with newborn immunobiology to finally become one single discipline.

As always in science, the spectacular advance in immunochemistry owed a lot to certain novel techniques that had become available to biochemical studies, e.g., ultracentrifugation, electrophoresis, and immunoelectrophoresis. These new tools permitted the separation of antibody molecules by size and charge. The early results did not make the lives of researchers any easier, as it turned out that antibodies were heterogeneous in size, the majority being smaller (7S by sedimentation in the ultracentrifuge), whereas some antibodies appeared much larger (19S). In addition, a substantial heterogeneity was
seen also in terms of their migration in electric field. The only light in the darkness was the observation that certain biological characteristics (e.g., complement binding) appeared to correlate with one or another physical property. Most helpful was in the molecular characterization of antibodies (by then called immunoglobulins, and later simply Ig) the finding that their cleavage by certain enzymes (i.e., papain and trypsin) or by reduction resulted in stable fragments of different sizes. It was then shown by Edelman and Poulik that Ig molecules were made up of two kinds of polypeptide chains, a larger one of ~50,000 molecular weight (heavy or H chain) and a smaller one of ~20,000 molecular weight (light or L chain). These results allowed Porter to propose a basic structure for Ig-s, consisting of two disulfide-bonded H chains, and two L chains, each joined to one H chain with a disulfide bond. Porter could also hypothesize that the antigen-binding site might possibly be formed by parts of both H and L chains (Fig. 1.2).

Edelman was then the one who came up with a more comprehensive structural interpretation, largely based on studies with myeloma proteins that turned out to be practically ‘monoclonal’ immunoglobulins, and were thus

![FIGURE 1.2](image-url) A simplified four-chain stick model of an immunoglobulin molecule. The molecule consists of two identical heavy and light chains, joined by disulfide bonds (-S-S-). The amino terminal portions of heavy and light chains are variable (VH, VL), whereas the remaining portions are constant. The two VH–VL pairs form two identical antigen-binding sites. The carboxy terminal ends of heavy chain constant regions form the Fc portion responsible for immunological effector functions. Based on References 47, 48.
suitable to protein sequencing. The final picture that emerged depicted Ig-s as being composed of two light chains (either $\kappa$ or $\lambda$), and two heavy chains, $\gamma$ for IgG, $\mu$ for IgM (a pentameric macroglobulin), $\delta$ for IgD (exists only in membrane bound form), $\alpha$ for IgA (mono- or dimeric), and $\varepsilon$ for IgE (responsible for allergies). The amino-terminal V (variable) portions of H and L chains were proposed to form the antigen-combining site, thus, each monomeric Ig was bivalent (possessing two binding sites). The carboxy-terminal, constant (C) part of the H chains (called Fc portion) was found to be responsible for the biological effector functions of the molecule (e.g., binding to Fc receptors, and fixation of complement). For their ground-breaking discovery, Edelman and Porter were awarded the Nobel Prize almost instantaneously.

The assembly of more and more amino acid sequences of Ig-s permitted Wu and Kabat\(^{50}\) to gain a more precise idea about the antigen-combining site. They plotted the number of amino acid variations at each position of the molecule (the ever-since famous ‘Wu-Kabat plot’), and found that within the V region of H and L chains there are, beside relatively conserved sections, three hypervariable regions that they assumed to fold into a single binding site. Subsequent X-ray crystallography studies\(^{51}\) confirmed this hypothesis.

Thus, the old dream of immunochemists finally came true. But what has the structure of immunoglobulins actually revealed? First of all, it has revealed itself, and second, it has substantiated our view of Ig-s as being ‘intelligent’ molecules with a specific portion to target a pathogen, and at the opposite end carrying the ‘weapon’, the immunological effector mechanism to rid the pathogen. Actually this had been assumed before. Evidently, the knowledge of Ig structure is absolutely essential for immunology, and it has also been instrumental for the development of future antibody technologies. But the expectation of the ‘dark ages’ that the structure of immunoglobulins would answer all questions of immunology was naturally not fulfilled.

1.5 ALLERGY: FROM DISEASE SYMPTOMS TO IGE

It has been known since the end of the eighteenth century that immune responses in certain instances are accompanied by adverse reactions ranging from local skin irritation to lethal anaphylactic shock. These conditions are lumped together under the umbrella of ‘hypersensitivity’, a term reflecting the earlier interpretation that they represent an overreaction to toxic components of the antigen. However, it had soon become clear that non-toxic substances, such as serum injected from one individual into another could also cause similar symptoms, hinting at an immunological rather than toxic mechanism. That certain human conditions, now known as allergies, including hay fever and asthma belong to the group of hypersensitivities was also proposed in the early twentieth century (for the early history of hypersensitivities see Silverstein\(^1\)). The idea, however, that immune responses might cause disease appeared to be irreconcilable with the protective function of immunity, and as a consequence, hypersensitivity
research was left to clinicians, and has remained outside of ‘mainstream’ immu-
nology for a long time.

Allergies usually triggered by otherwise harmless ‘environmental’ antigens
represent the most frequent type of hypersensitivity. Their pathomechanism
was a matter of heated debates in the first decades of the twentieth century.1
Interestingly, some of the early assumptions, e.g., that allergy is caused by a
special class of antibodies (called reagins), and that such antibodies are cytotro-
pic, have later been confirmed experimentally. Perhaps the most important early
contribution to understanding allergy was the Prausnitz-Künstner experiment.52
One of the authors, Künstner, was sensitive to cooked fish flesh, although his
serum showed no reactivity in vitro with the allergen. But a small amount of
his serum injected in Preusnitz’s skin provoked a local reaction upon injec-
tion of fish extract to the same site 24 h later. This experiment was the first
clear demonstration that allergy can be passively transferred with serum into an
insensitive recipient.

A major problem in the early phase of allergy research was that ‘reaginic’
antibodies were present at so low concentrations in the blood that they usu-
ally remained undetectable by available methods. The first sensitive method for
their detection, an often overlooked achievement, was ‘passive cutaneous ana-
phylaxis’ (PCA) developed by Zoltan Ovary. He studied, together with Guido
Biozzi in Rome, the role of histamine in vascular permeability and allergic reac-
tions.53 The simple and efficient in vivo assay he developed for this purpose
consisted of intradermal injection of a small serum sample into a test animal,
e.g., a guinea pig, followed (after a sensitization period) by intravenous injec-
tion of the antigen together with a blue dye. Local histamine release due to the
antigen–antibody interaction caused increased vascular permeability, and the
dye leaking from the blood appeared as a blue-stained spot in the skin of the
animal within a matter of minutes.54 The novelty of this test was that it assayed
‘reaginic’ antibodies through a defined biological activity, and in addition, it
was extremely sensitive, permitting the detection and quantitation of nanogram
amounts of antibody. The PCA assay was then used in countless studies of
allergy all over the world.

Dr. Ovary was one of the many exile Hungarians, who had to leave their home
country because of the absurdities of twentieth century politics. His name –
despite its orthographic identity with an English word – is Hungarian: its
approximate translation is ‘old castle’. Zoltan Ovary, in contrast to most exile
Hungarians, made the best out of his status. He lived in Rome, Paris, and New
York, he was a connoisseur in arts, music, architecture, practically in everything
that culture could offer. And being a pleasant and cultured man, almost every-
body who counted in twentieth century science and culture was his friend or
personal acquaintance, from Jacques Monod to Baruj Benacerraf, and from Bela
Bartok to Salvador Dali.55 In the last ~45 years of his career, he was Professor
at the New York University Medical School, where he was honored as a living
classic, and remained active until the age of 98 years! Zoltan Ovary was one of
the last renaissance personalities, after whose depart the Earth has become a bleaker place to live.

The decisive step in unravelling the secret of allergy was taken by the husband–wife team of Kimishige and Teruko Ishizaka, two outstanding experimenters, in 1966. They prepared a rabbit antiserum against the reagin-rich fraction of a serum from a ragweed-sensitive patient, and found that this antiserum neutralized the reaginic activity, and reacted with an immunoglobulin (Ig) that was different from all known Ig isotypes.\textsuperscript{56,57} The new Ig class was designated $\gamma_E$, later IgE.

The discovery of IgE permitted for the first time to ask relevant questions about the mechanism of allergy, e.g., why the isotype switch of Ig is shifted toward IgE, and what kind of environmental and genetic factors predispose to elevated IgE levels. Furthermore, the very existence of IgE as a distinct class of Ig implied that IgE-triggered effector mechanisms must have been selected to fulfill a special protective function. Indeed, it is conceivable that repeated exposure of the airways to pollen, molds, insect products, etc., could have been sufficiently noxious to select a distinct effector mechanism for the elimination of these allergens. But the protective effect of IgE responses has been difficult to assess, because allergens are neither toxic nor are they part of the fast-growing pathogens, and thus the harm that would be caused by a deficient IgE response may not be immediately obvious. Therefore, studies of the protective role of IgE fell short in allergy research compared to IgE-induced immunopathology. Along this line of reasoning, the allergic reaction can be regarded as an exaggerated form of a useful effector response as foreseen by Clemens von Pirquet\textsuperscript{58} as early as 1910.

REFERENCES

By the end of the immunological revolution in the late 1960s, the major questions of immunology appeared to have been answered. Indeed, more knowledge accumulated in this short period about the immune system than during the entire preceding history of immunology. What seemed to remain was just ‘to sort out some mechanistic details’. But as is well known, the devil is always in the detail, and thus some of the remaining puzzles have proven extremely difficult to crack, and others have persisted to date. Furthermore, as usually happens in science, the new discoveries have not only provided answers, but also posed new questions (an aspect that renders scientific quest an endless enterprise). As a result, the forthcoming 20–30 years have turned out to be just as exciting as, but much more contradictory than, the immunological revolution itself. As a matter of fact, the revolution, in retrospect from the turn of the millennium, appears to have just been the ‘picking of low-hanging fruits’.

In 1970, the major outstanding questions seemed to be the following:

1. The mechanism(s) of the generation of antibody diversity
2. The behavior of T lymphocytes
3. The role of the major histocompatibility complex in immune responses
4. The mechanism(s) of acquired immunological tolerance
5. The regulation of immune response.

On the way, these topics have revealed their internal complexities, ramifications, and even some unexpected, fanciful outgrowths, and all these expanded their history enormously.

As far as the experimental approaches are concerned, the 1970s were dominated by cell biology, which provided some important insights, but at the same time also created a huge amount of not always useful phenomenology. The 1980s then witnessed the massive entry of molecular biology into the field, and this has become a success story, so that molecular biology has remained ever since a permanent member in the immunological toolbox. Another victory of this era was that human immunology stepped out of the clinic, and claimed its place in basic science.
The experimental models have also undergone significant technical development. At the beginning were the genetically characterized inbred mouse and rat strains, followed by bone marrow chimeras, and toward the end came transgenic and gene knock-out animals.

At this point, the chronicler would like to introduce ‘Doctor G’, an active participant in the field, who is invited to provide interpretations and details that would have remained hidden for everyone else but the insider. His contribution is expected to facilitate understanding of this complex, fast-growing science.

REFERENCE

Chapter 2

A Very Special Location: The Basel Institute for Immunology

It was one of those wonderful summer mornings that can linger long in memory. The sun stood still low above the horizon, and radiated a warm light onto half of the garden, while the eastern half remained under the long shadows of cypresses in the neighboring lot. Doctor G woke up this morning earlier and less tired than usual.

‘What a megalomaniac idea to plant sky-scraping trees on such a small lot!’ was his first thought, and he felt a slight indignation at his late grandfather, who had sold that lot some 40 years ago. But after having his usual quadruple espresso, he became more positively tuned, and finally came the long-hatched decision in the bathroom during shaving: he will do research in immunology!

Until then, Dr. G’s special field of research had been experimental pathology, although it was not necessarily his field of interest. He got involved in it by chance, after he had received his DVM degree with summa cum laude qualification, but he could not find a job. He kept returning to a research institute of the Academy of Sciences asking about a possible opening, when one day the director said to him: ‘Our pathologist just walked out of my office, he will move to take a university position. So, if you are interested in pathology, you will have a job, if not, you won’t.’ ‘Of course, I am interested’ answered Dr. G immediately.

He was already used to take what he got, because it was made clear to him early enough that he was born into the wrong social class, and so he could, at best, expect to be tolerated, but not to be supported by the political system. His idea to go to research also had a political taint: namely, he had to choose an activity, for which the membership of the Socialist Worker Party (that he missed) was alone not sufficient. Furthermore, Dr. G learned everything with little effort, and also realized that occupations other than research would bore him to death.

‘After all, it would not hurt to learn some pathology’ he thought. But a few years and publications later, he could no longer envisage himself looking at histological sections eight hours a day for the rest of his life. His interest in immunology was awakened by his failure to distinguish between physiological and pathological conditions in sections of lymphoid organs. So he went to the
library and soon became familiar with all major findings of the immunological revolution.

‘A science where new cells are still being discovered is not only exciting, but also something to which I could contribute’ he thought and so he did.

Researchers at the Academy had the privilege of applying once a year for a foreign fellowship in the West. What bothered Dr. G most was that his applications had been flatly turned down for eight years in a row, while his party-member colleagues returned already from their second Western stay with boosted egos, and some convertible money. Thus in the ninth year, he was the one to be surprised most that a 10-month Swiss fellowship was granted to him. ‘The comrades at the Academy must have lost their vigilance’ he said sarcastically.

In the application form he had to list two Swiss institutions, where he would like to spend his time of fellowship. At the first place, he named an institute, where immunohistology research was conducted, and to the second place he put, after some hesitation, the Basel Institute for Immunology. Although the latter filled him with panic-like fear, because he had seen many publications coming out of there, and hardly understood a word of them. And as it happened, his first choice did not materialize, however, he soon received a nice letter from Niels Jerne, the Director, to personally inform him that he had been elected to be a Member of the Basel Institute for Immunology for the duration of his fellowship. The decision was probably based on a paper that Dr. G had published in Nature New Biology (a short-lived Nature branch) on his chicken immunology studies. (The choice of chicken fitted well with the profile of his Institute, and as an added benefit, the experimental animals were edible.) Thus, Dr. G had to face the fact that, whether he wanted or not, he would fall into the deep water of ‘big science’ immunology, like Pilatus into the Credo, so to say.

At first sight of the Basel Institute, his uneasy feelings got worse, if that were possible. It was, for the early 1970s, an ultra-modern building, made of glass and aluminum, with a work of techno-art, a revolving spiral on a long bowed metal stalk by Jean Tinguely at the entrance. (Tinguely was a Swiss artist famous for his complicated mechanical constructions, every part of which was moving and busily doing some absurdly useless work.) Dr. G had a hard time to find the entrance itself, because none of the aluminum-framed glass units had a door-handle. The interior of the Institute was just as confusing: a maze of laboratories without doors, interconnected with stairs and gaps between movable walls. Later on he learned that this was meant to promote communication, and to prevent researchers from encapsulating themselves in private cells. This, of course, made good sense, nevertheless the place remained frightening, like a futuristic nightmare-vision. It was a relief for Dr. G that at least the restrooms had doors.

Upon his arrival, Dr. G was led to Niels Jerne’s roof-top office by his secretary. Jerne’s person acted on him almost as disquietingly as the building. First of all, he did not fit the internal image Dr. G had of great scientists. He was slender, very well dressed, and moved quickly and energetically, like a corporate
top-manager. He had an impressive mane of well-combed grayish hair, almost too much for a man of his age. His voice was cold and commanding, and he spoke fast with an undertone of urgency that further strengthened his top-manager image. His face was a curious mixture of tough and almost childish soft features, and as the only scientist-like requisite, he wore fashionably designed but strong glasses.

‘This man seems to have been assembled of many incompatible parts’ was Dr. G’s first impression.

His deputy, Ben Pernis, the discoverer of allelic exclusion, was also present. Ben made a somewhat more familiar impression on Dr. G. He was bald-headed and bulky, also very well dressed, and because he was an Italian, he could also smile. He spoke very fast, as many Italians do, but he did it in an impeccable English, a very non-Italian trait.

Jerne asked Dr. G a few quick questions, and received some embarrassed stuttering answers, until one topic developed into a firework-like scientific discussion between Jerne and Ben, which made them completely forget about Dr. G’s presence. Finally they realized that they were not alone, told Dr. G that he would work in Ben’s lab, and also recommended him to go and look at the town now, because later on he would hardly have time to do so. This is how Dr. G’s first and last personal discussion with Jerne ended.

The Basel Institute for Immunology was founded and supported by Hoffmann–La Roche, one of the pharma giants in Basel. Because it was a family-owned firm, it could afford such extravagancies, and even more. For example, Mr. Sacher, a family member, formerly an artist himself, had strong Maecenas inclinations, and filled the company areal and buildings with pieces of modern art. The Institute also owed him the Tinguely work. Furthermore, he established the Scola Cantorum Basiliense, a meanwhile world-famous music school in Basel. Thus, Mr. Sacher was a good man, and as such lived a happy, and over 90 years long life.

The purpose of the Basel Institute was to provide talented scientists with a place, where they could work in complete academic freedom and with full financial support. A scientist’s Fairyland, so to say. Little wonder that the Institute, almost instantaneously after its opening became the number-one immunology site in Europe, and one of the leaders in the world. All the mother company asked for in return was the right for potential practical applications, and this was not too much. Another expected benefit was that scientists trained at the Institute could then be employed at the company’s own research department.

The Institute had no structural hierarchy: there was the Director and all others were Members. Another strict policy was that permanent memberships were non-existent, with a few exceptions. One was, for example, Dr. Trnka, a jolly, well-nourished, white-haired man, originally from Czechoslovakia. Trnka did some experimental work, but his major function was to run the administration of the Institute. So if it came to financials, it was advisable to be in good terms with Trnka, because he made all these decisions. But Trnka was such a
friendly person that it would have been really difficult not to be in good terms with him. Another permanent member was Ivan Lefkovits, a nice, relaxed and good-mannered man with an ever-youthful face, also from Czechoslovakia. Ivan took the fancy of constructing complicated, automated devices for bio-assays, e.g., for limit-dilution analysis, used to study the size of immune cell repertoires (one of Jerne’s prime interests), and later for the automated analysis of two-dimensional electrophoretic ‘fingerprints’. Ivan spoke a series of languages (including Hungarian), and all with a unique accent that could not be accorded to his mother tongue, and so it must have been his own individualized one. Dr. G assumed that these two men might have belonged to the court of Jerne’s previous kingdom, and they accompanied him to Basel.

There were also a few returning visitors, who spent part of every year at the Institute, and after a while assumed some special, ‘institutionalized’ role. One of them was Steve Fazekas de St. Groth, a very dignified and serious, pipe-smoking Australo-Hungarian virologist in his early fifties. He was the discoverer of a phenomenon that he termed ‘original antigenic sin’. This was the observation that persons infected with flu virus 20 years back or longer, kept making antibodies against the first virus upon every re-infection, although the newly infecting virus meanwhile mutated far away from the original one. Dr. G has been unable to understand this phenomenon to date. Steve, by the way, turned out to have, behind the serious façade, an excellent humor and a ruthless sarcasm. He was famous for expressing himself in highly sophisticated English, but with a strong Hungarian accent. He usually refused to speak Hungarian for no good reason, because he could immediately be spotted by his ex-fellow countrymen on the basis of his accent. Steve’s role at the Institute was unclear, but since he was extremely intelligent, he might have been one of Jerne’s regular discussion partners. Dr. G could not find out whether Steve also conducted his own research there, as a matter of fact, he saw Steve only once sitting in front of a sterile hood, repairing his shoe inside.

Another returning figure was Ruggiero Ceppellini, an Italian transplantation geneticist. He was an aggressive man of power, the type of professor whom Italians call ‘baroni’. Almost everybody in the Italian transplantation scene owed Ceppellini the beginning (or the end) of his or her carrier. He often gave seminars in Basel about the genetics of HLA, the human major histocompatibility complex (MHC), that most immunologists failed to understand, partly because they were not familiar with the topic, but mostly for acoustic reasons, due to Ceppellini’s extremely strong Italian accent. Jerne kept him at the Institute, probably because his almost infallible intuition suggested to him that the mysterious role of MHC in immunity might turn out to be something interesting. Besides, Ceppellini provided the majority of personnel for the Institute’s small transplantation immunology group.

But the most interesting ‘commuter’ was Melvin Cohn, a top theorist beside Jerne, who came from the Salk Institute for about 6 months every year. Mel was very sociable, Dr. G could always see him somewhere in discussion with
somebody, with a wide, provocative smile on his face. Mel’s role at the Institute was tutorial on the surface, as he gave regular seminars on immunological theory or new intriguing findings. But in reality, he was a mind-teaser. He always managed to raise tremendous opposition to what he said, and then skilfully channeled the aggression of his colleagues into scientifically meaningful directions. He was, in a way, similar to those life-size smiling puppets in entertainment parks, which everybody was allowed to hit as hard as he could, but they kept smiling, just a lamp lit up to show the strength of the blow. Dr. G admired Mel for his courage to take up this role that was certainly not imposed on him, he must have identified it for himself. Later on they came to know each other better, and have remained on friendly terms ever since.

There were many more interesting personalities around, who will be mentioned later on, in connection with their work. But most of the Members were very well-trained, aggressive and overexcited youngsters from Western Europe and the USA. Dr. G looked upon them as being the pampered products of the decadent West, but deep inside he envied them for their superior education, good English, and the freedom in behavior that they could afford. On top of these, they were all younger than himself, and so Dr. G felt sometimes to be literally nothing in comparison to them.

Most Members had 2-year contracts, just about enough time to complete a small piece of research work. But some contracts were extended to semi-permanency provided that the particular Member was working on a key project of Jerne’s interest. With his 10-month stay, Dr. G felt severely handicapped, not to mention that, in addition to the work, he also had to catch up with the science and with new methods during this short time: ‘Either I shall half-kill myself and make it, or just get peacefully forgotten’ was Dr. G’s attitude.

As a result of the fast-turnover policy, a whole generation of immunologists has grown up, almost every member of which spent some time at the Institute. They are often referred to as ‘The Basel Family’.

All Members, permanent or temporary, young or old, female or male, were united in one respect: they all worshipped Jerne. This attitude was further supported by the fact that Jerne never appeared in the crowd, although he was always present, and anybody could go to his office and discuss things with him.

‘This is a good method to maintain mysticism’ thought Dr. G, but he was unfair, as the reason behind Jerne’s isolation was his shyness. Nevertheless, he gave a seminar every now and then, where he revealed some interesting facets of his personality. For example, he turned out to be completely apolitical and sincere like a child. He made statements, such as: ‘I published only 16 papers in my life, and most of them were wrong’, for which the youth found him even more adorable. The Jerne cult finally culminated in a two-volume large ‘Festschrift’ for his seventieth birthday, in which every Member submitted his contribution as an offering on the Jerne altar. At this point Jerne retired, moved to his villa in the Province, and broke contact with all immunologists except Ivan Lefkovits.
The most important event in the lives of Members was the appearance of the ‘Annual Report of the Basel Institute for Immunology’. It was awaited with an impatient anticipation, as is Christmas by children. The report contained abstracts of the Members’ results, and an impressive list of usually several hundred publications. But the most important part was Jerne’s introduction, in which he described, in his crisp, clear and provocative way, his thoughts and reflections on the results of the year. Members whose contributions were dealt with in the introduction felt as happy as sportsmen upon winning an Olympic medal. But Jerne could sometimes also be skeptical making statements such as: ‘Immunology resembles more and more the science of meteorology: we have an ever-increasing number of parameters, but cannot tell what the weather will be like tomorrow in Basel.’

After Jerne’s retirement, Fritz Melchers, a leading B-cell immunologist and long-term Member took over the Director position. Fitz was rather arrogant on the surface, but otherwise a good person. He came from a strongly patriarchal family, and paternal rigor might have had molded him into what he became. His father was Emeritus Professor of Plant Genetics at the Max-Planck-Institute of Biology in Tübingen, a real old-fashioned German professor, six and a half feet tall, beyond 80 still erect and strong; a man made of steel and authority. Fritz had extremely high respect for his father. When he gave a lecture in Tübingen, his father was usually sitting in the first row, and Fritz addressed the audience thus: ‘Ladies and Gentlemen, Dear Father’. Under Melchers’s directorship the Institute had survived for almost another two decades. Around the turn of the millennium Hoffmann–La Roche lost interest in immunology, closed down the Institute, and sold the facilities for a nominal price of one Swiss Franc to an affiliated company.

But in the memory of all former Members the Institute lives on as a beautiful, exotic pearl among scientific institutions, and they cannot but regret that it is all over now.

REFERENCE

Immunological Specificity

Specificity is generally considered to be the all-pervasive principle that is effective when two entities interact, irrespective of whether the latter are atoms, macromolecules, cells, or human beings. Specificity has therefore been a preferred substrate for thinking in a number of disciplines including chemistry, biology, psychology, and, last but not least, philosophy.

In immunological thinking, specificity has occupied a prominent place ever since the discovery of antibodies and their capability to distinguish between pathogens more than 130 years ago. With some exaggeration, one could even regard the history of immunology as a continued quest for the meaning and the basis of immunological specificity. Of course, the concept of specificity has undergone many changes over the past 130 years, depending on the actual stand of experimental immunology. Based on the state of scientific-technological progress, the conceptual development of immunological specificity falls roughly into three periods.

1. The archaic period (∼1880–1920), when hypotheses of specificity were created in the absence of structural information about either antigen or antibody.

2. The chemical period (∼1920–1975), when experimental data accumulated on antigens and antibodies, culminating in the determination of immunoglobulin (Ig) structure, and the X-ray crystallography of antigen–antibody complexes.

3. The biological period (∼1975–2000), starting with the discovery of how antibody diversity is generated and concluding with concepts that attempt to place the available information into a biological-evolutionary context.

Immunological specificity in the sense used here is confined to describe the interaction between antibody and antigen. The specificity of the T-cell antigen receptor (TCR), a molecule similarly variable to Ig, differs in important details from that of Ig, and thus merits separate discussion. Furthermore, the history of TCR started in 1984, and thus skipped most detours of the first and second period. The focus of this discussion will be on how the modern concept of antibody specificity has evolved. Earlier concepts will be described to the extent needed for understanding the contemporary view. Interested readers will find the detailed history of immunological specificity, in particular the history of the first and second period, in Arthur Silverstein’s book.¹
The first coherent hypothesis of immunological specificity was set forth by Paul Ehrlich in his famous side-chain theory.\textsuperscript{2,3} Ehrlich considered specificity to be the consequence of interaction between chemically defined complementary molecular structures, and consequently, the antigen–antibody interaction, a strong, irreversible chemical bonding. Although his view incited heated debates over the following decades, in particular, concerning the irreversible nature of antigen–antibody interactions, the concept had remained essentially unchallenged until Karl Landsteiner published his work on synthetic haptens. In these studies, Landsteiner and Lamp\textsuperscript{4,5} investigated the specificity of antibodies raised against proteins substituted with two series of small chemical compounds (haptens). They found that a given antibody reacted most strongly with the immunizing hapten, but showed reactions of graded affinities also with chemically related haptens. While Ehrlich’s concept envisaged a one-to-one relationship between antigen and antibody, and cross-reactivity was explained by sharing a determinant (epitope) by two different antigens, Landsteiner’s data demonstrated that one antibody can react to a number of related epitopes with different affinities, which ruled out the requirement for a perfect fit.

Curiously, this was not the message that caught the fancy of most immunologists in connection with the Landsteiner study. Instead, they were amazed that antibodies could be produced against compounds that had never existed before in nature. Since the number of naturally occurring antigens alone was extremely large, with the added number of antigenic chemical compounds it was almost impossible to imagine that a vertebrate host could carry prior information for the production of all these antibodies. This view then led to ‘instructionist’ hypotheses, according to which antigens somehow mold the structure of antibodies to achieve a close fit. The idea of an almost infinite number of antibodies, often referred to as the ‘Landsteiner legacy’, was another unwanted outgrowth that lingered on in immunology for quite a while.

But the Landsteiner study also had long-lasting positive impacts. First, it has raised the possibility for the first time that antigenicity may not be determined by the chemical nature of the ligand. And second, haptens became important research tools of immunology to be used over the next 50–60 years. In contrast to the hapten study, Landsteiner’s other important contributions (the ABO blood group system for which he received the Nobel Prize, the first autoantibody, serodiagnosis of syphilis and poliomyelitis, transfer of delayed-type hypersensitivity with leukocytes, and many more) were treated as dry historical facts, taken for granted. Thus it is not surprising that Landsteiner himself felt he would have deserved the Nobel Prize for the hapten work instead of the ABO system.\textsuperscript{1}

Until the 1950s, the problem of specificity could only be approached reasonably from the ligand’s side, because organic chemistry was sufficiently developed to be able to synthesize a variety of small antigenic compounds, whereas protein chemistry was still in its infancy so that the antibody molecule remained unknown besides that it was a globulin. Experiments with small organic molecules yielded important though indirect information about the size and possible