Chapter 18. Outlook

A new scientific truth does not triumph
by convincing its opponents and making them see the light,
but rather because its opponents eventually die,
and a new generation grows up that is familiar with it.
-Max Planck, 1949.

You cannot fight against the future.
Time is on our side.
–William E. Gladstone, 1866

Better is the end of a thing
than the beginning thereof.
-Ecclesiastes 7, 8

Nobel Prizes were awarded in the 1980s to the immunologists Niels Jerne and Baruj Benacerraf, and their contributions to the field complemented each other very nicely. Jerne formulated the network hypothesis and Benacerraf and his colleagues published a large volume of data on suppressor T cells, (idiotypic and antiidiotypic) suppressor T cell factors (idiotypic and antiidiotypic) and the role of I-J.[316] I have had the privilege of developing a theory that links the ideas of Jerne to the experiments of Benacerraf and many other experimentalists. The network hypothesis has given rise to the symmetrical network theory.

There are three levels of understanding for cellular immunology. The first level is the first law of immunology, namely clonal selection. The second level is the second law of immunology, which states that the regulation of the adaptive immune system involves interactions between V regions. The immune system is an idiotypic network, and understanding the specific regulation of the system requires that we understand how this idiotypic network functions. The third level involves the very large number of molecules that do not have V regions. The third level includes the innate immunity that is already present in lower organisms. The very large number of components without V regions at the third level have more in common with the myriad complexities of biochemistry than they do with the cellular immunology of adaptive immunity in vertebrates. I believe a more comprehensive understanding of the third level in vertebrates will eventually emerge in the context of an understanding of the second level, the idiotypic network of V regions. This monograph documents that much of the phenomenology of cellular immunology can already be understood by

316 Germain R. N. and B. Benacerraf (1981) A single major pathway of T-lymphocyte interactions in antigen-specific immune suppression. Scand. J. Immunol. 13: 1-10.

focusing on the first and second levels, with relatively little reference to the third level.

In the first chapter I formulated a set of criteria for evaluating competing theories. The resolution of paradoxes was stressed as a key criterion. There are many immunoregulatory phenomena that are paradoxical in the context of basic clonal selection, in the absence of idiotypic network regulation. The most striking was the I-J paradox, but the scope of the theory is much greater than that. The theory was not tailor made in order to resolve the I-J paradox. The I-J paradox was solved in the context of a theory that had been developed in some detail prior to the discovery of I-J in 1976, and prior to the emergence of the I-J paradox in 1982. The resolution leads to testable predictions, including the prediction that anti-I-J^{B} antibodies made in an AαB immunization bind to $\alpha\alpha$B antibodies, that are produced in a BαA immunization.

The evidence for the existence and role of suppressor T cells is extensive and compelling. In this book I have reviewed a small sampling of the suppressor T cell literature. The existence of suppressor T cells is a paradox in the context of basic clonal selection theory, according to which each clone is independent of each of the others. The suppressor cells specifically suppress some lymphocytes but not others, and the only distinguishing feature between those that are suppressed and those that are not is the V region they bear. No one has been able to suggest a mechanism other than idiotypic network interactions that could make this possible. The symmetrical network theory includes an explicit, mechanistic basis for suppressor T cells.

Antigenic competition[317] is a phenomenon that likewise cannot be readily explained in terms of clones being independent of each other. In the symmetrical theory, the surfaces of non-specific accessory cells are arbiters of what happens in the presence of competing antigens, and when there is an ongoing response to one antigen (which includes an autocatalytic component involving antigen-specific and antiidiotypic specific T cell factors) a second antigen is unable to compete. The eigenmode in the shape space direction of antigen-specific and antiidiotypic specific T cell factors for the first antigen is activated first, and since there are a limited number of receptors on the accessory cell surfaces, the eigenmode for the second antigen does not have a chance to be excited.

Low dose tolerance is another phenomenon that is a paradox in terms of the basic clonal selection theory. A small amount of antigen should, in that simpler paradigm, result in a small increase in the number of responsive clones, not a decrease. The paradox was first resolved in the Richter theory, and subsequently also in the symmetrical network theory. The Richter theory

---

[317] Liacoupoulos, P, Couderc, J., Gille, M. F. Competition of antigens during induction of low zone tolerance. Eur. J. Immunol. 1, 359-363 (1971)

interpretation has not stood the test of time, since it is based on asymmetric V-V interactions, and a convincing case has been made for symmetry.

Something as simple as the high turnover rate of lymphocytes (about a third of them are replaced every day) is a paradox in the context of the basic clonal selection theory. This would appear to be metabolically very wasteful. In the context of the symmetrical network theory, however, it makes sense. The stable states of the theory involve active killing of cells. For example, the virgin state is interpreted to comprise a balance between killing by cells or antibodies of the opposite specificity and non-specific influx of cells into the system.

The Oudin-Cazenave paradox is the fact that different epitopes on a single antigen can elicit the production of antibodies with the same idiotypes. This paradox (in terms of basic clonal selection) can be resolved in terms of a co-selection process involving antigen-specific and antiidiotypic T cells specific for the various parts of the antigen. The non-linear co-selection process results in the selection of a homogeneous antiidiotypic T cell population, that stimulates B cells bearing a common idiotype, as defined by the idiotype of the antiidiotypic T cells.

Another example of a paradox in the context of basic clonal selection theory is the fact that the presence of a transgene, that encodes a particular idiotype, results in the production of antibodies with that idiotype, but using genes that are of host origin.**Error! Bookmark not defined.** This finding can be understood only in the context of idiotypic network regulation.

What comes first, theory or experiments? This is a chicken and egg question; each is dependent on the other. Without empirical data there is no need for theory, and without hypotheses there is no need for experiments. There is still an enormous body of immunoregulatory phenomena that can potentially be interpreted in the context of the symmetrical network theory, and extensions thereof.

The basic postulates of the symmetrical network theory are simple. Two components are responsible for the simplicity of the theory. The first component is the cross-linking mechanism underlying the stimulation of lymphocytes. The evidence supporting this, especially in the case of B cells, is compelling. This mechanism leads to the second component, namely the symmetry of stimulatory interactions between idiotypes and antiidiotypes. The theory unfolded from that key starting point. Symmetry in killing was also postulated in 1975, and this was confirmed experimentally in 1983.

As documented here, the scope of the theory is extensive; a long list of immunoregulatory phenomena can be understood in the context of the symmetrical network theory. Some aspects of the theory are surprising, for example the idea that serum IgG is a quasi-species, and that it plays a role in mediating self tolerance. However surprising aspects of the theory are accompanied by predictions, that are expected to help validate the theory.

The first paper on the symmetrical network theory invoked antigen-specific and antiidiotypic T cell factors as key regulatory elements (reference 111). It described four stable steady states of the system for a foreign antigen, namely the virgin state, the immune state, the suppressed state and the anti-immune state, and a mechanism for low dose tolerance. The next paper showed how a non-specific factor could be added to the theory, leading to a mechanism for the role of non-specific accessory cells in immune responses, explanations for high dose tolerance and responses to T-independent antigens and hapten-carrier conjugates (reference 70).

There is a large body of published data on the existence of antigen-specific and antiidiotypic T cell factors, that is important in the context of the symmetrical network theory, has been largely forgotten, and that again sees the light of day in this volume. Specific T cell factors play a central role in the theory, and they deserve to have a more concise name. I suggest that they be called simply "tabs". Then we have antigen-specific tabs, idiotype-specific or antiidiotypic tabs, helper tabs, suppressor tabs, allotype-specific tabs and so on.

As Jerne anticipated, mathematical modelling has been an important tool for the development of idiotypic network theory. Additional work in this area has been done by Sophie Royer and Don Mathewson,[318] including an N-dimensional network model. A great deal more can potentially be done on modelling ideas presented in this volume. Only the surface has been scratched in this area. Investigators who wish to contribute to this idiotypic network theory are strongly encouraged to look closely at what has been done here, and decide whether it is worthwhile to continue along this line, or alternatively to start from scratch with a completely different model. The latter option has been pursued by some, but has not been productive.

I have concentrated on the V region network, and said relatively little about the lymphokine network. The proof of the pudding is in the eating. I have been able to account for a wide range of phenomena with a model that concentrates mainly on V regions. This is not intended to imply that non-specific mediators are unimportant. I have however been concerned with the *antigen-specific* regulation of the immune system, and it is gratifying that we have been able to focus primarily on the V region repertoires of antibodies, lymphocytes and specific T cell factors in that endeavour. Non-specific factors, by their very name, have to do with aspects of regulation that are not antigen-specific. They are not the focus of this volume.

---

318 S. T. Royer, D. J. Mathewson and G. W. Hoffmann (1995) On network distance coefficients and network dynamics. J. Biol. Systems 3, 415-427. See also Sophie's MSc thesis, "Studies of the immune network based on shape-space and distant coefficient", Department of Physics, University of British Columbia, 1993, and Don's MSc thesis, "Mathematical models of immunity", Department of Physics, University of British Columbia, 1990.

My approach has been a combination of top-down and bottom-up. The top-down aspect includes using the fact that the system must have multiple stable states for any antigen, and a mathematical model of the postulates of the theory must exhibit this feature. The system has to be robust with respect to generalization from just two mutually regulating specificities to N specificities, where N can be very large. The bottom-up aspect includes data on suppressor cells, helper cells, antigen-specific and antiidiotypic tabs, contrasuppressor cells, classes of antibodies, and so on.

The theory makes numerous predictions. Some have already been validated, and others are marked by "Prediction" footnotes in this volume. Readers who understand the theory may be able to think of more predictions, and may decide to subject them to experimental tests.

At the time when the theory was first published, there was no evidence of antiidiotypic T cells, and since there was a lot of speculation about just what T cells recognized, their existence was not regarded by many as a given. The theory predicted correctly that such T cells exist.

In 1980 I published a symmetrical network theory paper in which the phenomenon known as MHC restriction was ascribed to being the result of positive selection of T cells by self MHC molecules. Following a large number of experiments, this has now become a widely accepted viewpoint.

In 1988 my colleagues and I published an idiotypic network model of AIDS pathogenesis, that dove-tailed with the symmetrical network theory. It was shown that, within the framework of the theory, AIDS could be an autoimmune disease. This was subsequently supported by experimental results on anti-collagen antibodies in homosexuals and HIV infected persons. It was also supported by the findings of anti-anti-self antibodies in both alloimmune and autoimmune mice, and the finding of anti-HIV antibodies in both alloimmune and autoimmune mice. Additional, previously puzzling aspects of HIV pathogenesis, that have been resolved by the idiotypic network theory, include the low frequency of HIV infected T cells (that increases with time), the high viral load in the lymph nodes, the latency that precedes pathology, the selection of several HIV proteins to be independently MHC-mimicking; the change in the HIV quasi-species with time, the difficulty of super-infecting an infected monkey with a second species or quasi-species of SIV, and the failure of recombinant HIV proteins to cause AIDS when used as vaccines (reference 234). An improved version of the idiotypic network model of HIV/AIDS pathogenesis, that was published in 1994, includes the postulate that HIV-specific T cells are preferentially infected. This postulate was validated in 2002.

The importance of the continued development of idiotypic network theory cannot be overstated. Autoimmune diseases, cancer and transplantation immunology are areas that stand to benefit from a thorough understanding of the idiotypic network, and ways in which it can be used to counter disease. An

obvious area for more detailed work concerns the roles of the many non-specific lymphokines, and how they are involved in adaptive immunity.

We need more theorists that have a thorough understanding of how experiments are done, and what their limitations are, so that they can see precisely where each experiment ends, and where the interpretation begins. There are very few theorists of this type in immunology. For the most part, the experimentalists are also the theorists. Many experiments are complicated, and they are designed by experimentalists. We need more interaction between professional network theorists and experimentalists. An enormous literature of immunological phenomena exists, that one might wish to interpret in terms of immune network theory, including many experiments that were not done in the context of the network concept. In this volume I have only scratched the surface in this regard.

Well-defined criteria have evolved for experimental papers being accepted into leading immunology journals. In chapter one I proposed a set of criteria for "good" theoretical work. The criteria are simplicity, scope, predictions, resolution of paradoxes, a mechanistic basis, rigor, robustness and aesthetic appeal.

The immune network theorist is an amazingly privileged person. An enormous amount of painstaking experimental work has been done, and it is all in the literature to be harvested by the theorist in building models. I have had the added privilege of being not only a theorist, but also supervising a laboratory. My experimental collaborators were able and willing to test ideas as they arose, thus refining and extending the theory. In contrast to many areas of physics, cellular immunology is mostly a low-tech business, and with the aid of a well-stocked refrigerator one can often obtain answers to important questions in days.

The rate of progress in this field can potentially be greatly accelerated by assembling teams of idiotypic network theorists and experimental immunologists to focus on building on the insights that have been gleaned so far in the formulation of the symmetrical network theory. It has been my aim in writing this monograph that this should occur.