Chapter 8. Early network findings and ideas

All great truths begin as blasphemies
-George Bernard Shaw
in Annajanska, 1919

I have not failed.
I've just found 10,000 ways that don't work.
-Thomas Edison

Jerne's idiotypic network hypothesis

Immunologists in the early 1970's were in the process of discovering a wealth of information about how the immune system worked. They had found that the system is eminently manipulable. They could take it apart, then put it back together, and it would work! There are many bits and pieces, so there are many ways of taking it apart and putting it back together, piece by piece. They could for example combine cells from different animals, some of which had been exposed to one part of an antigen, and some to another part, and found that the combined cells would respond much more vigorously to the complete antigen than either population when used alone. On the other hand, they were finding that some cells were capable of specifically turning off other cell populations. This latter finding, called suppression, was particularly influential in spawning network ideas; it was difficult to avoid the conclusion that cells were recognizing each other. The puzzle was to work out how it all works. Then Niels Jerne, the Director of the Basel Institute for Immunology, published the seminal papers that gave birth to the network way of looking at the system.[1]

Jerne's network hypothesis was a radical innovation. The essence of it was, paraphrased, "This idiotypic network exists, since if antibodies can recognize essentially anything, they can recognize the V regions of other antibodies. V-V recognition within the system cannot be avoided. I propose that immune system regulation involves V-V interactions in a fundamental way, and predict that understanding such interactions will be the key to understanding many immunoregulatory phenomena, including specific suppression." Previously each of the clones had been regarded as a separate entity; and now he was suggesting that they were all strongly interconnected. Recall that the first law of cellular immunology is clonal selection. Jerne introduced the second law of cellular immunology, which states that the regulation of the adaptive immune system involves interactions between V regions.

Jerne's proposal initially seemed to many immunologists to make a complex subject even more complex, in fact unmanageably so. In his hypothesis, the immune response to an antigen involves not only the cells with receptors

specific for that antigen, but also cells with receptors specific for those receptors. The injection of an antigen could furthermore potentially lead to a chain reaction. Cells with a given V region would proliferate and they would stimulate the proliferation of anti-V region specific lymphocytes, which could in turn stimulate anti-anti-V region specific cells, and so on. There were however also suppressive interactions in the model, that had the potential to limit the chain reaction.

The network hypothesis included the development of some new vocabulary. Jerne introduced the terms epitope, idiotope and paratope. He focused on the fact that V regions recognize and are recognized by each other, but he originally saw this as an asymmetric process, with idiotopes being recognized by paratopes and not vice versa. This distinction between idiotopes and paratopes did not prove fruitful. It corresponded to differentiating between the processes of recognizing and being recognized, a distinction that faded in significance in light of the fact that the specific stimulation of lymphocytes involves the cross-linking of receptors.[76] Mutually specific V regions on cells can then be symmetrically stimulatory, since if one divalent (or other multivalent) receptor is able to cross-link a second receptor, the converse is also true.

The importance of suppression

The phenomenon of suppression played a key role in the genesis of Jerne's network thinking. Some lymphocytes are able to specifically prevent other lymphocytes from responding to an antigen, and this suppression was found experimentally to be just as specific as the recognition of an antigen by an antibody. How can suppression work? The suppressor cell (or the V region of a molecule derived from it) must be able to recognize another lymphocyte in order to specifically inhibit the function of the latter. The only thing that distinguishes the target lymphocyte from other potential target cells is the V region of the specific receptors on the target lymphocyte. And the only thing on the surface of the suppressor cell that has the needed specificity to do the job is its own specific cell surface receptor. Hence the V region of one cell must recognize, or be recognized by, the V region of another cell. Functional V-V interactions must be of the essence for understanding specific suppression.

When formulated this way, the basic network idea becomes compelling and almost trivial. We return to the question of how (if V regions are able to recognize anything) can such recognition be avoided? Rather than the network immunologist having to prove that V-V region interactions occur, the onus is shifted to the skeptic to explain why they would not occur. And if they do

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[76] See chapter 3, "Switching on a B cell".

occur, why they should not be functionally significant. The existence of antigen-specific suppressor T cells is the compelling evidence that shows that V-V interactions not only occur but are also functionally significant.

Since antigen-specific suppression cannot be simply explained by theories of immune system regulation that do not include network interactions, those who reject immune network ideas characteristically deny the validity of a large body of published data on suppression.

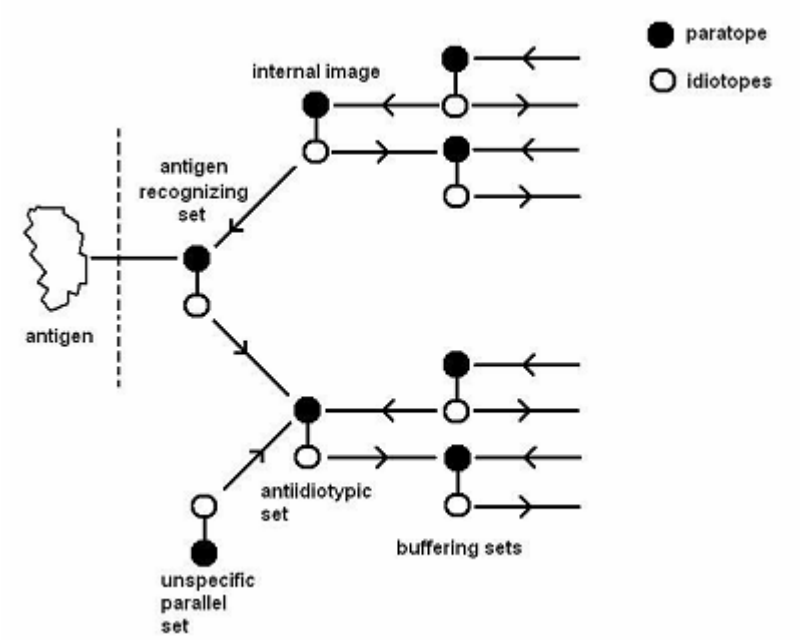
Dualisms

The number two played an important, almost metaphysical role in Jerne's thinking; he stressed a perceived importance of "dualisms". For example, there were two main kinds of cells involved (T cells and B cells) and two main kinds of interactions (stimulation and suppression). As network theory subsequently developed, the two main kinds of interactions were to become three with the substitution of inhibitory (blocking) and killing interactions for the mechanistically less well defined "suppressive" interactions (beginning with the Richter model described below), and the two main classes of cells were to become three when non-specific accessory cells were included (in the symmetrical network theory, see chapter 10).

Jerne's model of the network

Figure 8-1 shows the network as Jerne envisaged it in 1974. All of the interactions are asymmetrical. The arrows show the direction of stimulatory interactions, and for each stimulatory interaction there is a suppressive interaction in the opposite direction. The asymmetry results in the existence of the various sets shown if the figure. An epitope of an antigen stimulates a set of lymphocytes that have paratopes complementary to the epitope. These lymphocytes are the “antigen-recognizing set”, and in accordance with basic clonal selection theory, the antibodies they produce eliminate the antigen. The paratopes of cells in an “antiidiotypic set” recognize idiotopes of the antigen-recognizing set. The antigen recognizing set is assumed to stimulate the antiidiotypic set, and the anti-idiotypic set suppresses the antigen-recognizing set. The antigen-recognizing set is also stimulated by another set of lymphocytes called the “internal image set”, which resemble the epitope of the antigen in that their idiotopes had complementarity to the paratope of the antigen-recognizing set. And the antigen-recognizing set conversely suppresses the internal image set.

Figure 8-1. Jerne's model of the network. Each antibody/clone has V regions that include a recognizing part (paratope) and parts that can be recognized by other antibodies/clones (idiotopes). The antigen recognizing set is stimulated by both an epitope (antigenic determinant) of the antigen and idiotopes of antibodies/clones that are an internal image of the epitope (mimic the epitope in that they stimulate the antigen recognizing set). This figure shows only the stimulatory interactions. For each stimulatory interaction there is a suppressive interaction in the opposite direction. The interaction between the antigen and the recognizing set is of course asymmetric; the antigen stimulates the antigen recognizing set and the antigen recognizing set eliminates the antigen. It is assumed in this model that, as a first approximation, the interaction between the recognizing set and the internal image set is similarly asymmetric; the internal image set stimulates the antigen recognizing set while the antigen recognizing set suppresses or eliminates the internal image set. As a result of this asymmetry, there is another population that interacts with the antigen recognizing set called the antiidiotypic set, with the opposite interactions. The antigen recognizing set stimulates the antiidiotypic set, and the antiidiotypic set suppresses or eliminates the antigen-specific set. The asymmetry furthermore leads to the expanding definition of further sets that are either stimulatory or suppressive for each of the internal image set and the antiidiotypic set (buffering sets) including an unspecific parallel set that has idiotopes similar to the antigen recognizing set and paratopes that recognize different antigens. Each arrow denotes stimulation of paratope(s) by idiotope(s); not explicitly shown is suppression or elimination in the opposite direction. Adapted from N. K. Jerne (July 1973) Scientific American pp. 49-57.



The figure shows an expanding multiplicity of paratopes and their idiotypes that is readily envisaged to encompass the entire system. Jerne proposed that this system exhibited "eigen-behaviour", that is, dynamic behaviour that resulted from its structure, just as the oscillations of a guitar string or a drum surface depend on their respective geometries and the laws of physics.

Jerne envisaged that the immune response to an antigen involved firstly the removal of free preformed antibody by the antigen. This, he argued, would perturb the stable state of the system in two ways, both of which would contribute to antigen specific clones escaping from suppression. The removal of antibodies of the antigen recognizing set would mean they stimulate the antiidiotypic set less, so there is less suppression of the antigen recognizing set by that population. Secondly, the internal image set would be stimulated to a lesser degree, and hence the suppressive effect of that population on the antigen recognizing set would be diminished.

Jerne envisaged that the network interactions were playing a role already in the virgin state. With time it became apparent that no such model, that is also based on asymmetric interactions and is buttressed by mathematical modeling, would emerge. In the case of the Richter model (below) the interactions are asymmetric but are sub-threshold in the virgin state. In the symmetrical network theory (chapter 10 onwards) idiotypic interactions do play a role already in the virgin state.

Oudin and Casenave had shown that the various antibodies produced in an immune response to various epitopes of an antigen could unexpectedly resemble each other in having common idiotypic determinants.[77] In other words, idiotypes on the antibodies to one epitope of an antigen resembled idiotypes on antibodies to another epitope of the same antigen. In the context of basic clonal selection theory this was a paradox, and it was one of the phenomena that inspired the network hypothesis. Jerne made the case that it can be logically explained by assuming that cells with the same idiotypes but different specificities are specifically regulated by common antiidiotypic cells. There seems to be no alternative to some kind of an idiotypic network explanation for this phenomenon.

Jerne also made tentative suggestions regarding how some other immunoregulatory phenomena could be explained in the context of the picture of asymmetric interactions. These included the regulation of the immune response, in which the increase in the antigen recognizing set would reverse the immune response process, and take the system back to an equilibrium

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[77] J. Oudin and P. A. Casenave (1971) Similar idiotype specificities in immunoglobulin fractions with different antibody functions or even without detectable antibody function. Proc. Nat. Acad. Sci. (USA) 68, 2616-2620.

state. From his description it was not clear however, how the immune response could then exhibit memory. He proposed a mechanism for the paradox of low dose tolerance that involved complexes of antibody and antigen stimulating antiidiotypic cells. He suggested that the eigen-behaviour of the network may be such that it is unable to simultaneously respond to two different antigens as an explanation for the antigenic competition paradox. Additional phenomena for which he offered explanations were the inhibition of immune responses by antigen-specific IgG,[78] the idea, the ability of a cross-reacting antigen to break tolerance,[79] and the fact that immune responses are often accompanied by the production of antibodies that are not specific for the antigen. These non-specific antibodies can also express the same idiotype as the antigen-specific antibodies, again suggesting the two kinds of antibodies are under regulated by the same antiidiotypic antibodies and/or lymphocytes.

Jerne's model was ingenious in that it appeared to resolve some important paradoxes, but mathematical modelling has shown that the details have to be different. My initial attempts to mathematically model the interactions as illustrated in the figure showed that the system typically oscillates, rather than exhibit multiple stable steady states, as is needed for a system that has memory. Furthermore, the idea that the first important thing to happen in an immune response was binding of antigen to free antibody, rather than to cell bound specific receptors, was a departure from conventional clonal selection theory, and was reminiscent of a paper Jerne had published in 1955.[80] That paper was a precursor to Burnet's paper on the clonal selection theory (reference 12).

The analogy with the brain

Jerne stressed that there are many similarities between the immune system and the central nervous system. Indeed, his hypothesis may have been inspired largely also by this analogy. Both constitute networks of cells coupled by stimulatory and suppressive interactions; the number of cells are similar (to within a couple of orders of magnitude); both systems can respond to an enormous variety of stimuli; and, most notably, both systems are capable of learning (memory), without being able to pass the acquired information on to the next generation. This analogy made the hypothesis doubly exciting; it meant that progress toward understanding the immune system could lead to

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[78] C. Henry and N. K. Jerne (1968) Competition of 19S and 7S antigen receptors in the regulation of the primary immune response. J. Exp. Med. 128, 133-152. "19S" and "7S" refer to IgM and IgG antibodies respectively.

[79] W. O. Weigle (1973) Immunological unresponsiveness. Adv. Immunol. 16, 61-122.

[80] N. K. Jerne (1955) The natural-selection theory of antibody formation. Proc. Natl. Acad. Sci. USA 41, 849-857.

new ideas for understanding the brain (or vice versa). In the next section we see that the analogy played a role in the development of the Richter model.

The first mathematical model

Jerne recognized that mathematical modelling would have to play a role in the development of a more detailed immune network theory. He proposed the following differential equation to describe the dynamics of a typical clone consisting of L cells (lymphocytes)[81]

$$\frac{dL}{dt} = \alpha - \beta L + L\sum_{i=1}^{N}\varphi(E_i, K_i, t) - L\sum_{j=1}^{n}\psi(I_j, K_j, t)$$

There are four terms in the differential equation for *L*. These correspond to non-specific influx *(α)*, natural death *($-\beta L$)*, a stimulation term due to all the clones with idiotopes that fit into the paratopes of the clone (the first summation term) and a killing term due to all the clones with paratopes that recognize the idiotopes of the receptors of the clone (the second summation term). This equation incorporates the asymmetry between idiotopes and paratopes shown in Figure 8-1. No analysis of this equation has been published, and as it stands the system is incompletely specified. Jerne later further formalized the distinction between the antiidiotypic set and the internal image set by calling the former Ab2α, and the latter Ab2β.[82]

Limitations of the Jerne model

While Jerne's model was a huge conceptual advance, he candidly recognized it's limitations. He wrote in 1974 "The weakness of this incipient network theory lies in its lack of precision. This leaves an ambiguity in the answer to the question whether the relationship between two sets is suppressive or stimulatory or partly one and partly the other, and thus permits us to postulate interactions that suit our explanatory needs" (reference 1). He also wrote, "To become meaningful, a more explicit formulation of the network and its functional features would be needed."[81] The network concept and his model were nevertheless a revolutionary and vital first step. He opened up the field

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[81] N. K. Jerne (1974) Clonal selection in a lymphocyte network. In Cellular Selection and Regulation in the Immune Response, Edelman, G. M. ed, Raven Press, New York, op. cit. p. 39-48.

[82] N. K. Jerne, J. Roland and P.-A. Cazenave (1982) Recurrent idiotopes and internal images. EMBO J. 1, 243-247.

for theorists to formulate the more explicit network models that were needed, and to endeavour to interpret phenomena in the context of such network models. Adding the complexity of network interactions would mean that it would become possible to dispense with some of the less than elegant complexities of other ideas about immune system regulation, and a new, more satisfying picture of the immune system would emerge.

It is interesting to evaluate Jerne's model from the point of view of the eight criteria for a good theory that we formulated in chapter 1.

(a) Simplicity. When Jerne published the theory, many immunologists wailed, "It's too complicated." Complexity and simplicity are however in the eye of the beholder, and the idea that V regions are also antigens can be regarded as simpler than the alternative, namely that V regions are a special class of protein molecules that are somehow able to evade having a role as antigens. That alternative is not a complete theory until a mechanism for such a discrimination is specified. Figure 8-1 has an important simplicity, namely it is constructed according to the simple (even if ultimately erroneous) rule that epitopes stimulate paratopes, and paratopes suppress epitopes. This would later be replaced by the even simpler concept known as "first symmetry" (next chapter), in which the distinction between paratopes and idiotopes largely evaporates.

(b) Scope. The potential scope of the network hypothesis in general was enormous, since it provided a fundamentally new way of looking at immunoregulatory phenomena. As listed above, the phenomena that the Jerne model tentatively explained is impressive. The limitations in scope were also candidly acknowledged.

(c) Predictions. The Jerne model did not make explicit new predictions. The Richter theory and the symmetrical network theory that followed were more explicit with respect to the underlying mechanisms and consequently had stronger predictive power.

(d) Resolution of Paradoxes. The model provided explanations for several phenomena that are paradoxical in the context of a non-network clonal selection point of view. As mentioned, these included the phenomena of low zone tolerance, antigenic competition and the finding by Oudin and Cazenave that antibodies produced against different non cross-reacting epitopes of one antigenic molecule can have similar idiotypes.

(e) Mechanistic basis. The mechanistic basis was primarily "antibodies bearing paratopes suppress cells bearing receptors with complementary idiotopes and idiotopes stimulate cells bearing complementary paratopes." This was sufficiently mechanistic for Jerne to make the case that the model could resolve important paradoxes.

(f) Rigour. The proposed mechanisms were more at a handwaving level than at a rigorous level with some mathematical modelling.

(g) Robustness. The details of the interactions were not specified at a sufficiently detailed level to provide dynamics that could be investigated for robustness.
(h) Aesthetics. While experimental immunologists were divided on the question of whether this was an attractive theory, most theorists certainly saw it as very attractive. In addition to an intrinsic beauty, it gave them an exciting opportunity to contribute to progress towards understanding how the immune system is regulated.

Overall, the formulation of the network hypothesis was a huge step forward in the science of cellular immunology. It was also a break from the popular idea that such breakthroughs are made solely by young scientists. In 1974 Jerne turned 63 years old.

Comments on mathematically modelling the network

The immune system consists of a large number of clones of lymphocytes. These clones and the V region bearing molecules they produce are capable of interacting with each other to form a system that can learn and which has memory. The memory aspect of the system implies stability; if the system were not stable in some fundamental sense it is hard to see how it could exhibit memory. An idiotypic network description of the system is the specification of a set of rules for how the clones interact with other. Let the system consist of N clones. Let x_i be the population size (number of cells) of the i^{th} clone, and let K_{ij} be the interaction strength (most simply, affinity) between the V regions of clones i and j. The list of population sizes can be written as an N-dimensional vector $\mathbf{x}$ with components x_i, and the interaction strengths are a matrix with $N \times N$ terms, that can be written more simply as $\mathbf{K}$ with the elements K_{ij}. The sizes of the clones change with time, especially when the system is perturbed by a foreign antigen. Let the parameters associated with such a perturbing antigen be its concentration a and its affinity for each of the N clones, designated by an N dimensional vector $\mathbf{A}$. A set of rules (postulates) for the system can be expressed in the form of a differential equation for $\mathbf{x}$:

$$\frac{d\mathbf{x}}{dt} = \mathbf{F}(\mathbf{x}, \mathbf{K}, \mathbf{A}, a)$$

where t is time. The problem of immune system regulation, expressed in mathematical terms, is to find the function $\mathbf{F}$, and to provide an interpretation of $\mathbf{F}$ in terms of plausible mechanisms. We typically envisage the mechanisms first, then formulate the corresponding function $\mathbf{F}$. We can then determine,

by integrating the equations, whether $\mathbf{F}$ has dynamical properties corresponding to the properties of the actual immune system. The rate of change of a is given fairly generally by

$$\frac{da}{dt} = G(\mathbf{x}, \mathbf{A}, a)$$

where plausible, mechanistically based forms for G can be readily formulated.

The Richter theory

It did not take long for mathematical biologists to take up the challenge of translating Jerne's network hypothesis into a more concrete model or theory, with more explicit postulates about how the system might work.

The first detailed model (or "theory"[83]) based on the network hypothesis was developed by Peter Richter[84] of the Max Planck Institute for Biophysical Chemistry in Göttingen, Germany. The Richter theory does not attempt to take into account the separate roles of T and B cells, but it included the first mathematical model to demonstrate that the network could have interesting dynamical behaviour. The aim of the theory was to explain the fact that either low or high doses of antigen can induce unresponsiveness ("high dose tolerance" and "low dose tolerance"), while intermediate doses induce an immune response. This tri-phasic dose-response behaviour had been reported by Avrion Mitchison in the murine response to bovine serum albumin (BSA) (reference 17). Richter's model provided an elegant explanation for this dose-response behaviour.

Richter called the set of cells and antibodies that recognise the antigen "Ab-1", he called the set that is anti-idiotypic to Ab-1 "Ab-2", he called the set that is antiidiotypic to Ab-2 "Ab-3", and so on (Figure 8-2**)**. The network was thus simplified from Jerne's two-dimensional network (Figure 8-1) to a one-dimensional chain. Consistent with the Jerne description in terms of paratopes and idiotopes, the Richter model is based on asymmetric interactions between

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83 What are the differences between a hypothesis, a model and a theory? As used here, a hypothesis is something that is postulated, and alone may not have very much explanatory ability. A model is a set of hypotheses that together are designed to account for one or more phenomena in a more rigorous manner. A theory is a well-developed model that claims to be of broad applicability and validity. We will see that several mathematical models can be based on a single set of postulates, and can provide support for several aspects of a single theory.

84 P. H. Richter (1975) A network theory of the immune response. Eur. J. Immunol., 5, 350-354.

idiotopes and antiidiotypes. The antigen stimulates Ab-1 and is suppressed by Ab-1, Ab-1 stimulates Ab-2 and is suppressed by Ab-2, and so on.

The way in which Richter developed his theory is an elegant example of the importance of analogies in theory development. When formulating any theoretical model we often use things that we have learned about systems that have features in common with the system under consideration. The analogy between the immune system and the brain had already been discussed by Jerne, and Richter was familiar with neural network models in which short range activation and long range inhibition were key features.[85] Such models had been shown to exhibit multiple stable steady states, an essential feature of any model that, like the immune system, has memory. He was also familiar with reaction-diffusion models of biological pattern formation ("morphogenesis"), in which short range activation and long range inhibition were essential aspects.[86] He found that he was able to formulate an immune network theory based on "short range activation" and "long range inhibition", analogous to the interactions that had been postulated in the other systems. Since the systems are quite different, the analogies are loose ones. "Short range activation" for lymphocytes was activation to proliferate characterized by a relatively high threshold in the amount of the stimulus needed, and "long range inhibition" corresponded to killing of lymphocytes, with a lower threshold in the amount of antiidiotypic lymphocytes or antibodies needed for killing.

The Richter theory included three kinds of interaction, namely stimulation, inhibition (blocking) and killing. This three-ness was a step away from Jerne's emphasis on dualisms, which did not include killing as a phenomenon distinct from suppression.

Modes of response

In the Richter theory, injection with various amounts of an antigen causes a wave of activation that propagates to various extents along the chain of specific cells Ab-1, Ab-2, Ab-3, and so on. A small dose may initially cause proliferation of just the Ab-1 lymphocyte population. When the Ab-1 population reaches a certain threshold level (the stimulation threshold) it causes proliferation of the Ab-2, and when Ab-2 reaches a different level, the threshold level for killing, Ab-2 cells and/or antibodies kill the Ab-1 cells (Figure 8-3). The Ab-2 cells then persist at a level above the killing threshold level and below the threshold needed for stimulation of Ab-3. This requires

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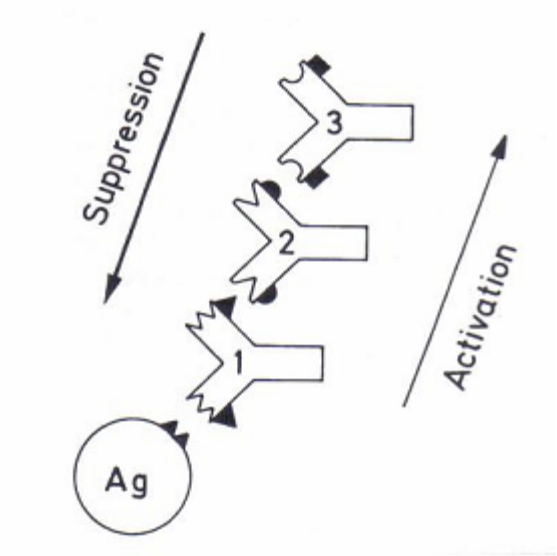
[85] H. R. Wilson and J. D. Cowan (1973) A mathematical theory of the functional dynamics of cortical and thalamic nervous tissue. Kybernetic 13, 55-80.

[86] A. Gierer and H. Meinhardt (1972) A theory of biological pattern formation. Kybernetic 12, 30-39.

Figure 8-2. The chain Ab-1, Ab-2 and Ab-3 of Richter's model. Ab-1 is the antigen recognizing set, Ab-2 is the antiidiotypic set, and Ab-3 is anti-antiidiotypic clones and is the lowest of the buffering sets in the picture of Jerne's model (compare **Figure 8-1**). The interactions are again asymmetric, with a clear distinction being made between paratopes that recognize and idiotopes that are recognized. All idiotypic interactions are assumed to be initially sub-threshold. The levels of the internal image set and the unspecific parallel set of the Jerne model consequently remain sub-threshold in this model, since they can only be suppressed by any increase in Ab-1 and Ab-2 respectively. The introduction of thresholds thus results in the more complex two-dimensional diagram of interactions of the Jerne model being simplified to become a one-dimensional chain, consisting of idiotype, antiidiotype, anti-antiidiotype, and so on. Reproduced from P. H. Richter (1975) Eur. J. Immunol., 5, 350-354.

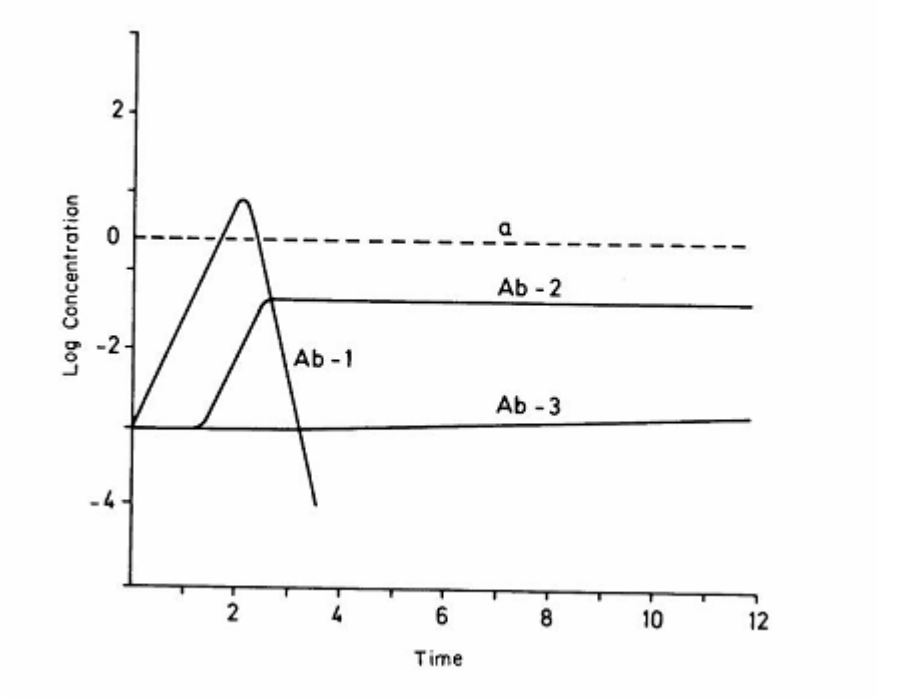


that the killing threshold be lower than the stimulation threshold. This sequence of events was hypothesized to account for the phenomenon of low dose tolerance.

An injection with a larger dose of antigen in this model causes an immune response, consisting of a wave of activation proceeding one step further along the chain. Then Ab-3 eliminates Ab-2, leaving Ab-1 free to respond to stimulation by the antigen, unencumbered by any restraining regulatory influence of Ab-2 (Figure 8-4).

An even larger dose of antigen takes the wave of activation one step further still, activating Ab-4, that eliminates Ab-3, permitting Ab-2 to emerge and

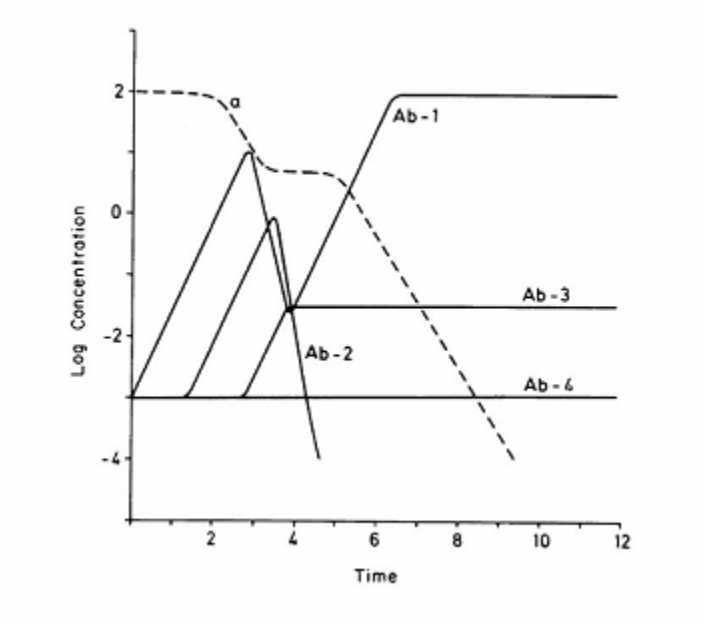
Figure 8-3. Low dose tolerance in the Richter model. Stimulation of Ab-1 by antigen leads to proliferation of Ab-1 clones until Ab-1 reaches a threshold level at which it stimulates proliferation of Ab-2. Ab-2 proliferates until it reaches a threshold for killing Ab-1 cells. Ab-1 is eliminated while Ab-2 persists at an elevated level that is below the threshold for the stimulation of Ab-3. Reproduced from P. H. Richter (1978) Theoretical Immunology, G. I. Bell, A. S. Perelson and G. H. Pimbley Jr. Eds, Marcel Dekker, New York and Basel..



eliminate Ab-1. Since the antigen-specific clones are eliminated, the animal cannot make antibodies, and we again have tolerance; in this case "high dose tolerance." (Figure 8-5).

When Richter first mathematically modelled the simple chain of interactions shown in Figure 8-2, he found that he was unable to obtain both low dose tolerance and the immune response; a reasonable mathematical model resulted only in the dynamical behaviour he was seeking for low dose tolerance (personal communication). This led him to add inhibitory interactions, as shown in Figure 8-6.

Figure 8-4. The immune response in the Richter model. A larger dose of antigen causes a deeper penetration of the perturbation into the network. The elimination of Ab-1 by Ab-2 is inhibited by the antigen, since the antigen and Ab-2 compete for binding to Ab-1 receptors. On the other hand Ab-2 continues to be stimulated by Ab-1 until Ab-2 reaches the threshold for stimulating proliferation of Ab-3. Ab-3 reaches the threshold for eliminating Ab-2 and this elimination leaves Ab-1 free to rebound and reach a high level, that eliminates the antigen and is unfettered by any regulation by Ab-2. Reproduced from P. H. Richter (1978) Theoretical Immunology, G. I. Bell, A. S. Perelson and G. H. Pimbley Jr. Eds, Marcel Dekker, New York and Basel.

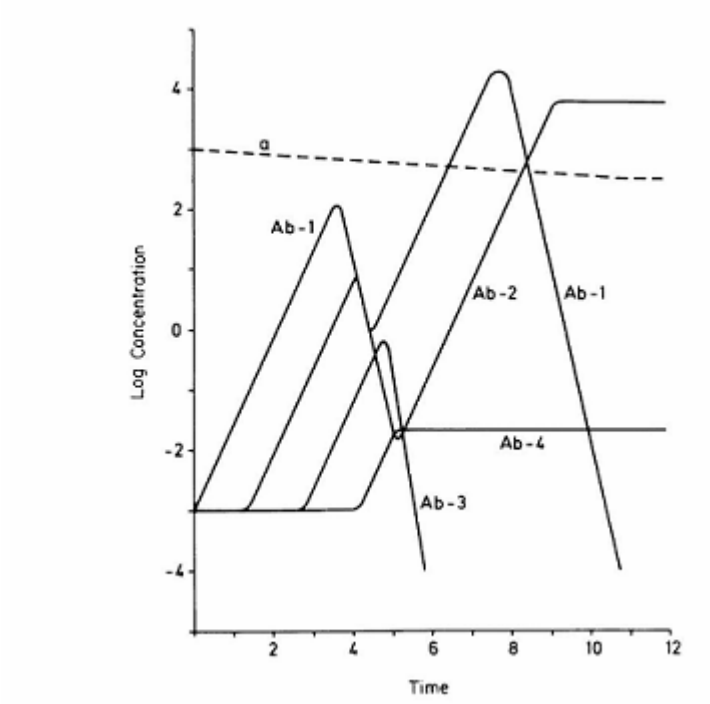


Richter's mathematical model

Richter translated the above ideas into differential equations, and Figures 8-3 to 8-5 are obtained by integrating his equations, which appear below. Such differential equations are often formulated with concentrations x_i as the variables, but Richter used dimensionless variables s_i for the size the clones. These variables can be interpreted as the product of a concentration and an affinity. The Richter equations have the form

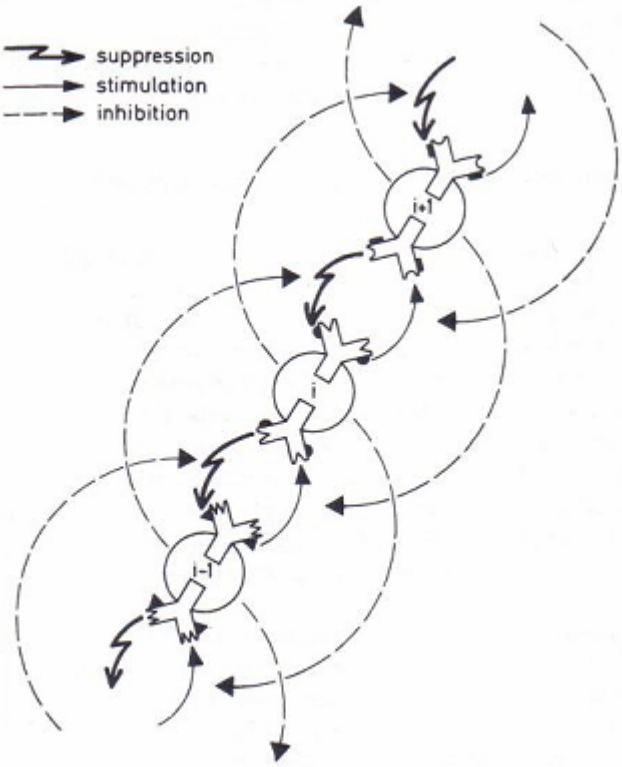
$$\frac{ds_i}{dt} = \frac{1}{\tau_b} f(s_{i-1}, s_i, s_{i+1}) s_i - \frac{1}{\tau_d} g(s_{i-1}, s_i, s_{i+1}) s_i$$

Figure 8-5. High dose tolerance in the Richter model. At still higher levels of antigen the perturbation of the network reaches Ab-4, which eliminates Ab-3, permitting Ab-2 to rebound and eliminate Ab-1. Reproduced from P. H. Richter (1978) Theoretical Immunology, G. I. Bell, A. S. Perelson and G. H. Pimbley Jr. Eds, Marcel Dekker, New York and Basel.



The first term describes birth, the second death. The functions *f* and *g* are threshold functions that for the rate of change of s_i depend on s_{i-1}, s_i and s_{i+1}. The thresholds play a key role in the model. Jerne had suggested that network interactions are operative before the antigen arrives. This is the case in the symmetrical network theory (see 10 onwards), but was not the case in Richter's model because of the thresholds. In Richter's model the V-V interactions are all sub-threshold prior to the appearance of the antigen.

Figure 8-6. Stimulatory, killing and inhibitory interactions were all found to be necessary by Richter in order for his model to work. For example, both Ab-3 and Ab-1 bind to the specific receptors of Ab-2, and the model includes inhibition by Ab-3 of Ab-1 binding to Ab-2. More generally, clone i – 1 inhibits killing of clone i by clone i + 1, and clone i + 1 inhibits stimulation of clone i by clone i – 1. Adapted from P. H. Richter (1975) Eur. J. Immunol., 5, 350-354.



τ_b and τ_d are birth and death time constants. The functions f and g are structured to model the thresholds that are inherent in the theory, with minimum values of 0 and maximum values of 1. In the case of the function f there are thresholds for stimulation (s_{i-1} dependence) and for inhibition of stimulation (s_{i+1} dependence). There is also a dependence on s_i, which accounts for the fact that the amount of stimulation depends on how many cells there are to stimulate or kill (buffering dependence). Mass action considerations lead to the following form for f:

$$f(s_{i-1}, s_i, s_{i+1}) = \frac{1}{1+(B_i / s_{i-1})^m}$$

This is a threshold function that has switch-like behaviour for large m. In that case (large m) f is close to zero for s_{i-1} less than B_i and the value switches to 1 when s_{i-1} becomes greater than B_i. The position of the threshold, B_i, depends on inhibitory and buffering interactions according to

$$B_i = B\frac{1+s_{i+1}}{1+\xi s_{i+1}}(1+\eta s_i)$$

where B, ξ and η are constants. Analogous equations for g, the function modelling death, are

$$g(s_{i-1}, s_i, s_{i+1}) = \frac{1}{1+(D_i / s_{i+1})^n}$$

with

$$D_i = D\frac{1+s_{i+1}}{1+\xi s_{i+1}}(1+\eta s_i)$$

An important aspect of the model is that the threshold for destruction of cells must be chosen lower than the threshold for birth. This prevents activation of the chain of clones from running out of control, and is achieved by making D suitably less than B. The values of the parameters used in the Figures 8-3 to 8-5 are: B = 0.1, D = 0.01, τ_b = 0.3, τ_d = 0.1, m = n = 5, and $\xi = \eta = 0.01$.

Achievements of the Richter theory

Since the Richter model had a clear, simple mechanistic basis, and it was the first one that successfully addressed what the theorists of the time regarded as the most interesting system-response behaviour, it can reasonably be called a theory. The Richter theory was also an important precursor of symmetrical network theory that followed. It achieved several things. Firstly, it showed that Jerne's network concept could be reduced to manageable proportions, which

was something about which Jerne himself had not been optimistic. Secondly, the Richter theory showed that there are three basic types of specific interactions which are important for such models - stimulation, inhibition (blocking) and elimination (killing). Thirdly, it illustrated a potential importance of thresholds in stabilizing the immune system. A major constraint on workable idiotypic network models is the problem of stability. The Richter theory showed that an immune network model can exhibit stable memories.

The publication of the Richter theory was thus a big step towards making the network concept plausible. When I went to Basel in late 1974 I heard two disparaging comments about the newly publicized immune network idea. One was "it can't be right, because the network goes on forever." This unbounded nature of the network did not fit within the bounds of their "common sense." The Richter model demonstrated that when thresholds played a role, it did not have to go on forever. A comment from the theorist Mel Cohn on the Jerne network hypothesis was that the network "is just a buffer". The Richter theory included buffering, but it exhibited dynamics that clearly reflected the potential for much more than just buffering.