Scand. J. Immunol. **54**, 4–9, 2001

DISCUSSION FORUM

Essay 1: The Danger Model in Its Historical Context

P. MATZINGER

National Institute of Allergy and Infectious Diseases, National Institutes of Health, 9000 Rockville Pike, Building 4, Bethesda, MD 20852, USA

(Received: 3 May 2001; Accepted 21 May 2001)

INTRODUCTION

Because I have been asked many times to delineate the differences between the Danger model [1] and models based on self-nonself discrimination (SNSD), intensively discussed in [2] I would like to start by pointing out one similarity. Both types of models agree that there is a need for some sort of discrimination at the effector stage of the immune response. As Mel Cohn puts it, the immune system cannot use a universal glue as an effector molecule [3]. It *must* make some distinctions so that it can eliminate pathogens without destroying the body's own tissues in the process, and this need has important evolutionary consequences. It is one of the reasons for the specificity of T and B cells. The more antigen specificity shown by the effector cells and molecules of the immune system, the more the response can be tailored to the pathogen and the less autodestruction will occur during an immune response. The critical need to discriminate is thus the evolutionary selection pressure behind the complex set of mechanisms that endow T-cell receptors (TCRs) and antibodies with their enormous range and exquisite degrees of specificity. Up to this point the Danger model does not differ from the others.

Where the Danger model parts company with the SNSD models is that it does not assume that the discrimination between self and nonself is the critical element in the decision to *initiate* an immune response. All SNSD models have made this assumption and suggested that an immune response is generated whenever the body encounters something that is foreign. Although this has been a useful concept, many phenomena have surfaced over the last 50 years that do not fit with it. The Danger model instead suggests that an evolutionarily useful immune system should concentrate on those things that are dangerous, rather than on those that are simply foreign. There are two reasons for this shift in viewpoint. Firstly, there is no need to make a response to everything foreign. There is a lot of harmless foreign material in the air we breath and the food we eat. Why should we make an immune response to these things? There is also no need to make a response to a virus that enters a cell, makes a few copies of itself and leaves without doing any damage. (We might even want to welcome such viruses for the genes that they could bring us.) There is no need to eliminate the commensal bacteria in our guts that provide us with vitamin K, or the foetuses that make the next generation.

The second reason is that 'self' changes. Classical SNSD models generally assume that each individual's immune system 'learns' the difference between self and nonself early in life. This is usually thought to be accomplished by the deletion of self reactive T and B cells early in their ontogeny in the thymus or bone marrow. Thus, early in (and throughout) life, only the lymphocytes that do not react to the self components are allowed to mature. If bodies never changed, and if there were no tissue-specific antigens that are not expressed in the thymus or bone marrow, this would be a useful way to create a definition of self. However, peripheral antigens do exist [4], and bodies do change. We go through puberty, pregnancy, ageing. We are not the same 'self' throughout life. How can the immune system keep up? Why don't frogs, mice and humans kill themselves at puberty? Why don't mammalian females reject their own newly lactating breasts when they begin to produce milk proteins that were not part of self until that time? In short, how can the immune system deal with a changing self?

In addition, there are a wealth of other questions that classical SNSD models do not answer very well. For example, if the immune system fights anything that is foreign or new, why do we so often need to use adjuvant? Why doesn't the immune system rid the body of those tumours that are known to express tumour-specific antigens? Why are livers more easily transplanted than other organs? Why is the hamster cheek pouch (a place in which hamsters carry nuts, with all of their concomitant fungi and bacteria), an immunologically privileged site? Why does oral administration of antigen sometimes lead to vaccination (as in the polio vaccine) and sometimes to tolerance? What is the difference that leads to gene therapy versus DNA vaccination? Why do so many people have autoreactive T and B cells without any sign of autoimmunity? Why do others get autoimmune diseases?

Musing on these kinds of questions led to the creation of the Danger model, which proposes that damage, rather than

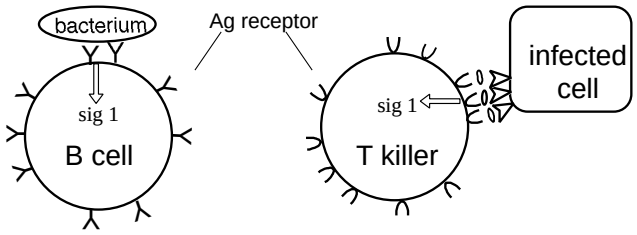

Figure 1. The antigen is in control (Burnet): recognition of antigen (signal one) leads to B- and T-cell activation. The same principle was later applied to T cells.

'foreignness', is what initiates an immune response. Many parts of the model are not new, as it incorporates a series of features from familiar SNSD models, but it adds a small twist, a twist that takes us down a new path, that has rather surprising consequences, and that allows for explanations for almost all of the questions above.

HISTORICAL FOUNDATIONS

The giants on whose shoulders the Danger model stands

It starts (of course) with Burnet, who proposed that B cells carry clonally distributed antigen-specific receptors and that the interaction of these receptors with antigen initiates a signal (now known as signal one or stimulation) that is sufficient to turn on the B cell and initiate an immune response (Fig. 1). To ensure that immune responses are directed only against nonself, Burnet and Medawar incorporated Lederberg's suggestion that autoreactive cells are deleted early in ontogeny [5–7].

This elegant and simple version of the SNSD model lasted until 1969, when Bretscher and Cohn added a new cell and a new signal, creating the Associative Recognition model, more commonly known as the Two Signal model [6], which has been updated and expanded over the years by Langman and Cohn [2, 9]. They were driven to do this by the finding that B cells, upon activation by an antigen, hypermutate their antigen-specific receptors, thus allowing the possibility that new, autoreactive

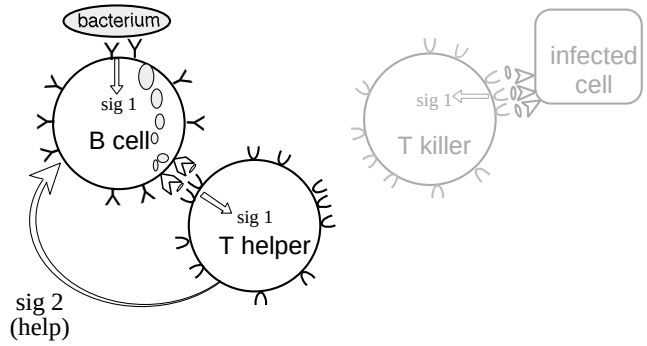

Figure 2. The helper cell is in control (Bretscher and Cohn): signal one leads to B-cell death, but the addition of help (signal two) leads to activation.

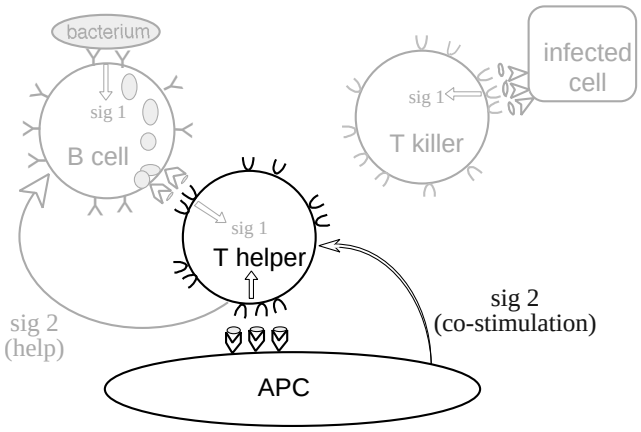

Figure 3. The APC is in control (Lafferty and Cunningham): T helpers die if they recieve signal one alone and are rescued and activated by the receipt of co-stimulatory signals (signal two) from an APC.

specificities could appear and lead to unstoppable autoimmunity. Realizing that autoimmunity would be rare if the initiation of an immune response required the activation of *two* cells recognizing different specificities on the same antigen, they invented a second signal, called 'help' (Fig. 2). They suggested that recognition of antigen (signal one) would lead to death of the B cell unless it was rescued by the receipt of timely and appropriate help from a helper cell. After many years of study, this part of the two-signal model has become well established. It is now known that the B cell takes up the antigen to which it has bound, internalizes it, processes it and re-expresses it in the groove of MHC class II molecules [10], waiting for recognition by the T-helper cell, which then sends helper signals using such molecules as CD40, CD40 ligand, interleukin (IL)-2, IL-4, IL-5, etc. The B cell can wait about 24 h, after which it dies if no help appears [9] (Fig. 2).

This version of the SNSD model lasted until 1974, when Lafferty and Cunningham modified it by adding yet another new cell (the accessory cell, now known as the antigen-presenting cell (APC)) and a new signal (costimulation). The problem they were trying to solve stemmed from the finding that T cells tend to respond more strongly against cells from a member of their own species than from a member of another species. For example, chicken lymphocytes respond more strongly to other chicken cells than to quail cells [11, 12], and human T cells respond better to cells from another human than to mouse cells [13], but dog T cells seem not to be so picky. In other words, alloreactivity is often stronger than xenoreactivity. To explain these findings Lafferty and Cunningham proposed that T-helper cells are not constitutively active and that, like B cells, the signal they receive from the recognition of antigen is not enough to bring about full activation. They proposed a two signal model for helper cells (Fig. 3), suggesting that these T cells need a costimulatory signal that is supplied by the APC and that the costimulatory signals are species specific [14]. In a later article, they followed Bretscher and Cohn's lead and proposed that signal one alone would lead to tolerance of the T cell [15].

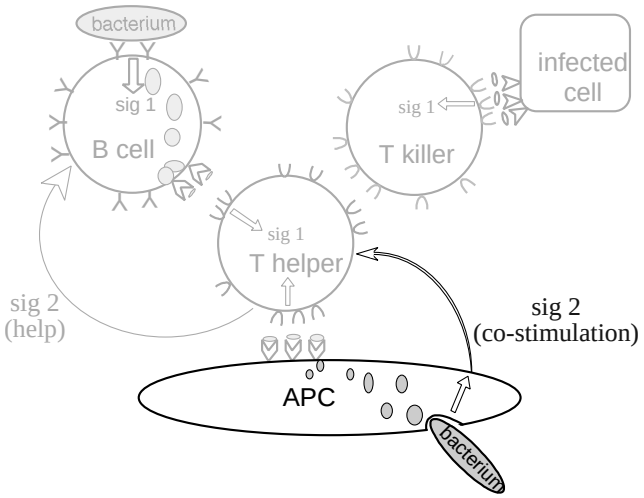

Figure 4. PRRs are in control (Janeway): APCs are not constitutitively active. They receive activating signals through pattern recognition receptors (PRRs) that recognise conserved molecules on evolutionary distant oranisms like bacteria.

For the next 13 years, Bretscher, Langman and Cohn's second signal (help) was studied while Lafferty and Cunningham's second signal (costimulation) was all but ignored. Then, in 1987 Jenkins and Schwartz discovered that gluteraldehyde-fixed APCs were unable to stimulate T-cell clones (see Appendix, note I) [16], and the immunological community rapidly began to collect evidence for costimulatory interactions discovering such moleulces as B7.1, B7.2, CD28, CTLA-4, CD40 and it's ligand, etc. Why had it taken so long? Why had the T helpers and their helper signals been applauded and carefully studied while the costimulatory signals of APCs remained ignored? I believe that the main reason is that costimulation did not fit into a self-nonself model. Unlike help, which comes from populations of T-helper cells that are antigen specific and can be depleted of self-reactive cells, costimulation comes from APCs, which cannot distinguish self from nonself because they have no clonally distributed antigen-specific receptors. They can present anything they pick up. If immune responses are initiated by signals from APCs, it is very difficult to see how the immune system can focus only on nonself antigens. Therefore APCs and costimulation made people uncomfortable. Even after its re-discovery, costimulation was often dismissed [9] or ignored [17] until, in 1989, Charlie Janeway found an ingenious way to meld costimulation with self-nonself discrimination. He expanded the SNSD model to include a set of genetically encoded able to recognise evolutionarily distant nonself [18, 19].

To explain the finding that responses to many antigens do not occur unless adjuvant is coadministered, he suggested that macrophages (later including other cells and molecules of the innate immune system [20]), like their counterparts of the adaptive immune system (T and B cells), are not constitutively active. This was an extremely important suggestion, counter intuitive to the prevailing concept of an active and constantly surveilling immune system, in which he essentially proposed that the baseline state of the immune system is 'OFF'. In order to maintain a form of self–nonself discrimination, he then suggested that the innate immune system discriminates between 'infectious non self' and 'noninfectious self' [19]. To do this, he proposed that APCs express pattern-recognition receptors (PRRs) that recognize conserved patterns of molecules found only on evolutionarily distant organisms, like bacteria (Fig. 4). (For example, resting macrophages carry PRRs for bacterial products like lipopolysaccharides (LPS)). Binding of the bacteria (or bacterial adjuvants) to PRRs induces activation of the APCs, which then internalize the bacteria (and any associated antigens), re-express the bacterial antigens as peptides in MHC class II molecules, and upregulate costimulatory molecules in order to activate T cells and initiate adaptive immune responses (Fig. 4).

Thus, there were now two different types of nonself recognition. A genetically encoded set of PRRs assigned to the cells and molecules of the innate immune system and a somatically generated set of receptors expressed by the cells of the adaptive immune system. Only in the presence of the evolutionarily distant patterns recognized by the innate PRRs would costimulation be upregulated and an immune response be triggered: a neat solution to the problem of how to incorporate costimulation into a SNSD model.

Taken together, the models of Burnet, Bretscher/Langman/Cohn, Lafferty/Cunningham, and Janeway comprise a rather complete SNSD model that attempts to deal with the findings of the past century under the premise that the immune system functions primarily to clear the body of foreign material. Because the critical event in all of these theories is the recognition of foreign antigen, immunologists have put a lot of energy into the study of antigens and the receptors that recognize them. For half a century, we studied the genetics of antibodies and TCRs and the intricacies of their mutational mechanisms. We analyzed the structure and minimal sizes of the carbohydrates and peptides seen by B cells. We studied the structure of the MHC molecules seen by T cells and the structure of the agonist, antagonist, dominant and cryptic peptides they display. We discovered superantigens and immune response genes. We finally incorporated adjuvants into the model by suggesting that they stimulate the innate recognition by the PRRs against bacterial nonself. In short, we spent half a century studying self–nonself discrimination. We have learned a lot, however, we have not yet achieved a consistent, interrelated set of answers for most of the questions listed above. Janeway himself pointed out [21] that the addition of PRRs, though explaining immune responses to bacteria and other evolutionarily distant pathogens, cannot explain the immune response to transplants or tumours, nor the dysfunction(s) that lead to many autoimmune diseases. How then can we explain these responses?

Essentials of the Danger model: a small step that lands us in a different point of view

The Danger model, like Janeway's proposal of PRRs, was also driven by the quest to incorporate costimulation into a

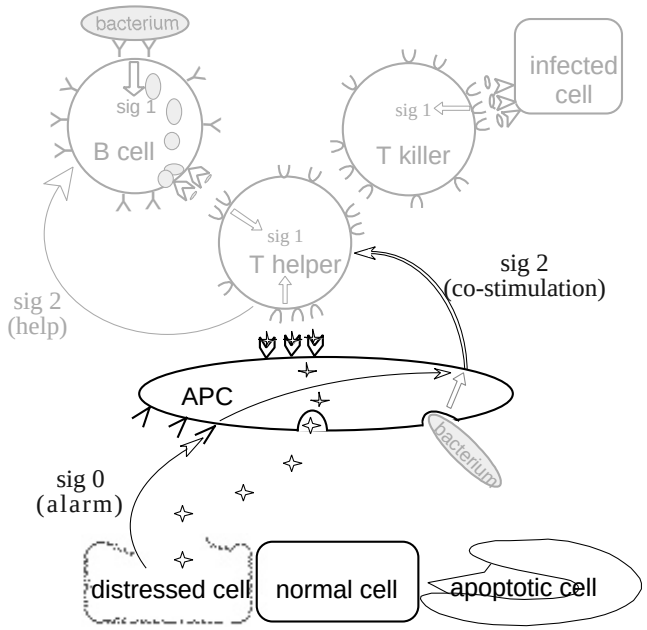

Figure 5. The tissues are in control (Matzinger): APCs receive activating signals from injured cells, but not from healthy cells or from cells dying by normal physiological cell death.

functioning model of immunity. However, many discussions with Ephraim Fuchs [19] made it clear that this was exceedingly difficult to do as long as we continued to hold on to the self–nonself viewpoint. We therefore abandoned the concept that the immune system is primarily concerned about nonself, whether individually determined or evolutionarily conserved, and took a step even further back in evolution to look for the controlling elements of immunity. The Danger model is based on the idea that the ultimate controlling signals are endogenous, not exogenous. They are the alarm signals that emanate from stressed or injured tissues.

In effect, Ephraim Fuchs and I followed tradition and added another cell and another signal [1,22–24]. We brought into the conversation every tissue in the body, suggesting that these are the cells that are in ultimate control of immunity (and bringing the traditional line of reasoning to its ultimate end because there are no cells left to add). We proposed that the cells of normal bodily tissues, when distressed, send signals, which we call 'danger' or 'alarm' signals, or signal zero, that serve to activate local APCs. Thus, like Janeway's expanded SNSD/PRR model, the Danger model assumes that APCs are not constitutively able to offer costimulatory signals and that they must first be activated (Appendix, note II). However, unlike the expanded SNSD model, which holds that a nonself signal is essential, the Danger model suggests that the activation state of an APC depends on the health of the cells in its neighbourhood [23,24]. Cells that are healthy do not send danger signals and in fact, may send calming signals to local APCs [25], whereas injured cells, namely cells that are abnormally distressed, damaged, die an abnormal death, or are destroyed necrotically, should activate their local APCs [25]. In contrast, cells that die by a process of normal, programmed cell death send 'eat me' signals to a neighbouring scavenger that should not induce the expression of costimulation (Fig. 5.) (see Appendix, note III).

Thus, the idea is that the 'foreigness' of a pathogen or a toxin is not the relevant trigger for an immune response. A foreign entity that does no injury should not evoke a response, regardless of how it disseminates in the body (Appendix, note IV), and an abnormality of physiology that causes stress or injury to a tissue could kindle a response in the absence of any foreigness.

This small step leads us to a new viewpoint that turns out to have enormous explanatory and predictive power. If we view immunity from the position that a response is triggered by alarm signals, rather than signs of foreigness, we can design a model that offers an internally consistent set of explanations for known immunological reactions and also for many of the occasions when the immune system does not do what we would hope. In the essays that follow, I will cover the known [26], and as yet unknown, alarm signals, the need for adjuvant, how the immune system can constantly adapt to a changing self, why mothers don't reject their foetuses; why transplants are rejected; why tumours are often not rejected even when they carry 'foreign' tumour-specific antigens; why we are often infested with parasites to which we respond quite poorly; the difference between oral 'tolerance' and oral vaccination; the difference between gene therapy (no immune response) and DNA vaccination; the causes of graft versus host disease; the causes of autoimmune diseases; allergy, anergy and asthma; 'useful' autorecognition and the control of effector class; and finally, immune responses that occur in the absence of danger.

IS IT MERELY SEMANTICS?

Because an immune system acting under Danger principles ends up becoming roughly self tolerant, and because self and non-self are such engrained concepts, people often ask whether the differences between the Danger model and SNSD models might be merely semantic or, alternatively, whether danger is not simply another useful addition to the SNS framework. The answer is that some of the differences are semantic, but I would remove the term 'merely'. Semantics, or the study of meaning, is critically important to any conceptual or theoretical discussion, and such discussions can easily get derailed if the discussants assign different meanings to the same words. For this reason the Danger model stays away from a discussion of 'self' and 'non-self'. It is not that these are not useful terms. They constitute a convenient way to partition the antigens of the universe into two different sets, and they can be applied effectively in such descriptions as 'self tolerant' or 'self-reactive'. There are, however, two reasons why I prefer not to define them. The first is that each model has a different definition of ''self'', ranging from: (1) anything persistently present from the moment the immune system develops; (2) anything persistently present at a high enough concentration; (3) anything present in the thymus; (4) anything present in the

thymus and/or present at a high enough concentration and for long enough in the secondary lymphoid organs all else being ignored; and (4) anything part of the immunological homunculus. In 1986, at a weeklong tolerance workshop in Basel, 60 immunologists could not come up with a definition of self that we could all agree to use, even for the week! How can we hope to communicate if we have different definitions for the words we use?

The other problem is that 'non-self' has a second meaning that is so engrained in our collective immunological consciousness that it is almost invisible. 'Non-self' as it is commonly used, does not simply mean 'something that is not self'. It also usually means 'something that elicits an immune response'. The most important distinction between the Danger model and other models is that it removes this trigger function from the definition of non-self and gives it to the alarm signals emanating from distressed tissues. Both Janeway and Zinkernagel have taken steps in this direction, one saying that only infectious non-self can trigger a response and the other suggesting that non-self must reach the secondary lymphoid tissues in order to elicit immunity. However, though both of these models assume that non-self is not enough, they nevertheless insist that it is a necessary feature. In both models (with their different definitions of self), self antigens should not trigger a response. What then of autoimmunity?

Because the Danger model holds that immune responses are triggered by alarm signals, it suggests a different way of functionally partitioning the universe of antigens: those that are associated with danger and those that are not. Antigens associated with danger should be dealt with, and those that are not should be tolerated. Under these definitions self need not be ignored and non-self need not always be attacked. This distinction allows the boundaries of self to change as the body changes, matures, procreates and grows old. It also means that the lack of complete self tolerance is not usually a problem. As long as the thymus and bone marrow continue to produce, there will exist T and B cells specific for peripheral self antigens but, because these antigens are not usually associated with danger signals, they will not normally elicit fulminant autoimmune disease (exceptions will be covered later). Finally, if self need not be ignored, then useful autoreactivity also becomes possible, freeing the way for functional subsets of autoreactive cells, such as NKT cells, autoreactive intraepthelial lymphocyte (IELs) and dendritic epidermal T cell (DEC) cells, that seem to respond to self molecules expressed by stressed cells.

On what basis could a person choose between the models? We believe that a good model should fulfil certain criteria. It should have a short set of clear assumptions, bringing to light those that are hidden or commonly held. It should explain as much of the existing data as possible without the addition of situation-specific assumptions. It should make clear predictions and, if possible, be of some practical use. Under ideal conditions, it would also be based on a luminously intuitive basic principle.

I believe that we should choose our models carefully because the way we think has enormous influence on what we do. For half a century we have studied immunity from the point of view of various forms of SNSD models in which immunity is controlled by the adaptive immune system, an army of lymphocytes patrolling the body for any kind of foreign invader. Recently, there has been a shift to include the cells and molecules of the innate immune system, an army of cells and molecules patrolling the body for the subset of foreign invaders that are ancient enemies. Although this shift has meant a move from the study of signal one (antigen recognition) to the analysis of signal two (costimulation), the models are still firmly based on the discrimination of some sort of nonself. Consequently, after 50 years we still cannot explain many of the things that the immune system does, and doesn't, do.

Perhaps it's time to stop running a cold war with our environment?

The Danger model does not allow an army to control immunity. It expands the definition of the innate immune system to include the extended, highly interactive family of bodily tissues. It allows for a flexible system that adapts to a changing self while launching immune responses to dangerous pathogens. It also allows us to live without maintaining a rigid sterility that segregates us from the environment. We become a habitat, welcoming the presence of useful commensal organisms and allowing the passage of harmless opportunistic ones. With such an immune system we live in harmony with our external and internal environment.

REFERENCES

1 Matzinger P. Tolerance, danger, and the extended family. Annu Rev Immunol 1994;12:991–1045.
2 Langman RE, Cohn M. Self-nonself discrimination revisited. Introduction. Semin Immunol 2000;12:159–62.
3 Cohn M, Langman RE. The protection: the unit of humoral immunity selected by evolution. Immunol Rev 1990;115:11–147.
4 Boyse EA, Carswell EA, Scheid MP, Old LJ. Tolerance of Sk-incompatible skin grafts. Nature 1973;244:441–2.
5 Lederberg J. Genes and antibodies. Science 1959;129:1649–53.
6 Burnet FM. The Clonal Selection Theory of Acquired Immunity. Vanderbilt University Press, Nashville, TN, 1959.
7 Billingham RE, Brent L, Medawar PB. 'Actively acquired tolerance' of foreign cells. Nature 1953;172:603–6.
8 Bretscher P, Cohn M. A theory of self-nonself discrimination. Science 1970;169:1042–9.
9 Langman RE, Cohn M. A short history of time and space in immune discrimination. Scand J Immunol 1996;44:544–8.
10 Lanzavecchia A. Antigen-specific interaction between T and B cells. Nature 1985;314:537–9.
11 Simonsen M. The impact on the developing embryo and newborn animal of adult homologous cells. Acta Pathol Microbiol Scand 1957;40:480.
12 Payne LNaJWP. Graft-against-host reactions produced in chick embryos with blood from heterologous avian donors. Transplant Bulletin 1962;30:20.
13 Widmer MBaBFH. Allogeneic and xenogeneic response in mixed leukocyte cultures. J Exp Med 1972;135:1204.

14 Lafferty KJ, Cunningham A. A new analysis of allogeneic interactions. Aust J Exp Biol Med Sci 1975;53:27–42.

15 Cunningham AJ, Lafferty KJ. A simple conservative explanation of the H-2 restriction of interactions between lymphocytes. Scand J Immunol 1977;6:1–6.

16 Jenkins MK, Schwartz RH. Antigen presentation by chemically modified splenocytes induces antigen-specific T cell unresponsiveness *in vitro* and *in vivo*. J Exp Med 1987;165:302–19.

17 Zinkernagel R. Immunology taught by viruses. Science 1996;271:173–8.

18 Janeway CA Jr. Approaching the Asymptote? Evolution and Revolution in Immunology. Cold Spring Harbour Symposium Quant Biol 1989;54:1–13.

19 Janeway CA Jr. The immune system evolved to discriminate infectious nonself from noninfectious self. Immunol Today 1992;13:11–6.

20 Medzhitov R, Janeway CA Jr. Innate immunity: impact on the adaptive immune response. Curr Opin Immunol 1997;9:4–9.

21 Janeway CA Jr, Goodnow CC, Medzhitov R. Danger - pathogen on the premises! Immunological tolerance. Curr Biol 1996;6:519–22.

22 Fuchs E. Reply from Ephraim Fuchs. Immunol Today 1993;14:236–7.

23 Matzinger P, Fuchs EJ. Beyond 'self' and 'non-self': Immunity is a conversation not a war. Journal of NIH Research 1996;8:35–39.

24 Matzinger P. An innate sense of danger. Semin Immunol 1998;10:399–415.

25 Gallucci S, Lolkema M, Matzinger P. Natural adjuvants: endogenous activators of dendritic cells. Nat Med 1999;5:1249–55.

26 Gallucci S, Matzinger P. Danger signals: SOS to the immune system. Curr Opin Immunol 2001;13:114–9.

27 The Tolerance Workshop. ed. P. Matzinger. Editiones, Roche; Basel, Switzerland, 1987.

28 Bendelac A, Rivera MN, Park SH, Roark JH. Mouse CD1-specific NK1 T cells: development, specificity, and function. Annu Rev Immunol 1997;15:535–62.

29 Morita CT, Tanaka Y, Bloom BR, Brenner MB. Direct presentation of non-peptide prenyl pyrophosphate antigens to human gamma delta T cells. Res Immunol 1996;147:347–53.

30 Constant P, Davodeau F, Peyrat MA, et al. Stimulation of human gamma delta T cells by nonpeptidic mycobacterial ligands. Science 1994;264:267–270.

31 Groh V, Steinle A, Bauer S, Spies T. Recognition of stress-induced MHC molecules by intestinal epithelial gammadelta T cells. Science 1998;279:1737–40.

32 Boismenu R, Havran WL. An innate view of gamma delta T cells. Curr Opin Immunol 1997;9:57–63.

APPENDIX

I. This finding is a nice example of serendipity in science. Jenkins and Schwartz were not looking for co-stimulation. They were studying the nature of the peptide/MHC complexes to which T cells respond. In attempts to stabilize the peptide/MHC complexes, they used gluteraldehyde to fix antigen-loaded APCs, and found that these fixed APCs no longer functioned to stimulate T-cell clones. Helen Quill, from the same laboratory, was putting peptide/MHC complexes into synthetic lipid bilayers, and also finding that these perfectly good antigens would not stimulate T-cell clones. Thus, it seemed that something other than antigen was necessary. Interestingly, Lafferty and Cunningham's paper on the need for co-stimulation had been ignored for so long that Jenkins, Quill and Schwartz failed to cite it and incorrectly referred instead to Bretscher and Cohn's second signal (help).

II. The idea that APCs are normally inactive and that immune responses cannot occur if they remain inactive is, to me, the most important area of overlap between the two types of models. It is a major step away from the view that the mere 'foreigness' of an antigen is sufficient to trigger an immune response.

III. Although normal versus abnormal death are often equated with apoptosis versus necrosis, this may be an oversimplification, as there are likely to be abnormal forms of apoptosis. Hence, I prefer to use the terms 'normal' or 'physiological' programmed cell death versus abnormal death. We do not yet know the defining charateristics that differ between the two, but the ability to be promptly scavenged is likely to be one of them. Cells that are scavenged do not leak their interior contents into the vicinity of local APCs. If they have died by normal programmed cell death, they are also unlikely to have elaborated other alarm signals and thus should not activate local APCs.

IV. There is at least one exception here. If a harmless foreign entity enters an APC, it may live quietly for some time and then be eliminated as the result of an immune response that has occurred because the APC became activated by alarm signals that result from the damage done by an unrelated pathogen.