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A Theory of Self-Nonself Discrimination

Paralysis and induction involve the recognition of one and two determinants on an antigen, respectively.

Peter Bretscher and Melvin Cohn

Although an animal can be induced to make antibodies against most foreign antigens, it does not produce antibodies against its own constituents. The administration of a foreign antigen to an animal can either induce the synthesis of antibody specific for the antigen (antibody induction) or prevent an antibody response to a subsequent and normally antibody-inducing dose of the antigen. The latter process is called paralysis, and the animal is described as having acquired an unresponsive state with respect to that antigen. We assume that the ability of an animal to discriminate between self antigens and nonself antigens is intimately related to the mechanisms of paralysis and antibody induction.

One feature of self-nonself discrimination can be discussed without reference to the mechanisms of paralysis and induction, and this feature imposes restrictions on the way in which we are allowed to analyze these two processes. We can ask whether the self-nonself discrimination is coded for genetically, or whether an animal possesses an intrinsic ability to respond to its own antigens and has to *acquire* an unresponsive state toward them. Genetic coding of this discrimination would occur if germ-line structural genes coded only for antibody molecules with specificity against foreign antigens. Such a situation would severely hinder evolution, since most mutations affecting any self-constituent would result in an autoimmune reaction (*1*). Therefore we consider genetic coding of the discrimination implausible and conclude that an animal possessing an intrinsic ability to respond to self antigens must *acquire* an unresponsive state toward them. This conclusion is strongly supported by experiment. Furthermore, we know that, in order for an adult animal to maintain an unresponsive state toward an antigen, the continuous presence of the antigen is required. For example, mice rendered unresponsive to foreign serum proteins by neonatal administration of the antigen regain their responsiveness to the serum proteins unless the serum proteins are continually present (*2*).

We designate as "historical" theories of antibody induction those theories which take account of the fact that the decision by the immunological system to respond to an antigen depends on whether it has encountered that or related antigens in the past. We discuss two "historical" theories, one of which was proposed by Lederberg (*3*), the other by us (*4*).

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"Historical" Theories of Self-Nonself Discrimination

Both theories rely on the concept of an antigen-sensitive cell. Most immunologists conceive this cell to have, on its surface, receptors that, on interaction with antigen, initiate a specific signal to the cell. A receptor is envisaged as being an antibody molecule whose corresponding structural genes are in the cell. One kind of signal leads to the multiplication of that cell and the production of large amounts of antibody of specificity identical to that of the receptor antibody which interacted with antigen (antibody induction), and another kind of signal paralyzes that cell (*5*). It is further postulated, for reasons discussed below, that this antigen-sensitive cell has only one kind of receptor on its surface.

Lederberg (*3*), in his theory of self-nonself discrimination, proposed that stem cells, unable to recognize antigen, mature to antigen-sensitive cells that can be induced to form antibodies ("inducible cells") by passing through a paralyzable state (see Fig. 1). Consequently an individual accumulates inducible cells with nonself specificity, which cannot be paralyzed. Although the facts of immunology known in 1959 were consistent with this hypothesis, more recent observations are inconsistent with the minimal form of Lederberg's theory and suggest a different explanation of self-nonself discrimination.

In our model (see Fig. 1), each antigen-sensitive cell always has the potentiality of being paralyzed or induced to form antibody; hence there is competition at the level of a single cell between paralysis and induction. The

crucial difference between paralysis and induction is that paralysis involves obligatory recognition of only one antigenic determinant whereas antibody induction involves obligatory recognition of two determinants on an antigen by different antibody molecules. One of these antibody molecules is the same molecule that is bound by antigen during paralysis, and is the receptor antibody in the membrane of the antigen-sensitive cell. This antibody has specificity identical to that of the antibody that will be produced after induction. We call the second antibody molecule carrier antibody, and we call the determinant recognized by it the carrier determinant. Since we believe that the interaction with carrier antibody is *mandatory* for induction, we postulate that a conformational change occurs in carrier antibody on binding antigen which leads to a second signal to the antigen-sensitive cell (*4*). Carrier antibody is probably a special class of antibody, as discussed below.

We refer to the antigen-sensitive cell whose induced antibody product we measure as the humoral antigen-sensitive cell. Experimental evidence leads us to conclude that carrier-antibody formation can be both specifically induced and paralyzed, and we show below that the mechanisms of paralysis and induction for the carrier-antigen-sensitive cells are identical to those for the humoral-antigen-sensitive cells.

This model accounts for a very wide range of experimental data and at the same time accounts for the stability of tolerance to self-components. However, before discussing the model in detail, we shall show in a simplified form how it accounts for self-nonself discrimination (*6*).

There is good reason to believe that antigen-sensitive cells, associated with more or less random specificities, are generated throughout the life of an immunologically competent individual. Consider a situation in which a self-component A has 20 determinants on its surface, a_1, a_2 . . . a_{20}. Suppose a new antigen-sensitive cell arises, bearing a receptor with specificity against the a_5 determinant; since induction involves the associated recognition of two determinants, the cell cannot be induced by the self-component A. It can only be paralyzed. Thus, once tolerance is established and the self-component is continually present at a concentration at which it does not escape the immune system, the stability of tolerance is maintained. Cells bearing receptors with specificity against a foreign antigen which is not continually present can accumulate, and when the antigen is administered they can cooperate to produce an antibody response (*7*).

Experimental Facts and Their Relationship to the Minimal Model

We outline here the most pertinent experimental facts and discuss different interpretations that have been given them. All the facts we consider here come from studies in which antigen is administered to an animal and the increase in serum antibody (that is, humoral antibody) is measured. It is clear that there are many questions about induction and paralysis on which such data cannot give us information; for example, they do not bear on the question of whether a "hormone" is required for paralysis. Here we are principally concerned with the types of specific recognition that occur in induction and paralysis.

1) It is known in certain cases that, in order for an antigen to be immunogenic, at least two antigenic determinants to which the animal is not tolerant must be present on it. Several examples come from studies with molecules which, though they are themselves nonimmunogenic, can combine with specific antibody. Such antibodies are raised by conjugating the nonimmunogenic molecule (hapten) to an immunogenic one. In guinea pigs that do not respond to poly-L-lysine (PLL), this antigen cannot act as an immunogenically effective carrier for a hapten, although it can do so in guinea pigs responsive to PLL alone (*8*). However, antibodies to the hapten are induced in nonresponders if the hapten-PLL conjugate is complexed with, for example, bovine serum albumin (BSA), but antibodies are not induced if the animals are made unresponsive to BSA (*9*). The simplest interpretation of these observations is that, in order to induce antibody to the hapten, the carrier must be recognized by antibody. This requirement cannot be fulfilled in nonresponders when they are challenged with the hapten-PLL conjugate because these nonresponders possess no carrier antibody against PLL; in order to obtain an antihapten response, the hapten-PLL conjugate must be complexed with an immunogenic molecule so that the carrier can be recognized. This evidence shows that the antibody recognizing the carrier determinant is specific. Furthermore, the inability to raise an effective antihapten response when the animal has been paralyzed with BSA shows that the *carrier* antigen-sensitive cells against BSA *are paralyzable*.

2) To achieve a good secondary response to a hapten, the hapten (H) must be conjugated to a protein against which the animal has been immunized.

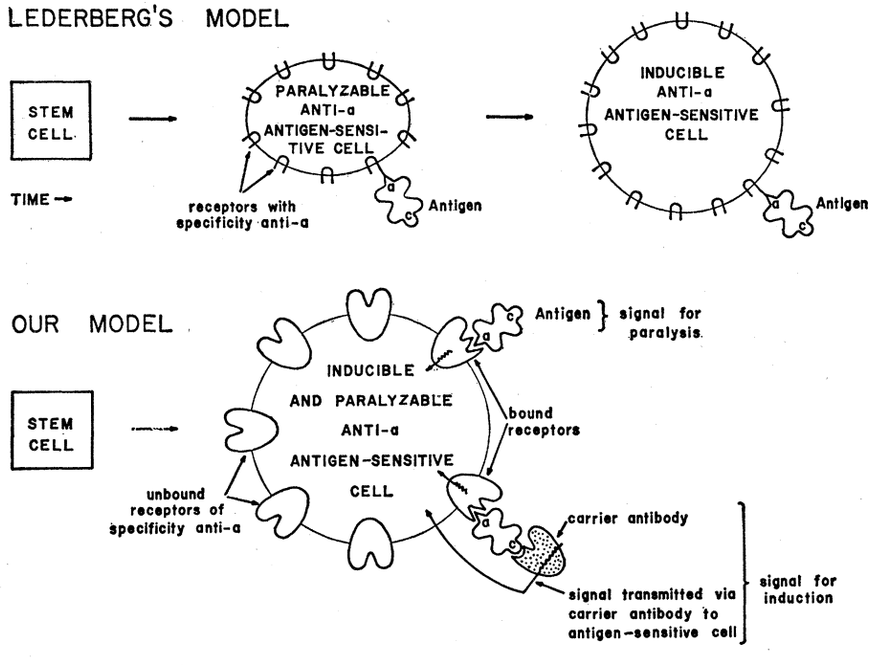

Fig. 1. Two "historical" models of induction and paralysis.

If an animal is immunized with a conjugate H-X, and with a protein Y which does not cross-react with X, a good response to the hapten is obtained when the animal is challenged with H-Y (*10*).

We interpret this evidence as showing that the increased antibody production in the secondary response is partly a consequence of an increase in the animal's ability to provide specific carrier antibody after primary immunization. Thus, carrier antibody must be inducible. We stress the fact that carrier antibody cannot be in great excess in the unprimed animal. If it were, priming with H-X and challenge with H-Y should have resulted in a strong, not a weak, anti-H response. What is limiting in this case must be carrier antibody directed against Y.

A different interpretation of this latter result is provided by the local environment hypothesis (*11*; *12*, p. 293). This hypothesis states that the receptor on the antigen-sensitive cell recognizes the hapten and part of the carrier that is contiguous to the hapten. Thus, an animal primed with H-X cannot give an accelerated anti-H response on secondary challenge with H-Y because the anti-(H-X) receptors do not recognize the hapten when it is conjugated onto Y. This hypothesis, however, cannot explain the observation that, if an animal is primed with H-X and Y, a secondary response to the hapten is obtained when the challenge is made with H-Y.

3) An animal rendered unresponsive to a given antigen, which we call a paralogen, can be induced, by injection of an antigen which cross-reacts with the paralogen, to make antibodies which combine with the paralogen.

For example, a rabbit rendered unresponsive to bovine serum albumin (BSA) can make antibodies to horse serum albumin (HSA) some of which can combine with BSA. If the original paralogen (BSA) is administered in fairly small amounts with the cross-reacting antigen, then induction of these cross-reacting antibodies to BSA is prevented (*13*).

We can symbolically represent the above results in the following way. Antibodies to a paralogen A (BSA), with determinants a_1-a_{20}, can be induced in an animal unresponsive to A by the injection of antigen B (HSA), having determinants $\tilde{a}_1$-$\tilde{a}_5$ which cross-react with a_1-a_5, and foreign determinants b_1-b_{15}. Since antibody which combines with the a_1-a_5 determinants can be induced by the injection of B, there must be some antigen-sensitive cells with specificity against some of the determinants $\tilde{a}_1$-$\tilde{a}_5$. However, challenge with paralogen A only prolongs the unresponsive state. We interpret this to mean that there is insufficient carrier antibody with specificity against A for a response to take place, a situation similar to that discussed above for self-constituent A. A cell with specificity anti-$\tilde{a}_5$ can be induced by B, however, as B has the foreign sites b_1-b_{15} which can act as carrier determinants. The local-environment hypothesis (*11*; *12*, p. 293) would explain these observations by postulating that those antibodies to A that are induced are so weak in their binding to the A determinants a_1-a_5 that the corresponding cells (with specificity against $\tilde{a}_1$-$\tilde{a}_5$) were never paralyzed by A. This view, however, is very difficult to reconcile with the fact that the formation of the antibody to A (anti-$\tilde{a}_1$-$\tilde{a}_5$) can be inhibited by an amount of A that is small relative to the amount of B. In terms of our model, A can act only as a paralogen and therefore can only suppress the response against the $\tilde{a}_1$-$\tilde{a}_5$ determinants. The observation that A suppresses this response when given simultaneously with B also provides the strongest evidence that the competition between paralysis and induction takes place at the level of the antigen-sensitive cell, and is incompatible with Lederberg's model (*3*), where the inducible cells (anti-$\tilde{a}_1$-$\tilde{a}_5$) would not be paralyzable (Fig. 1).

4) It appears that an antigen, in order to be immunogenic, must in general be macromolecular. Aggregation of antigen favors induction in the competition between induction and paralysis. In several cases it is known that deaggregation or fragmentation of the antigen favors paralysis (*14*).

Both these observations are expected on the basis of our hypothesis because aggregated and large molecules will in general have more "foreign" sites on their surface, and therefore, for a given determinant, there will be a greater number of possible carrier determinants. Although two foreign sites are obligatory for induction, probably more than two are actually required. As there is always competition between induction and paralysis, induction may occur at too slow a rate to take place before paralysis if only two foreign sites are available (*15*).

The evidence outlined above has also been used by others to infer that there is a carrier effect in paralysis—that is, that the part of the antigen that is recognized by cells during paralysis extends over a wider area than the part that is recognized by antibody (*16*). A statement with similar implications is that an antigen, in order to be paralytic, must be immunogenic (*12*, pp. 75, 319; *17*). Our hypothesis is that paralysis involves the obligatory recognition of only one determinant by the receptor antibody, and that therefore a hapten—that is, a nonimmunogenic molecule—can paralyze antigen-sensitive cells (*18*). The observation that, in an animal unresponsive to BSA, the continued presence of BSA is required to maintain the unresponsive state shows that a nonimmunogenic molecule can paralyze. It is therefore not mandatory that paralogens be potentially immunogenic, and the implication that there is an obligatory carrier effect in paralysis (*12*, pp. 75, 319; *17*) does not hold. Our hypothesis accounts for all the observations on which the existence of a carrier effect in paralysis has been based.

Part of the confusion arises from the fact that it is difficult to assay for the ability of a nonimmunogenic molecule to paralyze. An example will clarify this point.

With the lactate dehydrogenase (LDH) isozymes, tetramers composed of subunits A and B, it appears that in certain rabbits one of the forms, LDH-I (B_4), is nonimmunogenic, while the other form, LDH-V (A_4), is immunogenic. The hybrid molecule LDH-III (A_2B_2), which contains subunits of both types, can induce both anti-LDH-I (B_4) and anti-LDH-V (A_4) antibodies. In an animal injected with LDH-I (B_4), no paralysis specific for the B subunit was detected by challenge with LDH-III (A_2B_2). This immunization resulted in a normal titer of antibody with specificity against LDH-I (B_4). It is not correct to conclude on these grounds that LDH-I (B_4) cannot paralyze antigen-sensitive cells (*19*). In the first place, no assay for its paralyzing effect on carrier-antigen-sensitive cells has been performed, and it is conceivable that paralysis of humoral-antigen-sensitive cells occurred but was very effectively broken by the hybrid LDH-III (A_2B_2) molecule, in a manner identical to that described for the BSA/HSA system (see point 3 above). This evidence cannot be used to show that there is a carrier effect in paralysis (*20*).

Table 1 shows three extreme cases in which an animal could be opera-

tionally unresponsive to an antigen, U. The humoral responses to various challenges are given. H_1U is a molecule with one hapten on each molecule of U, and UP is a conjugate of U with an immunogenic molecule P, which does not cross-react with U.

5) The dosage of antigen given an animal is of crucial importance in determining whether the animal will respond to an antigen or whether it will be rendered unresponsive to a later, normally immunogenic, dose of that antigen. For BSA when administered to adult mice, a schedule of doses which maintains a blood concentration of about $10^{-8}M$ for a few weeks results in a specifically unresponsive animal (low-zone paralysis) (*21*). Medium-sized doses of antigen resulting in blood concentrations of about $10^{-7}M$ lead to induction of antibody, while high doses ($10^{-5}M$) again lead to an unresponsive state (high-zone paralysis). For certain antigens, such as lysozyme, low-zone paralysis is not found. Below the lowest dose at which an antibody response is detected, no paralysis is observed. However, lysozyme can produce an unresponsive state when given at high doses (*21, 22*).

We have postulated that carrier antibody is obligatory for induction. We can imagine a dose of antigen at which both the carrier antibody and the receptor antibody are saturated, so that associated interactions, and hence induction, are prevented. It is then expected that, as the dose of a monomeric antigen is increased so that the blood concentration of the antigen is greater than the binding constants of typical antibody molecules (10^{-9} to $10^{-5}M$), a zone of paralysis is entered. Thus our hypothesis that there is obligatory associated recognition (carrier effect) in induction and no obligatory carrier effect in paralysis predicts the existence of high-zone paralysis and the approximate blood concentration of a monomeric antigen at which the transition from induction to high-zone paralysis takes place ($\sim 10^{-5}M$ for both bovine serum albumin and lysozyme) (*23*).

6) Once an animal has been brought to an unresponsive state, the presence of the paralogen is required to maintain that state. Recovery from the unresponsive state occurs in the absence of the paralogen (*2, 24*). This fact is interpreted as showing that antigen-sensitive cells are continually being produced during the lifetime of an individual. It is important to note that doses of antigen which are normally effective in raising an antibody response can be used to maintain the unresponsive state. For example, lysozyme at a concentration of $10^{-8}M$ can maintain unresponsiveness, and so can BSA at $10^{-7}M$; these concentrations lead to antibody induction in naïve animals. In the adult animal there is a difference between the establishment and the maintenance of an unresponsive state (*25*).

Table 1. The postulated humoral-antibody response of animals unresponsive to an antigen (U) measured soon after challenge with various antigens (see text).

Challenge with various antigens	Cell populations assumed to be paralyzed against U		
	Humoral-antigen-sensitive cells and carrier-antigen-sensitive cells	Humoral-antigen-sensitive cells	Carrier-antigen-sensitive cells
U	No anti-U induced	No anti-U induced	No anti-U induced
H_1U	No anti-U induced	No anti-U induced	No anti-U induced*
H_1U	No anti-H induced	*Anti-H induced*	No anti-H induced
UP	No anti-U induced	No anti-U induced	*Anti-U induced*
UP	Anti-P induced	Anti-P induced	Anti-P induced

*See (*41*).

In point 3, above, we discussed the situation in which an animal, unresponsive to the paralogen BSA, could make antibodies against BSA when injected with the cross-reacting antigen HSA. We inferred that there were humoral antigen-sensitive cells with specificity against BSA, since antibody to BSA could be induced, but that BSA could not induce these cells because there was insufficient carrier antibody with specificity against BSA available. The hypothesis that high-zone paralysis occurs under conditions where both receptor antibody and carrier antibody are saturated is greatly strengthened by the fact that, under conditions where the effective concentration of carrier antibody is postulated to be too low to permit induction—that is, in an unresponsive animal—maintenance of unresponsiveness occurs over the whole dose range. This difference in the response of paralyzed and naïve animals to the same dose of antigen must be the result of a difference in the quantity of some antigen-specific receptor in the two kinds of animals, because it is brought about by antigen-specific paralysis. Unresponsiveness to BSA does not affect the responsiveness of the animal to different doses of, for example, lysozyme. The conclusion that maintenance of unresponsiveness occurs over the whole dose range must apply also to self-components. This avoids the awkward view that, "if in a tolerant animal, new antigen-reactive cells are generated from more primitive precursors at a time when antigen concentrations in the animal are not in the tolerance-inducing ranges, then tolerance will break down" (*26*).

It has been widely argued that the carrier effect is a local concentrating or trapping device for antigen, and that carrier antibody is not obligatory for, but merely aids, induction (*27*). It has been maintained that, a priori, there must be some form of concentrating device, because antibody with a binding constant in the range 10^{-6} to $10^{-7}M$ can be induced by blood concentrations of immunogen in the range 10^{-8} to $10^{-9}M$ (*28*). We feel that these inferences are misleading because it is not obvious whether a concentrating device should favor induction or favor paralysis in the competition between these two processes. The argument for a concentrating device, if it were valid, would presumably apply even more strongly to the case of low-zone paralysis. However, if we assume that there are 10^6 receptors on an antigen-sensitive cell, and that paralysis is produced by the binding of one molecule of antigen, we can ask what concentration of antigen maintained for 10 days will paralyze 99.0 percent of the specific cells. When known kinetic constants are used for the reaction between hapten and antibody against hapten (*29*), the calculation shows that a concentration of hapten of $10^{-19}M$ should suffice (*30*). This calculation is an extreme one, and it *may*, for example, be necessary for two haptens to bind two different receptors simultaneously in order to paralyze a cell. The above calculation is consistent with our hypothesis that low- and high-zone paralysis and maintenance of the unresponsive state do not involve obligatory associative recognition of the antigen.

At the present state of our knowledge it is not possible to propose a unique mechanism for the transition from low-zone paralysis to intermediate-zone induction as the concentration of antigen is increased. We had postulated earlier (*4*) that one molecule of

antigen interacting with the receptor (bound configuration) paralyzed a cell and that two molecules of antigen interacting with *one* receptor (stretched configuration) gave rise to induction. This suggestion was made in order to explain the transition from low-zone paralysis to induction when medium-sized doses of antigen are given. Under certain conditions where the rates of both reactions are limited by the presence of antigen, the rate of paralysis would depend linearly on the antigen concentration and the rate of induction would depend on the square of the antigen concentration. The *relative* rate would then depend on the antigen concentration, a fact that would explain the transition from low-zone paralysis to induction at medium-sized doses. We still regard this explanation of the transition as plausible, but not as the only possible one (*31*).

The data are insufficient for deciding whether the paralytic or the inductive signal would be dominant under conditions in which an antigen-sensitive cell simultaneously receives both signals. The relative (and possibly the absolute) number of receptors receiving each signal will be important in determining which signal is dominant, and it may be incorrect to assume that one of the two signals invariably dominates the other.

The location of carrier antibody when it is acting in the inducing event is not crucial to the theory. We will, however, briefly consider three possibilities. The carrier antibody could be free in the serum, passively absorbed onto a cell (for example, a macrophage or reticular cell), or be associated with a unispecific cell. No evidence for deciding between these alternatives exists, but we tend to favor the view that the carrier antibody belongs to a unique immunoglobulin class characterized by absorption onto a cell (*4*). The third alternative requires interaction of cells that are presumably fairly rare. If carrier antibody were passively absorbed onto a commonly occurring cell, it could without difficulty interact with a rare antigen-sensitive cell for induction. A rough calculation shows that a cell with a diameter of 10 microns could absorb at least 10^6 antibody molecules, and thus a collision between the antigen-sensitive cell and a cell with passively absorbed carrier antibody would have a good chance of leading to induction in the presence of sufficient antigen.

Self-Nonself Discrimination

We have seen that, under different experimental situations, the carrier antigen-sensitive cell can be either paralyzed or induced. In order to account for the stability of tolerance in terms of our model, certain propositions are essential.

1) The recognition of a carrier determinant is obligatory for induction of humoral antibody.

2) The recognition of two determinants on an antigen is obligatory for the induction of carrier antibody.

3) Both the humoral-antigen-sensitive cells and the carrier-antigen-sensitive cells are paralyzable by self-components.

If associative recognition were not necessary, an autoimmune response would occur when a single humoral-antigen-sensitive cell, specific for a self-component, appeared in an adult. This is the reason for the first proposition.

If carrier antibody were itself inducible without associative recognition, a self-component could induce carrier antibody. The appearance of a single humoral-antigen-sensitive cell with specificity against that self-component could then lead to an autoimmune response. Hence the need for the second proposition.

If self-components could only paralyze the carrier-antigen-sensitive cells (while humoral-antigen-sensitive cells were not paralyzable), autoimmune responses would occur on an encounter with an immunogen which shared some determinants with host constituents (this must be a common situation). The fact that BSA can inhibit the induction by HSA of antibody against BSA in an animal unresponsive to BSA strongly suggests that BSA can paralyze humoral-antigen-sensitive cells (*13*). If self-components could paralyze only the humoral-antigen-sensitive cells, then the appearance of one humoral-antigen-sensitive cell could again lead to autoimmunity. This is the basis for the third proposition (see *32*).

The induction of a carrier-antigen-sensitive cell requires carrier antibody, whereas paralysis of the cell does not involve obligatory associated recognition. We have no reason to suppose, insofar as antigen-specific steps are concerned, that the induction of carrier antibody is at all different from the induction of humoral antibody.

Interpretation of the Model in Cellular Terms

We do not have space here to critically review the experimental data on the cellular aspects of our theory. However, we will briefly comment on our interpretation of the cellular data in terms of the model. All the experiments we refer to were performed on mice, and it is very probable that some interpretations given are not applicable to other animals.

It has been known for some time that recovery from unresponsiveness to foreign serum protein antigens is prevented, or at least hindered, by removal of the thymus. As this unresponsiveness is specific, it is clear that the presence of the thymus is necessary for the generation of cells which bear the characteristic of some specific recognition for antigen. It has been shown that an x-rayed host given either bone marrow cells or thymus cells produces a poor response to red blood cells of sheep, but that when both cell populations are given with antigen the response is considerably greater than that expected from summing the activities of the separate populations. Furthermore, the antibody-forming cell has been shown to be derived from the bone marrow population (*33*).

The simplest interpretation of these results that is consistent with a very wide range of data not covered here is that the thymocytes give rise to the carrier-antigen-sensitive cell against red blood cells of sheep. The epithelial elements of the thymus provide a "hormone" which allows precursor cells to differentiate into thymocytes. We expect tolerance to self-components to involve a specific deletion in both the humoral-antigen-sensitive cell population and the carrier-antigen-sensitive cell population, though unresponsiveness would occur if either population were paralyzed. Some evidence that both populations can be paralyzed is available (*34*).

If, as we believe, the thymus is necessary for the differentiation of stem cells to carrier-antigen-sensitive cells, and if carrier antibody is obligatory for induction, all antigens are in this sense thymus-dependent.

It has been suggested that certain antigens are "thymus-dependent" in another sense; neonatal thymectomy considerably diminishes the ability of an animal to respond to such an antigen, whereas other antigens are, by this cri-

terion, "thymus-independent" (*35*). We do not believe that this distinction between "thymus-dependent" and "thymus-independent" antigens should be interpreted to mean that carrier antibody is not obligatory for the induction of antibody to all antigens. The antibody response to red blood cells of sheep is thymus-dependent if thymectomy is performed a day or so after birth, but thymectomy at the age of 1 month does not affect the animal's competence to respond to this antigen when challenged shortly after thymectomy. We think it most plausible to conclude that, in the case of "thymus-independent" antigens, the thymus had already played its part in generating the carrier-antigen-sensitive cells before thymectomy was performed.

Concept of the Antigen-Sensitive Cell

There is evidence (*36*) consistent with the view that a unispecific cell is involved in the antibody response to an antigen. However, the experimental evidence is not detailed enough to show that this unispecific cell is identical to the antigen-sensitive cell as we conceive it.

The strongest theoretical arguments in favor of our concept of the antigen-sensitive cell come from a consideration of some of the early steps that must be involved in paralysis and antibody induction. The argument rests on the rejection of instructive theories of antibody formation, from which it follows that, if an animal is induced to make a specific antibody, that antibody must be present before induction can take place. We assume, therefore, that specific recognition of an antigen can occur only through an interaction between that antigen and antibody.

One of the initial steps in antibody induction and paralysis must be an interaction between antigen and receptor antibody. This interaction must be recognized by another cellular component, which we call the "interaction sensing unit" (see Fig. 2). We will assume for the moment that this unit binds to the receptor antibody. The amino acid sequences of antibody molecules are known to consist of variable and invariant regions (*37*). As a consequence of our rejection of instructive theories, we can state that a cell cannot adjust the "interaction sensing unit" to the variations that are produced in the antibody molecule (*38*). Hence the

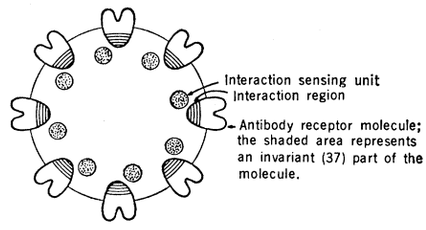

Fig. 2. The concept of the antigen-sensitive cell.

"interaction sensing unit" must be complementary to an invariant part of the receptor-antibody molecule.

From these considerations we conclude that the interaction between receptor antibody and antigen must result in conformational changes in an invariant part of the molecule (*39*). The "interaction sensing unit" can, in principle, bind to either the free or the bound form of the receptor. We call the invariant region of the antibody molecule that binds to the "interaction sensing unit" the "interaction region" (see Fig. 2).

Since the recognition of an interaction between a given receptor antibody and an antigen must lead to a specific signal, the "interaction sensing unit" for two antibody molecules of different specificity but with identical "interaction regions" must be physically isolated from one another. This condition is satisfied if each cell possesses on its surface no more than one kind of receptor specificity associated with any particular "interaction region." Thus the maximum number of different types of receptor which an antigen-sensitive cell can bear is the number of invariant regions used for recognition; for example, the "interaction sensing unit" could be specific to a class of antibodies. However, for simplicity we have called this cell unispecific, though in principle it could be oligospecific (*40*).

Conclusions

1) Induction of humoral antibody formation involves the obligatory recognition of two determinants on an antigen, one by the receptor antibody of the antigen-sensitive cell and the other by carrier antibody (associative interaction).

2) Paralysis of antibody formation involves the obligatory recognition of only one determinant by the receptor antibody of the antigen-sensitive cell; that is, a nonimmunogenic molecule (a hapten) can paralyze antigen-sensitive cells.

3) There is competition between paralysis and induction at the level of the antigen-sensitive cell.

4) The mechanisms of low- and high-zone paralysis, and maintenance of the unresponsive state, are identical.

5) High-zone paralysis occurs when both the carrier antibody and the receptor antibody are saturated, so that associated interactions cannot take place.

6) The mechanisms of paralysis and induction for the carrier-antigen-sensitive cell are identical to those for the humoral-antigen-sensitive cell.

7) The formation of carrier-antigen-sensitive cells is thymus-dependent, whereas humoral-antigen-sensitive cells are derived from bone marrow. Since carrier antibody is required for induction, all antigens are thymus-dependent.

8) The interaction of antigen with the receptor antibody on an antigen-sensitive cell results in a conformational change in an invariant region of the receptor and consequently paralyzes the cell. As the receptor is probably identical to the induced antibody, all antibody molecules are expected to be able to undergo a conformational change on binding a hapten. The obligatory associated recognition by way of carrier antibody (inductive signal) involves a conformational change in the carrier antibody, leading to a second signal to the antigen-sensitive cell.

9) The foregoing requirements provide an explanation for self-nonself discrimination. Tolerance to self-antigens involves a specific deletion in the activity of both the humoral- and the carrier-antigen-sensitive cells.

References and Notes

1. Two observations also argue against this possibility. (i) It is known that animals can respond to antigens of their own species if they themselves do not possess such an antigen; it would be very difficult to ensure that an offspring was not given maternal genes which allowed it to react to one of its own paternally derived antigens, and vice versa; (ii) autoimmune reactions do occur, in which chemically heterogeneous antibody to a self-component is made, showing that individuals do possess the potentiality of expressing genes which code for antibodies directed against self-components.
2. A. W. Dresser and N. A. Mitchison, *Advan. Immunol.* **8**, 129 (1968).
3. J. Lederberg, *Science* **129**, 1649 (1959).
4. P. A. Bretscher and M. Cohn, *Nature* **220**, 444 (1966); M. Cohn, in *Control Processes in Multicellular Organisms*, G. E. W. Wolstenholme and J. Knight, Eds. (Churchill, London, 1970), p. 255.
5. We use the word *paralysis* to denote the process by which antigen interacts with an antigen-sensitive cell to prevent that cell from making antibody in the future (for example,

by killing the cell); the word *tolerance* to describe the immunological state of an animal with respect to its own antigens; and the word *unresponsiveness* as an operational term for describing the state of an animal to which antigen has been administered and which cannot subsequently respond to that antigen but which can respond to other non-cross-reacting foreign antigens. We have not tried to introduce a new nomenclature at this point but have tried, rather, to use in a restricted sense terms already employed.

6. We consider only humoral-antibody induction in our discussion, but we believe that the mechanism of self-nonself discrimination, and hence the features of induction and paralysis that we describe, will be applicable to cell-mediated reactions—for example, homograft rejection and delayed hypersensitivity.
7. No evidence is available to rule out the more complex model of self-nonself discrimination which is a hybrid between Lederberg's model and ours. In this hybrid model the antigen-sensitive cell initially goes through a paralyzable state and then differentiates into a cell which is both paralyzable and inducible.
8. These experiments are reviewed by H. O. McDevitt and B. Benacerraf, *Advan. Immunol.* **11**, 31 (1969).
9. If a hapten is *heavily* conjugated onto a nonimmunogenic molecule, an antihapten response can presumably be obtained; the determinant against which the humoral antibody is directed and the carrier determinant can be identical.
10. N. A. Mitchison, *Cold Spring Harbor Symp. Quant. Biol.* **32**, 431 (1967); K. Rajewsky, V. Shirrmacher, S. Nase, N. K. Jerne, *J. Exp. Med.* **129**, 1131 (1969).
11. B. B. Levine, *J. Exp. Med.* **121**, 873 (1965); G. W. Siskind, W. E. Paul, B. Benacerraf, *ibid.* **123**, 673 (1966); W. E. Paul, G. W. Siskind, B. Benacerraf, *ibid.*, p. 689.
12. B. Benacerraf, in *Immunological Tolerance*, M. Landy and W. Braun, Eds. (Academic Press, New York, 1969).
13. W. O. Weigle, *J. Immunol.* **92**, 791 (1964); J. H. Humphrey, *Immunology* **7**, 449 (1964).
14. These cases are reviewed by B. Benacerraf, W. E. Paul, I. Green, *Ann. N.Y. Acad. Sci.* **169**, 93 (1970). There are cases in which the injection of low-molecular-weight compounds like arsanilic L-*N*-acetyltyrosine [S. Leskowitz, *Science* **155**, 350 (1967)] or dinitrophenyl hepta-L-lysine [S. F. Schlossman, A. Yaron, S. Ben-Efraim, H. A. Sober, *Biochemistry* **4**, 1638 (1965)] induce an immune response. Although it could be argued that two properly spaced determinants are sufficient for induction and that these compounds meet this requirement, such an interpretation is probably not correct. In practice, more than two foreign determinants are probably necessary to induce a measurable response. It is more likely that these substances are aggregated in vivo by interaction with themselves or with the animal's components.
15. Aggregated material may be more immunogenic for a further reason. Such material has several identical sites present on its surface and so its effective affinity for multivalent antibody can be much higher than that of unaggregated material. This may allow such material to be immunogenic at lower doses.
16. N. A. Mitchison, *Progr. Biophys. Mol. Biol.* **16**, 3 (1966); S. Bauminger and M. Sela, *Israel J. Med. Sci.* **5**, 182 (1969).
17. J. Sterzl, *Nature* **209**, 416 (1966); ———, in *Immunological Tolerance*, M. Landy and W. Braun, Eds. (Academic Press, New York, 1969), p. 28; N. K. Jerne, *Cold Spring Harbor Symp. Quant. Biol.* **32**, 600 (1967); G. M. Edelman and W. E. Gall, *Annu. Rev. Biochem.* **38**, 460 (1969); C. Collotti and S. Leskowitz, *J. Exp. Med.* **131**, 571 (1970); J. F. A. P. Miller and G. F. Mitchell, *ibid.*, p. 675.
18. A hapten which does not cause the postulated conformational change on binding to receptor antibody cannot be paralytic. This might be the case if the hapten does not fully occupy the binding site of the receptor antibody.
19. K. Rajewsky and E. Rottlander, *Cold Spring Harbor Symp. Quant. Biol.* **32**, 547 (1967).
20. While we are really interested in obligatory carrier effects, we should point out that specific humoral antibody given passively to an animal will in many cases affect the outcome of administering antigen to the animal. The most important ways in which such antibody might affect the response are by (i) aggregating the antigen, (ii) affecting the distribution of the antigen in the animal, (iii) covering up determinants on the antigen, and (iv) mediating the breakdown of the antigen by, for example, complement or macrophages.
21. The concentrations referred to here are those measured in the extravascular fluid and do not include antigen which is sequestered in phagocytic cells. This is probably the best estimate available for the concentration of free antigen in the environment of antigen-sensitive cells. See N. A. Mitchison, in *Regulation and the Antibody Response*, B. Cinader, Ed. (Thomas, Springfield, Ill., 1969), p. 54.
22. N. A. Mitchison, *Proc. Roy. Soc. Ser. Biol. Sci.* **161**, 275 (1964); ———, in *Immunological Tolerance*, M. Landy and W. Braun, Eds. (Academic Press, New York, 1969), p. 113.
23. The principal selective pressure driving antibody molecules to be specific is presumably self-nonself discrimination. The counteracting pressure arises because the greater the specificity the larger the number of different antibody molecules needed to interact with all foreign determinants. Since we believe the physiological significance of carrier antibody is to provide a mechanism for self-nonself discrimination, we expect to find that humoral antibody and carrier antibody are equally specific and that their binding constants are of the same magnitude. In the light of this argument, it would be wasteful if carrier antibody were either more or less specific than humoral antibody, or if the range of specificities that could be generated in either class were not the same. Therefore, we reject the suggestion that the carrier-antigen-sensitive cells are genetically restricted in the range of their specificities. See K. Rajewsky, V. Shirrmacher, S. Nase, N. K. Jerne, *J. Exp. Med.* **129**, 1131 (1969).
24. R. T. Smith and R. A. Bridges, *ibid.* **108**, 227 (1958).
25. Protein antigens have been classified into strong and weak immunogens. Lysozyme, which induces an antibody response in mice in the low-zone range ($\sim 10^{-8}M$), is called a strong immunogen, whereas BSA, which paralyzes at $10^{-8}M$, is called a weak immunogen. The difference in the immunogenic properties of these two antigens is probably a result of lysozyme having more determinants which are "foreign" in the mouse than BSA has. An alternative explanation is that the difference in behavior of the two immunogens is due to some difference in a nonspecific property of the antigens (for example, their half-life in the animal). The observation that lysozyme at a concentration of $10^{-8}M$ can maintain the unresponsive state is in accord with the former view.
26. G. J. V. Nossal, *Harvey Lect.* **63**, 206 (1969).
27. N. A. Mitchison, in *Mediators of Cellular Immunity*, H. S. Lawrence and M. Landy, Eds. (Academic Press, New York, 1969), p. 97; R. B. Taylor, *Transplant. Rev.* **1**, 143 (1969); G. M. Edelman, in *Control Processes in Multicellular Organisms*, G. E. W. Wolstenholme and J. Knight, Eds. (Churchill, London, 1970), p. 316; J. F. A. P. Miller, *ibid.*, p. 299; O. Makela and A. M. Cross, *Progress in Allergy* (Karger, Basel, Switzerland, in press); G. J. V. Nossal, *Harvey Lect.* **63**, 179 (1969); G. Möller, in *Homeostatic Regulators*, G. E. W. Wolstenholme and J. Knight, Eds. (Churchill, London, 1969), p. 219. See numerous views on the so-called trapping mechanism in *Immunological Tolerance*, M. Landy and W. Braun, Eds. (Academic Press, New York, 1969); the problem is discussed in M. Cohn, *Essays Comp. Microbiol.*, in press.
28. N. A. Mitchison, in *Immunological Tolerance*, M. Landy and W. Braun, Eds. (Academic Press, New York, 1969), p. 17.
29. L. A. Day, J. M. Sturtevant, S. J. Singer, *Ann. N.Y. Acad. Sci.* **103**, 611 (1963).
30. Let the concentration of free hapten which causes 99.0 percent paralysis be $[H]$. The number of receptors which bind antigen per second will be

$$\Delta\,[RH]/\text{sec} = k_{on}[H]\,[R],$$

where $[R]$ is the receptor concentration, $[RH]$ is the receptor-hapten concentration, and k_{on} is the kinetic constant of association. So long as $[RH]$ is much smaller than $[R]$, the fraction, per second, of receptors which bind hapten will be given by

$$\frac{\Delta\,[RH]}{[R]} \Big/ \text{sec} = k_{on}\,[H],$$

and the fraction per 10 days ($\sim 10^6$ sec),

$$\frac{\Delta\,[RH]}{[R]} \Big/ 10^6 \text{ sec} = k_{on}\,[H]\,10^6$$

Since $k_{on} = 10^8 M^{-1}$ sec^{-1} (see *27*), then

$$\frac{\Delta\,[RH]}{[R]} \Big/ 10^6 \text{ sec} = [H]\,(10^8 M^{-1}\text{ sec}^{-1})\,(10^6 \text{ sec})$$

If, on an average, five receptors out of the 10^6 which exist on one cell have interacted with hapten, the number of cells which have not reacted with hapten at all will be about 1 percent (on the assumption that the interactions between hapten and the receptors are random). We thus set

$$\frac{\Delta\,[RH]}{[R]} = \frac{5}{10^6}$$

Hence

$$[H] = \left(\frac{\Delta\,[RH]}{[R]} \Big/ 10^6\right) 10^{-14} = \left(\frac{5}{10^6}\right) 10^{-14} \simeq 10^{-19} M$$

For a macromolecule (unlike a small molecule, for which the above calculation was made) this concentration is closer to $10^{-18}M$, as the forward rate constant appears to be diffusion-limited. A calculation can be made based upon the equilibrium

$$R + H \overset{K}{\rightleftarrows} RH$$

If the reaction of one receptor out of 10^6 with H to give RH leads to paralysis, then at K dissociation of 10^{-5}, $[H] = 10^{-11}M$, and at K dissociation of 10^{-9}, $[H] = 10^{-15}M$. Again, low-zone tolerance would occur and no assumptions concerning a transport or concentrating mechanism need be made.

31. If the cell-bound receptor antibody and carrier antibody are functionally bivalent, the postulated cell-to-cell interaction could be maintained by two types of antigen bridges—one in which the receptor antibody and the carrier antibody have one molecule of antigen between them (Fig. 1, monogamous bridge) and one in which two molecules of antigen are bound between each receptor-carrier pair (bigamous bridge). This latter structure can undergo a conformational change known as stretching [see C. S. Henney and D. R. Stanworth, *Nature* **210**, 1071 (1966); C. S. Henney, D. R. Stanworth, P. G. H. Gell, *ibid.* **205**, 1079 (1965); R. C. Valentine and N. M. Green, *J. Mol. Biol.* **27**, 615 (1967); A. Feinstein and A. J. Rowe, *Nature* **205**, 147 (1965)]. Although stretching has been considered a possible component of the inductive signal, the minimal theory analyzed here does not *require* this [for discussion of this point, see (*4*)]. However, because of its great stability due to cooperative binding [see F. Karush, *Ann. N.Y. Acad. Sci.* **169**, 56 (1970)], the bigamous bridge might bind two cells together during induction of antibody formation. The rupture of a bigamous bridge will take place at a concentration of antigen roughly an order of magnitude above the binding constant [S. Kontiainen and O. Mäkelä, *Ann. Med. Exp. Biol. Fenn. Helsinki* **45**, 472 (1967); O. Mäkelä, *J. Exp. Med.* **126**, 159 (1967); ———, *Immunology* **10**, 81 (1966)]. As the antigen concentration is increased into the high-zone paralytic range, the rupture of a bigamous bridge will take place at roughly the same concentration as that at which rupture of a monogamous bridge occurs.
32. For many self-antigens which are present as the immune system matures, the establishment of tolerance is analogous to the maintenance of tolerance, because the animal will not be immunologically competent at any time with respect to such an antigen. This case is very different from that considered earlier for BSA in adult mice, where the requirements for establishing unresponsiveness were more stringent than those needed for maintaining the unresponsive state. For the establishment of tolerance to self-antigens which are not present during the embryological development of the immune system, either there will have to be some special mechanism or the concentration of these antigens will increase in a manner that allows them to go through low-zone paralysis or into high-zone paralysis.
33. See collection of articles in *Transplant. Rev.* **1** (1969).

34. J. M. Chiller, G. S. Habicht, W. O. Weigle, *Proc. Nat. Acad. Sci. U.S.* **65**, 551 (1970).
35. J. L. Gowans, in *Immunological Tolerance*, M. Landy and W. Braun, Eds. (Academic Press, New York, 1969), p. 169; J. F. A. P. Miller, in *Control Processes in Multicellular Organisms*, G. E. W. Wolstenholme and J. Knight, Eds. (Churchill, London, 1970), p. 251; R. B. Taylor, *Transplant. Rev.* **1**, 116 (1969).
36. R. I. Dutton and R. I. Mishell, *J. Exp. Med.* **126**, 443 (1967); G. L. Ada and P. Byrt, *Nature* **222**, 1291 (1969).
37. We use the word *invariant* to include both those residues in the region usually designated the common region of the antibody molecule and those in the "variable region" which are invariant.
38. The argument that the "interaction sensing unit" must be invariant is independent of the assumption that it is complementary to the receptor antibody.
39. This conclusion depends on the assumption that the "interaction sensing unit" is complementary to the receptor antibody. We believe this to be the only plausible hypothesis in the case of paralysis, since the receptor is the only molecule which specifically recognizes the antigen and can, therefore, be the only molecule which specifically transmits a signal to the cell. For induction the signal could be transmitted through either the receptor antibody or the carrier antibody, or both. We favor the last alternative, since the carrier antibody must be recognized in order to be mandatory for induction, and since the antigen must, according to the model for paralysis, cause a conformational change of the receptor on binding it. This hypothetical scheme has the added attraction that it ensures that cells which are nonparalyzable because the receptor is unable to transmit the paralytic signal will be noninducible.
40. These considerations are consistent with the existence of allelic exclusion at the level of the antigen-sensitive cell. In an animal homozygous for a particular class of antibody molecules, an individual antigen-sensitive cell is expected to express receptors for only one of the two alleles. If both alleles were expressed, and if they coded for antibodies of different specificity, as is to be expected, the induction of antibody could not be specific, as the interaction of antigen with one of the two kinds of receptor present would lead to induction of both alleles. The argument presented above thus demands allelic exclusion at the level of the antigen-sensitive cell if the antibody-secreting plasmacyte is to be unispecific. The above argument for allelic exclusion has been made for a homozygous animal, but it can be reasonably extended to animals heterozygous for a particular class of antibody molecule. A system in which the "interaction region" is allotype-specific leads to difficulties; if the "interaction region" is not allotype-specific, the argument applies to heterozygous animals with the same force that it applies to homozygous animals. These considerations also show that an antigen cannot interact with a "stem cell," which possesses receptors of very many different kinds, to provide a signal for the cell to differentiate into a unispecific cell, as proposed by B. D. Brondz and N. E. Goldberg, *Folia Biol. (Praha)* **16**, 1 (1970).
41. We predict that no anti-U will be induced in spite of the fact that the hapten could in principle provide a carrier determinant to induce anti-U. We base this prediction on the fact that more than one carrier site is, in most cases, required to get a measurable response, as discussed in the text.
42. The formulation of our theory, as presented here, corrects and supersedes any previously published accounts—that is, P. A. Bretscher and M. Cohn, *Nature* **220**, 444 (1968); M. Cohn, in *Immunological Tolerance*, M. Landy and W. Braun, Eds. (Academic Press, New York, 1969); ———, in *Control Processes in Multicellular Organisms*, G. E. W. Wolstenholme and J. Knight, Eds. (Churchill, London, 1970); and ———, in *Essays in Comparative Microbiology*, E. Borek, Ed. (Columbia Univ. Press, New York, in press). We are extremely grateful to Jacques Monod for his critical comments. This study has been supported by a Damon Runyon Memorial Fund Fellowship to Peter Bretscher and by National Institutes of Health grant No. A-105875 and training grant No. CA 05213 to Melvin Cohn.

Administering and Managing the U.S. and Soviet Space Programs

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The American and Soviet space programs have, from the management and organizational standpoint, much in common. Yet there are a number of fundamental differences. Because of some of these differences the United States has so far reaped greater benefits, in a social sense, from its space efforts than has the Soviet Union. Because of others, however, the scales could tip in favor of the Soviets. The fundamental issue is whether the United States will continue willing to do the things necessary to match the continuity, purposefulness, and concentration of effort that characterize the Soviet approach.

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Features in Common

Complexity and resources. The two programs have been roughly equal in complexity and in input of resources. If, as has been asserted, the U.S. moon undertaking represented a task equal in technological complexity to the total of all the great tasks performed by man from the building of the pyramids through explosion of an atomic bomb, hardly less can be said of Soviet space enterprises. So far, the U.S.S.R. has not aimed at anything that quite matches the moon landing. It has, however, in numerous other particulars been the pioneer, working at the cutting edge of space knowledge and exploration. In its space efforts it has had to penetrate the unknown as much as the United States has, if not more. Many of the pathfinding firsts were Soviet achievements. Beyond this, the U.S.S.R. has kept pace with the United States in the continued development and improvement of general capabilities to operate in space, including the range of capabilities that made possible the U.S. moon landing.

For one program as much as the other, the space task has presented problems for which no solution was available. Each program, over and over again, has required doing something for the first time, with a high degree of uncertainty as to what was needed to do it or as to the precise results that would follow. Each has required working against long lead times, in which it takes years to move from the conception of a mission to its realization. Each has required the development of new tools and new ways of using tools, new mechanisms of propulsion, new systems of life support, new guidance systems, new computer technologies, and all with a degree of reliability never before attempted in human undertakings.

We have no way of determining how Soviet budgetary figures compare with the $33 billion the United States will have spent on its civilian space activities by the end of the current fiscal year and the added $23 billion for related military programs, for a total of something over $56 billion. We can nevertheless be reasonably sure that the Soviet investment has been comparable to that of the United States, if not substantially greater. This follows