Ontogeny of the Immune Response

The development of immunologic responses by the fetus has interesting pathobiologic implications.

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With the exception of some rudimentary metabolic processes, the fertilized ovum is probably incapable of any specialized activity other than cell division. Continued proliferation from this simple beginning leads to the differentiation of cells, organs, and systems capable of every form of specialized biologic function. Before a given stage of development, the organism is unable to perform certain of these functions. As in other systems, a knowledge of the time at which immunologic competence develops, of the cells and organs concerned with that development, and of the relation to other concurrent biologic events cannot fail to shed light on its basic nature and significance.

I shall not attempt a comprehensive review of the extensive data in this field (*1*). Rather, I shall restrict the discussion to certain aspects of fetal immune responses and how they seem to grow. The data will be examined in relation to current theories of immunologic function, with emphasis on those peculiarities of the response that do not appear to accord well with theory.

It will become clear that maturation by the mammalian fetus of a functioning immunologic apparatus may lead to a number of extremely curious events of general biologic interest. These concern the well-being of the fetus itself and also the relation of the fetus to its mother. The development of immunologic competence not only furnishes the maturing animal with an impressive mechanism for defense against infection, but it may also provide the very basis for the development of disease as well.

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Immunologic Tolerance

Any discussion of the ontogeny of the immune response must include an outline of the nature and implications of immunologic tolerance, since this condition is so intimately related to the response not only of the developing organism, but also to its maturing cell systems. Extensive reviews on immunologic tolerance have recently appeared (*2*), and only the pertinent factors will be examined here.

One of the longstanding points of dogma in immunology has been that the body would respond immunologically only to antigens foreign to itself, and not to native substances. This rule was embodied in immunologic scripture by Paul Ehrlich in the term *horror autotoxicus* and, with only a few exceptions, stands firmly to this day (*3*). For reasons not well understood, the organism is able to distinguish between native and foreign antigens, tolerating endogenous substances and developing a variety of specific responses to those from outside the body.

In 1945, Owen (*4*) made the startling observation that certain nonidentical twin calves might each have two completely different sets of red cell antigens, its own and that of its twin. Such animals are called erythrocyte mosaics or chimeras. Owen correctly assumed this mosaic state to result from the establishment of vascular connections between the twins in the uterus, with a subsequent exchange of hematopoietic elements which conferred upon each animal a persisting source of production of its twin's red cells. But why did each calf not form antibodies against the foreign red cells of its sibling, as it would certainly have done had they been introduced after birth rather than before? This question was answered with remarkable insight by Burnet and Fenner (*5*), who suggested that before the maturation of its immunologic mechanisms, the fetus exists in an immunologic "null" state, unable to respond to any antigenic stimulus. With the acquisition of competence, the maturing organism was thought to develop a recognition mechanism whereby all antigens present at this critical time were acknowledged as "self-antigens," unable thenceforth to stimulate an immune response. Antigens arriving on the scene after this supposed cataloging would then appear to be foreign and thus be capable of stimulating the immunologic apparatus. Pursuing this line of reasoning, Burnet and Fenner postulated that a foreign antigen, introduced artificially into the developing animal, would be accepted and tolerated as "self" along with the native antigens already present.

This forecast was soon shown to be correct. The calf "chimeras" were shown to accept skin grafts from the respective twins without the intervention of the usual immunologic graft rejection process, indicating that each of the fraternal twins had become tolerant of the other's transplantation antigens. Within the past decade, a great variety of antigens, both living and dead, have been shown to be capable of inducing tolerance in the developing young of many species. In some species, tolerance could only be invoked in the fetus; in others, tolerance could be established well into the neonatal period.

Burnet and others (*6*) advanced further suggestions concerning the nature of the relation between immunologic tolerance and the maturation of immunologic competence in the developing young. They proposed that immunologic maturation occurs with the appearance in the young animal of clones of cells that are able to synthesize specific antibody under genetic control. Antigen was supposed to "select" cells with the appropriate specificities by stimulating them to proliferation and protein (antibody) formation. Tolerance, on the other hand, was supposed to result from the specific destruction of appropriate clones by antigen during a critical stage of their maturation. But it was soon noted that perpetuation of the tolerant state requires a persistence of antigen in the animal (*2*). If adequate amounts of the tolerated antigen were not maintained, then the animal would regain its capacity to form antibodies against the previously tolerated antigen. Even more perplexing were observations that the administration of massive doses of cer-

Table 1. Earliest appearance of immunologic activity against different antigens in the fetal and neonatal lambs.

Antigen	Gestation age* (days)	Newborn age (days)
Bacteriophage ϕX174	< 41	
Ferritin	66	
Homograft rejection	85	
Egg albumin	125	
Salmonella typhosa		> 42†
Diphtheria toxoid		> 42†
BCG		> 42†

* The ages given represent the earliest detected response. In each instance, the antigenic stimulus had been given earlier, so that active response must have commenced some days before it was detected. † At the time that the study was discontinued 6 weeks after birth, antibody response to these antigens had not yet appeared. Adult sheep, however, were found to respond to each of them satisfactorily.

tain antigens into mature adults might result in the development of a state of tolerance analogous to that observed in young animals.

Treatment of the immunologically mature animal with x-rays or immunosuppressive drugs such as 6-mercaptopurine may also set the stage for the relatively easy establishment of tolerance (*2*). Since such treatment is known to damage immunologically mature cells, the effect may be, in a sense, to induce a reversion akin to the primitive fetal state wherein immature cells newly emerging are more sensitive to excesses of antigen. These considerations, together with some other consequences of immunologic tolerance for the developing fetus, emphasize the need for further clarification of the factors involved in immunogenesis.

Fetal Response to Antigen

The newborn of many species usually responds poorly, if at all, to a variety of immunizing agents (*7*), while immunologic tolerance could be induced after birth in such widely used experimental animals as the mouse, rat, and rabbit (*2*). Thus, it is not surprising that the belief developed that all mammals mature immunologically only at or shortly after birth, and that this maturation occurs as a discrete cellular development affecting the entire immunologic apparatus at once. In line with this belief were the observations (*8*) that human fetuses, for example, had only very immature lymphoid tissue and did not form the plasma cells that would signal the production of antibodies.

However, many responses appear only after a suitable stimulus, and the mammalian fetus is normally well protected from exogenous stimuli by the efficient placenta. Should the placenta allow passage to the fetus of pathogenic organisms, then such diseases as congenital syphilis and congenital toxoplasmosis may occur, accompanied by the stimulation of plasma cell differentiation and undoubtedly antibody formation (*9*). This sequence is supported by studies on germ-free animals, reared under sterile conditions. In this partial extension of the protected fetal environment, these animals also are retarded in their general lymphoid development and in plasma cell formation (*10*).

The belief that the mammalian fetus exists in an immunologic "null" state, only slowly developing its capacities after birth, has slowly given way as evidence to the contrary has been presented. In addition to the demonstration of plasmacytosis in the human fetus, premature children were found to form antibodies and to develop delayed hypersensitivities (*11*). The newborn rabbit, thought to be immunologically incompetent prior to the third week of life, forms antibodies against certain antigens during this period even while rendered tolerant of others (*12*). Even at earlier stages of development, the fetal calf in the uterus and the opossum embryo in the pouch form antibodies (*13*) and the fetal guinea pig develops delayed hypersensitivity (*14*), while the fetal lamb rejects skin homografts in a true immunologic manner (*15*).

It would appear, therefore, that the development of immunologic capabilities is not keyed to the birth process, and in fact may exhibit great variation among different species. There is also evidence that immunogenesis in the developing animal is not a single act of maturation, but may occur as a slow and perhaps stepwise process. Since there are more data on the response of the fetal lamb to antigenic stimuli than for any other species, it may be useful to outline these results in some detail to emphasize the characteristics of this maturation process and some of the problems which the data pose.

Antibody Formation

After 150 days of gestation, the lamb is born a relatively mature animal. It has hair, can walk immediately, and is not as dependent upon its mother as are the newborns of some other species. Most of this maturation takes place during the final third of the gestation period. Before this time, the lamb is quite immature, and yet it is able to form circulating antibodies in the uterus in response to intrafetal immunization (Table 1). This response has been observed in lambs immunized as early as the 35th day of gestation and tested for a response 6 days later. The earliest age at which a fetus is able to form antibodies has yet to be established; it is technically quite difficult to inject these small fetuses at an earlier age. We may conclude that the ovine fetus develops some degree of immunologic maturity during the first third of gestation, but probably not before the 20th to 30th day of embryonic life since mesenchymal differentiation is minimal before this age.

The immunization of fetal lambs at different ages with a variety of different antigens led to a surprising observation (Table 1). Some of these antigens, such as diphtheria toxoid, *Salmonella typhosa*, and Bacillus Calmette-Guérin (BCG) do not stimulate the formation of detectable circulating antibodies at any time during fetal life, or even in the first weeks of extrauterine life. Only relatively long after birth do animals respond to these antigens in the characteristic manner. On the other hand, the bacteriophage virus ϕX174 stimulates active antibody formation in the fetus at the earliest time thus far injected—35 days gestation. Curiously, the age of the fetus at the time of phage immunization had no significant effect upon the amount of antibody produced within a given period of time. There was no question that the antibodies observed in the blood of these fetuses were of fetal rather than maternal origin since γ-globulins are known not to cross the ovine placenta, and in no instance did the mother's blood contain detectable antibody.

At the time that the fetus was able to initiate antibody formation against the bacteriophage virus, the fetus still could not respond immunologically to such protein antigens as ferritin and egg albumin. At about the 65th to 70th day of gestation the fetal lamb began to produce antibody to ferritin, whereas not until the 125th day of gestation was the first antibody to egg albumin detected in the fetus.

Thus immunologic maturation in the fetus appears not to represent the

achievement of competence by a single general mechanism by which the fetus thenceforth can respond to all antigens. The mechanism seems rather to be a slow stepwise development that allows the fetus and newborn to respond first to one, then to another, and ultimately to all antigens. The basis for this antigenic hierarchy is at present not clear. The difference may reflect the varying capacities of the several antigens to penetrate the cells and stimulate the immune mechanism, or it may truly represent the maturation of the different immunologic specificities at different times. Possibly all immunologic capabilities mature early, but the enzyme systems required to degrade each antigen into a useful form (*16*) might not all appear simultaneously. Whatever the explanation, it is clear that before a given age, the immunologic mechanism of the fetal lamb does not appear to recognize certain substances as antigenic; after that time recognition occurs, and a specific response ensues.

The first antibodies to appear in the fetal circulation after immunization are high-molecular-weight β_{2M}-macroglobulins, sensitive to the action of 2-mercaptoethanol. Later, γ-globulin antibody of lower molecular weight appears in the circulation. This sequence is typical of the immune response of both newborns and adults of many species, and the subject is discussed in detail by Uhr (*17*). In the case of the fetal lamb, there is some suggestion that formation of 7*S* γ-globulin may appear later in the response than in the case of adult animals.

A significant point about the existence of more than one type of antibody protein is the possibility that each may be produced independently by a different cell population. If this were true, then the development of immunologic capabilities in the fetus might imply the maturation of several different mechanisms rather than the maturation of a single, unique response. This may represent another situation in which evolution has provided the organism with several modes of response to a given stimulus.

Homograft Rejection

The rejection of skin homografts is widely recognized as a specific immunologic process (*18*). Here too, the fetal lamb demonstrates a competence which seems to develop at a discrete time in gestation (*19*). Skin homografts applied to the fetus before approximately the 75th day of gestation are accepted as though they were not of foreign origin and they survive unmolested by the recipient. After this time, however, the fetus copes with the homograft in the manner typical of the adult sheep, rejecting it specifically within 7 to 10 days. This is true regardless of the origin of the graft, whether from unrelated fetal or adult sheep, or even from its own mother.

The ability to reject a homograft does not appear to develop slowly in the fetal lamb. It seems almost to arise fully formed. Either the fetus tolerates the graft without any response, or it proceeds to reject it with the rapidity and competence of the adult animal.

In addition to valuable information on the ontogenesis of the immune response, experimental studies may simultaneously clarify some fundamental problems in immunology. There has been much debate about the nature of the mechanism of homograft rejection. Whether the rejection of solid tissue grafts is mediated by circulating antibodies, or whether it is based upon a cellular mechanism related to delayed hypersensitivity is unknown.

Since the fetal lamb has almost no γ-globulin in its blood, it has been possible to study the rejection of homografts in the presence of excess circulating rabbit antibody to sheep γ- and β_{2M}-globulins, without harm to the fetus (*15*). In such a model system, γ-globulin antibodies formed by the fetus in its attempt to destroy the graft would be neutralized in the circulation and would thus be unavailable to participate in the rejection process. But despite the presence of persisting antibodies to ovine globulins, the fetus was found to reject homografts as rapidly and capably as control fetuses uninjected with such antibodies. These data strongly support the view that conventional circulating antibody is not an obligatory participant in the rejection of solid tissue homografts.

Fetal Lymphoid Development

The lymph nodes and spleen are known to constitute the primary seat of immunologic activity in the body. Most immunologically competent cells seem to arise in these tissues, and the greater part of the circulating antibodies that appear in response to immunization is formed in them. These tissues also constitute the principal source of those immunologically competent cells that venture into the blood to participate in immunogenic inflammatory reactions elsewhere in the body. The role of the thymus in the maturation of lymphoid tissues and their immunologic capabilities has been reviewed by Miller (*20*), and therefore will not be discussed here.

The maturation of lymphoid tissue in the normal mammalian fetus is a slow and protracted sequence (*9*, *19*). The unstimulated lymph nodes of the younger fetus show primarily medullary channels lined by endothelium, an assortment of rather immature-appearing mesenchymal cells, and only minimal lymphopoiesis. There is little demarcation between cortex and medulla, and there is no follicular activity. The tissue is only slowly populated by lymphocytes as gestation continues, until at birth there may be primary lymphoid nodules, generally without the formation of secondary follicles. Cells identifiable as having immunologic function are not seen in these immature nodes.

After birth there is an abrupt acceleration of this development in the normal animal, presumably in response to the host of bacterial and other stimuli that come flooding in from its new environment. The germ-free animal, protected at least from living pathogens, is appreciably retarded in its lymphoid development, since stimulus is minimal. Thus the final stages of the maturation process appear to require a suitable stimulus. Whereas immunologic response may be observed morphologically in the development of certain types of cells and cell organizations, the mere readiness to furnish an immune response (immunologic competence) may offer no overt morphologic indicators.

Should the placenta fail in its protective function, allowing infection of the fetus, or should the fetus be artificially immunized *in utero*, then stimulation of lymphoid functions may occur. In both the infected human fetus and the immunized fetal lamb, the stimulus to antibody formation is accompanied by the differentiation of plasma cells and by a greater or lesser degree of precocious lymphoid activity. There is increased cellularity of the lymphoid tissue and often the formation of secondary follicles. But it must not be thought

that these two developments invariably proceed hand in hand. Pronounced plasmacytosis in a lymph node that showed no other signs of precocious lymphoid development is often seen. Similarly, a highly activated lymphoid tissue with mature reaction centers can be seen in response to the same congenital infectious process, with no signs of plasmacytosis (*9*).

The possibility exists that these stimuli to lymphoid activity may have at least two components, a nonspecific lymphoid stimulant and an immunologically specific antigenic stimulus. The antigenic stimulus would presumably be responsible for the proliferation of immunologically competent cells and the formation of antibody. The immunologically nonspecific component of the stimulus may be operating when a young fetus is immunized with a Freund's adjuvant containing antigens to which the fetus cannot yet respond. In this instance, there is an abrupt and precocious maturation of lymphoid tissue in the fetus, with the formation of large amounts of 7*S* γ-globulin lacking in demonstrable antibody activity —a possible contradiction to the idea that all γ-globulin represents specific antibody for one or another antigen. This "normal" γ-globulin may in fact represent the product of a more general nonimmunologic lymphoid function, of which specific antibody may be only a special case (*21*).

Some peculiarities in the lymphoid response to homografts in the fetal lamb (*19*) should be mentioned here. When the animal responds immunologically to the foreign graft by rejection, the lymph nodes draining the graft site undergo a pronounced change, showing extensive hyperplasia and the formation of large numbers of large pyroninophilic lymphocytes and small lymphocytes. But plasma cells do not accompany this lymphadenopathy and the nodes, despite their immunologic hyperactivity, do not form γ-globulins to any appreciable extent. These observations lend additional support to the view that homograft rejection is mediated by a cellular mechanism, without the obligatory participation of humoral antibody.

Immunogenic Disease

Discussions of disease caused by immunologic factors generally center on either the common allergies such as hay fever, asthma, and the like, or else on autoimmune diseases such as hemolytic anemias, thyroiditis, allergic encephalomyelitis, and similar conditions resulting from the development of immune responses to presumably native antigens. There are several other disease processes. however, intimately associated with the process of immunogenesis in the fetus, that provide a new insight into the role of immunobiologic factors in the pathogenesis of disease.

Many disease processes cannot be explained adequately on the basis of the direct effects of the pathogenic agent on infected host tissues. Many pathologic changes also reflect the active response of the host in its contest with the pathogen. I shall cite two examples to illustrate that when the host for some reason cannot respond to the pathogenic organism, disease may not ensue despite infestation with the pathogen. Thus, the response by the host to infection may in some instances be kindled by purely immunologic mechanisms.

Lymphocytic choriomeningitis (LCM) is a naturally occurring viral disease of mice. Innoculation of the virus into normal laboratory mice produces a severe and often fatal illness. This virus may persist in the blood and tissues of certain mice, however, without causing signs of disease, and the disease cannot be evoked in these animals by injection of additional virus. Mice that were infected but not diseased have been shown to have received the virus *in utero* from their nonlethally infected mothers (*22*). Thus, infection with virus during early developmental stages seemed to render the mouse thenceforth resistant to the disease. To explain this curious phenomenon, Burnet and Fenner (*5*) suggested that immunologic tolerance of the virus had occurred owing to the presence of this antigen during immunologic maturation. With the establishment of tolerance and with a persistence of the virus in the mouse, the virus would never thereafter be able to induce an immune response in the host.

A paradox is thus presented by the lymphocytic choriomeningitis virus. We are accustomed to consider that pathogens may ravage a host unable to defend itself immunologically, and that only a well-functioning immune system offers protection against extensive disease induced by viral pathogens. Here is a situation where inability to develop an immune response to a viral pathogen appears to render that pathogen innocuous, while the "proper" function of the immunologic apparatus spells disease for the host. The lymphocytic choriomeningitis disease in mice, then, would appear to be not so much a "viral disease" as an immunologic disease of the host, triggered by the virus. The symptoms of this disease may represent nothing more than an immunologic reaction of the host to the viral antigens (*23*).

The contributions of immune reactions to lymphocytic choriomeningitis disease are emphasized by the absence of the disease process when immune mechanisms are specifically suppressed. Another instance where the host cannot develop an immune response to an antigenic pathogen is encountered in the developing young, before its immunologic capabilities have matured. At this stage the foreign antigen goes unrecognized, presumably because competent cells have not as yet appeared on the scene.

In the case of human fetal infection with German measles during the first trimester of gestation, immunologic factors appear to be absent. The virus seems to interfere directly with cellular metabolism and organ development, resulting in congenital deformities. On the other hand, transuterine infection of the human fetus with *Treponema pallidum* results in congenital syphilis of the fetal host with an extensive inflammatory response. In this instance, immunologic factors appear to participate, since the fetus forms plasma cells as an integral part of its response to this highly antigenic organism.

Congenital syphilis is usually not considered an "immunologic" disease, but rather its lesions seem to include at best a minor immunologic component. But the typical disease is never seen much before the 5th or 6th month of gestation, the age at which the placenta was first supposed capable of transmitting treponemes from mother to fetus. However, treponemes have been reported in rare instances in younger fetuses (*24*), but the typical pathologic picture of the disease congenital syphilis was lacking. The possibility exists that the organism might infest and grow in the fetus without eliciting a typical host response, because the fetus at that age is not yet capable of responding.

This situation might thus represent another instance of a "pathogen" appearing to be innocuous and failing to incite a disease process. The disease proper, with its attendant lesions and

embarrassment of the fetus, might only appear when the fetal response mechanisms become mature, presumably at about 5 to 6 months gestation (*9*). The rarity of a finding of fetal treponematosis without overt disease is readily understandable since in the absence of active disease, the fetus would not precipitate abortion and would rarely be seen. Also, in the absence of the overt inflammatory lesions typical of congenital syphilis the tissues would rarely be searched for the presence of treponemes.

Both the instances discussed raise important questions about the nature of pathogen-host interactions that result in disease processes. They suggest also that the ontogenesis of immunologic capabilities in the developing young may have its drawbacks as well as its advantages.

Maternal-Fetal Relations

The acquisition of immunologic competence by the human fetus and its intra-uterine formation of antibodies may have suicidal consequences. The close proximity of the fetus to its mother raises the question also of whether she too might participate in some manner in the general fetal response to infection.

The normal human fetus does not form γ-globulins. Any such proteins found in the fetal circulation are of maternal origin, since the human placenta is permeable to a number of these immuno-globulins (*25*). Only the infected fetus, attempting to combat a pathogen, is incited to an active formation of γ-globulins on its own behalf (*9*). It is probable that certain of these fetal γ-globulins would find their way across the placenta into the maternal circulation, perhaps with consequences for the fetus.

The γ-globulins within a number of mammalian species are not all identical, but may differ in antigenic structure from one individual to another (*26*). The formation of these "allotypic" γ-globulins is under a genetic control similar to that which determines the antigenic makeup of the animal's red cells. In the human, several such γ-globulin determinants have already been described (*26, 27*).

When the human fetus produces paternally determined red cell antigens (Rh, A, or B blood types) that are lacking in the mother, it sometimes happens that these antigens cross the placenta and induce an antibody response in the mother. The passage of these maternal antibodies across the placenta leads to an immunologic reaction with, and destruction of, the fetal red cells, causing the disease erythroblastosis fetalis. Here the fetus is not actively engaged in an immune response, but merely suffers passively from the destructive effects of its mother's antibody on its own paternally derived antigens.

In a similar way, a fetus might respond to an infection with the formation of paternally determined γ-globulins with antigenic determinants not shared by the mother. Crossing the placenta, these proteins would elicit an antibody response in the mother. Again the maternal antibodies, finding their way across the placenta to the fetal circulation, might lead to an allergic reaction in the fetus, in a manner analogous to that accompanying erythroblastosis fetalis. It is significant in this respect that the placental pathology in both erythroblastosis fetalis and congenital syphilis are so similar that they are often confused (*24*). In neither case has a satisfactory basis been provided for the pathogenesis of the placental lesions. In both instances, the placenta would represent the first tissue in which maternally derived antibody might react with antigen from the fetal circulation, giving rise to an allergic reaction that would prove embarrassing to the fetus.

Only an abnormal fetus, infected with a pathogenic organism that had stimulated its immunologic responses, would actively form γ-globulins before birth. A maternal mechanism permitting a destructive response to such aberrant fetal activity would thus constitute a significant contribution to the maintenance of species integrity.

Summary

Three principal points emerge from this brief examination of immunogenesis in the mammalian fetus. The first is that the fetus of at least some species may engage in immunologic responses if suitably stimulated with antigen. Whether maturation of immunologic competence is merely the by-product of some more general biologic development or whether it constitutes a distinct biologic function of its own remains to be established.

Second, the fetus does not appear to develop its immunologic competence simultaneously with respect to all antigens. It recognizes and responds specifically to some of them very early in gestation, to others only later, and to several antigens only some time after birth. The nature of this apparent stepwise maturation is not clear, but its existence poses interesting theoretical questions.

Finally, the acquisition of immunologic competence presents the fetus with an efficient mechanism of defense and, at the same time, with a disease-producing mechanism. Certain organisms may only cause disease when they can stimulate an immune response. Immunologic nonreactivity to otherwise pathogenic agents may render them innocuous to the host.

The possibility that the mother might also respond to antibody formed by the fetus in a manner detrimental to fetal well-being is another indication of the broad pathobiologic implications of the development of immunologic responses by the mammalian fetus.

References and Notes

1. J. D. Ebert and L. E. Delanney, *Natl. Cancer Inst. Monograph No.* **2**, 73 (1960); J. F. A. P. Miller and A. J. S. Davis, *Ann. Rev. Med.*, in press.
2. M. Hasek, A. Lengerova, T. Hraba, *Advan. Immunol.* **1**, 1 (1961); R. T. Smith, *ibid.*, p. 67.
3. B. H. Waksman, *Medicine*, **41**, 93 (1962).
4. R. D. Owen, *Science*, **102**, 400 (1945).
5. F. M. Burnet and F. Fenner, *The Production of Antibodies* (Macmillan, Melbourne, 1949).
6. F. M. Burnet, *The Clonal Selection Theory of Acquired Immunity* (Vanderbilt Univ. Press, Nashville, 1959); D. W. Talmadge, *Science* **129**, 1643 (1959); J. Lederberg, *ibid.* **129**, 1649 (1959).
7. J. J. Osborn, J. Dancis, J. F. Julia, *Pediatrics* **9**, 736 (1952); R. T. Smith and R. A. Bridges, *J. Exptl. Med.* **108**, 227 (1958).
8. R. A. Bridges, R. M. Condie, S. J. Zak, R. L. Good, *J. Lab. Clin. Med.* **53**, 331 (1959); M. M. Black and F. D. Speer, *Blood* **14**, 848 (1959).
9. A. M. Silverstein and R. J. Lukes, *Lab. Invest.* **11**, 918 (1962); A. M. Silverstein, *Nature* **194**, 196 (1962).
10. G. J. Thorbecke, *Ann. N.Y. Acad. Sci.* **78**, 237 (1959).
11. J. W. Uhr, J. Dancis, E. C. Franklin, M. S. Finkelstein, E. W. Lewis, *J. Clin. Invest.* **41**, 1509 (1962); J. W. Uhr, J. Dancis, C. G. Newman, *Nature* **187**, 1130 (1960).
12. D. B. Shaul, *Bull. Res. Council Israel* **10E**, 45 (1962).
13. K. L. Fennestad and C. Borg-Petersen, *J. Infect. Diseases* **110**, 63 (1962); S. E. Kalmutz, *Nature* **193**, 851 (1962); M. F. La Via, D. T. Rowlands, M. Block, *Science* **140**, 1219 (1963).
14. J. W. Uhr, *Nature* **187**, 957 (1960).
15. P. G. Schinkel and K. A. Ferguson, *Australian J. Exptl. Biol. Med. Sci.* **6**, 533 (1953); A. M. Silverstein, R. A. Prendergast, K. L. Kraner, *Science* **142**, 1172 (1963).
16. B. Benacerraf, A. Ojeda, P. H. Maurer, *J. Exptl. Med.* **118**, 945 (1963).
17. J. W. Uhr, *Science*, in press.
18. G. E. W. Wolstenholme and M. P. Cameron, Eds., *Transplantation* (Little, Brown, Boston, 1962).
19. A. M. Silverstein, R. A. Prendergast, K. L. Kraner, *J. Exptl. Med.* **119**, 955 (1964).

20. J. F. A. P. Miller, *Science*, in press.
21. J. Sterzl, J. Kostka, I. Riha, L. Mandel, *Folia Microbiol.* **5**, 29 (1960); A. M. Silverstein and R. A. Prendergast, *Blood* **22**, 770 (1963); A. M. Silverstein, G. J. Thorbecke, K. L. Kraner, R. J. Lukes, *J. Immunol.* **91**, 384 (1963).
22. E. Traub, *J. Exptl. Med.* **69**, 801 (1939).
23. J. Hotchin, in *Cold Spring Harbor Symp. Quant. Biol.* **27**, 479 (1962).
24. D. Stowens, *Pediatric Pathology* (Williams and Wilkins, Baltimore, 1959), p. 187.
25. F. W. R. Brambell, *Biol. Rev.* **33**, 488 (1958).
26. J. L. Fahey, *Advan. Immunol.* **2**, 41 (1962).
27. E. C. Franklin, H. Fudenberg, M. Meltzer, D. R. Stanworth, *Proc. Natl. Acad. Sci. U.S.* **48**, 914 (1962); M. Harboe, C. K. Osterland, M. Mannik, H. G. Kunkel, *J. Exptl. Med.* **116**, 719 (1962).
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Earth Science Today

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Earth, air, fire, and water, the "elements" of the Aristotelian philosophers, remain the foci of interest for the modern devotees of Ge or Gaia, Greek goddess of the earth, who gave her name to the science of geology, or, more broadly, earth science. It is ironical that the Latin or "scientific" term should have had to be translated to its English or "vulgar" equivalent to give the subject its present healthy breadth. This happened because geology as practiced up to the forties had come pretty generally to imply specifically the study of those parts of the solid earth accessible to direct methods of observation. The use of indirect methods of observation to study the solid earth became known as geophysics, and the realms of air and water were temporarily abdicated. Fire, in the form of volcanology, remained in the bosom of geology, but the problem of the sources and gradients of terrestrial heat was shared with the geophysicists. Geochemistry and paleontology remained linked with the mother science in the basic methodology of direct observation, and usually in name, although they have outside affiliations and have had their separationist movements.

Why is it that we now see, all over the world, not only a continued proliferation of subdisciplines and specialties, but also an ever-increasing overlap of interest between fields once thought remote from one another, and growing cohesive forces of the type manifested by the increasing use of *earth science* to include air and water as well as earth and fire? This reflects what I consider to be the most distinctive and stimulating feature of modern science as a whole—the renewed realization, after a long period of isolationism, that all forms of truth and comprehension are interrelated, and that all of science, whether pure or applied, has a basic coherence under the universal laws of physics and mathematics, with chemistry and biology as first-order derivatives. What unites the earth sciences as an independent affiliated grouping of derived and integrating disciplines is their common interest in the structure, composition, dynamics, and history of the solar system, and, in particular, the earth. What is most characteristic philosophically, and most gratifying to me personally, about the earth sciences today is their blending of the useful parts of classical science with the most exciting aspects of advancing science.

Obsolescence, if recognized, is the surest sign of progress. It is manifested in classical science by diminishing productivity in ideas or useful applications of some area once at the forefront of advancing science. It is manifested in advancing science by the discovery that what once looked like the mainstream or an important short cut has proved on travel to be a bayou or a blind alley, or by the simple exhaustion of the new things that can be discovered by a given technique. Another characteristic and healthy feature of earth science in the modern world is the rapid rate of obsolescence in both classical and peripheral efforts. All of the systematic sciences, and I use *systematic* in the broad sense of classifying *and* explaining, are in a state of ferment as new equipment, new measurements, and improved computer facilities provide different and in some instances more fundamental bases for classification and rapid quantitative methods of evaluation—this is true, not only of mineralogy but also of paleontology and petrology. In geochemistry and geophysics, once promising methods of investigation of geologic age, geothermometry, and remote sensing of physical properties are abandoned almost as regularly as new ones are invented. We must expect both fewer striking advances and fewer flat failures in the remaining useful areas of classical science, because so much has been tried already, and both more striking successes and a larger number of flat failures in advancing science, because so much is new. It is merely important to bear in mind that a good balance of the two is necessary—the new because the largest individual gains are likely to be made here, the classical not only because it provides the annealing matrix, the tempering perspective, and the ultimate base line against which advances in the forefront fields are measured, but because it is here that most of the questions arise and here that many of them will continue to be answered.

It is sobering to bear in mind also that the current revolution in science is based largely on, and probably could not have happened without, the revolution in instrumentation born of mortal conflict between nations. As happened after the invention of the plain-light microscope, the Nicol prism, and other important tools, the more significant new things that can be learned with this new instrumentation will also tend to become mined out. This makes our findings no less exciting, but reminds us that the revolution can be sustained only in a framework of continually advancing in-

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