

The Journal of Allergy

VOL. 27

MAY, 1956

No. 3

Original Articles

BACTERIAL HYPERSENSITIVITY

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DISCUSSIONS of the hypersensitive states usually follow a simplified category; these states are referred to as immediate or delayed in type. The former includes those allergic situations in which reactivity to antigen is likely to be rapid, in which a rather limited number of tissue types become involved in the reaction, and in which humoral antibody is demonstrably related to the reactive state. The delayed states encompass those which we also know by the terms "infectious hypersensitivity" and "contact allergy." In these, reactivity following exposure to antigen is relatively slow in appearing; there may be a wide range of cellular types involved in the reaction; and no conclusive evidence of relationship of humoral antibodies to these hypersensitivities has yet been put forward. It seems doubtful that in the long run these characterizations will remain intact. There is some question, for example, about the second point—whether in delayed hypersensitivity tissue reactivity is really as widespread as has generally been thought—and there is current question also as to whether or not an unusual kind of humoral antibody may be concerned in delayed hypersensitivity. Whatever time may bring forth in the way of clarification of these and other questions, the fact remains that the contact and infectious allergies do show certain striking differences from the immediate hypersensitivities, and consequently will probably always require special consideration.

Most of you here deal chiefly with the various manifestations of immediate hypersensitivity and, in the area of delayed hypersensitivity, with contact allergy in your practices. Unless I am much mistaken, few of you are ever directly concerned with the bacterial allergies, and this is so in part because these hypersensitivities are in a sense hidden among the multiple events transpiring during the courses of infectious diseases. In most such diseases it seems doubtful that hypersensitive reactivity plays an important role in the

From the Department of Medical Microbiology, Stanford University School of Medicine.
Read before the American Academy of Allergy, St. Louis, Missouri, Feb. 7, 1956.
Received for publication Feb. 6, 1956.

pathogenesis of the total infectious process; in the restricted instances in which it does, as in tuberculosis or lymphogranuloma venereum where tissue destruction is chiefly the result of such allergic reactivity, the medical responsibility falls outside your scope.

This means that the subject of bacterial hypersensitivity really represents for many clinicians an exercise in the intellectual effort to understand these processes, whatever their immediate implications with respect to therapy or control. I assume that it is chiefly for this reason that you have asked me to discuss this subject and, acting on this assumption, I shall try to present three of the principal facets of these hypersensitivities: first, the mechanism through which the bacterial hypersensitivities develop; second, the cellular origin of these immunologic responses; and, third, the tissues and cells concerned in the reactive state.

1. *The Induction of Bacterial Sensitivity.*—It has been known for many years that the delayed allergic states which accompany infectious processes cannot be reproduced by the isolated antigenic substances of the causative organisms. Conversely, it has also been known that animals infected, for example, with the tubercle bacillus and highly sensitive to constituents of this organism in the delayed fashion might frequently be anaphylactically totally unreactive.^{1, 2} These observations indicate that the two states—the immediate anaphylactic and the delayed infectious—are not disposed to appear under the same circumstances of antigenic stimulation, despite the fact that they can both be responses to the same antigen. This may be restated in simplified experimental terms: if the proteins from the tubercle bacillus are injected into appropriate experimental subjects, these soon become anaphylactically sensitive but never sensitive in the delayed sense; conversely, if tubercle bacilli are introduced into experimental animals, they develop bacterial hypersensitivity to the same protein, and may or may not become anaphylactically sensitive also.

A few years ago we began to make a study of the various isolatable constituents of the tubercle bacillus in relationship to immunologic responses, and soon found that when bacilli had been deprived of lipids extractable by chloroform they simultaneously lost the ability to induce bacterial hypersensitivity, although the protein antigenicity of the treated bacillary bodies remained virtually intact. Upon re-adding extracted constituents to these defatted bodies, and administering the various combinations to animals, it was then found that a fatty substance characterized by Anderson³ as a “wax” was essential for the sensitizing process, and further that the activity of this substance was of nonantigenic character; that is, the presence of this substance in the tissues simultaneously with antigenic proteins of the organism in some way causes the responding animal to develop the bacterial type of hypersensitivity. Subsequent and still continuing studies have brought us closer to appreciation of the nature of the active principle of the lipid; this consists of an 88 carbon fatty acid called mycolic acid esterified with a polysaccharide of molecular weight probably in the neighborhood of 8,000 to 10,000.⁴⁻⁹ More

recent studies in conjunction with Drs. Lederer and Asselineau of Paris indicate further that this activity in the sensitization process is possessed by other esters of mycolic acid; for example, galactose or a trisaccharide mycolate, or even the simple methyl mycolate, will also act in this fashion.^{10, 11} Furthermore, such lipoidal factors serve to direct sensitization to antigens unrelated to the tubercle bacillus, as, for example, egg albumin¹² and piceryl chloride.¹³ The mechanism through which the lipid plays its role is not yet known; whether it increases cellular permeability to antigen, stimulates the proliferation of certain cell types which may be responsible for the origin of delayed hypersensitivity, or simply stimulates existing cells to increased activity are questions which themselves require extensive discussion and which I have not included for consideration here.¹⁴

This chemical explanation for the development of one of the major bacterial hypersensitivities is unfortunately not readily transposable to hypersensitive states in the case of other infectious agents. During the past several years we have attempted to demonstrate a similar chemical-biologic relationship of lipids and antigens in the development of sensitivity to a hemolytic streptococcus, to the fungus *Aspergillus niger*, and to a virus, vaccinia. In all three instances there have been suggestive results, but in no case has there been the clear-cut delineation of this relationship so readily seen in the case of tuberculosis. This may be accounted for by our ignorance of the specific chemical nature of the substances for which we seek and improper manipulations in trying to remove them from cells, and it may depend in part upon the lesser degree of sensitization to these infectious agents than occurs in tuberculosis, with increased difficulty in assessing observations. In any case, our observations, though not definitive, have been sufficiently suggestive to keep us on this track.

2. Origin of Delayed Hypersensitivity.—The problem of cellular origin of bacterial hypersensitivity may be stated in this way: Are the cells which are responsible for the manufacture of humoral antibody also responsible for the development of bacterial hypersensitivity? If so, then the bacterial hypersensitive response may be considered a somewhat aberrant variant of the humoral antibody response, perhaps in the sense that atopic reagins possess distinctive peculiarities in relation to the more conventional serologically active antibodies. If not, then bacterial hypersensitivity may constitute a response which is fundamentally different from the humoral antibody response.

All of you know that there is no clear answer to this question now, but there are a number of interesting trails of evidence which may be converging upon the goal.

First, since we are considering the origin of delayed hypersensitivity on a basis of comparing this with the origin of humoral antibodies, we should briefly survey what is known about the source of antibodies. In past years it was generally thought that macrophages of the reticuloendothelial system synthesize antibodies, and a good deal of cogent evidence was advanced to support this viewpoint, including the fact that these cells take up foreign

material, soluble as well as particulate, that "blockade" of the phagocytic system results in suppression of antibody formation, and that macrophages observed while living appear to shed cytoplasm (possibly antibody globulin) and in tissue cultures appear to manufacture globulin.¹⁵ This viewpoint has gone by the board for, although the ability of these cells to ingest foreign substances has never been in question, newer methods of searching for antibodies in tissues have failed to reveal them in macrophages.¹⁶⁻¹⁹ About ten years ago the lymphocytes came into prominence in this respect, chiefly on the basis of evidence provided by the effects of adrenal cortical extracts upon antibody formation,^{20, 21} and at about the same time evidence was adduced from cytologic studies of patients with myelomatosis and hypergamma-globulinemia,^{22, 23} as well as from direct studies of antibody production that plasma cells may manufacture globulin and antibody.²⁴⁻²⁸ The question as to the relative place and importance of these last two cell types in antibody manufacture has not yet been fully resolved. Lymphocytes appear to have some vital role in the total process of antibody synthesis, as indicated especially by the fact that cellular suspensions consisting almost entirely of lympho-

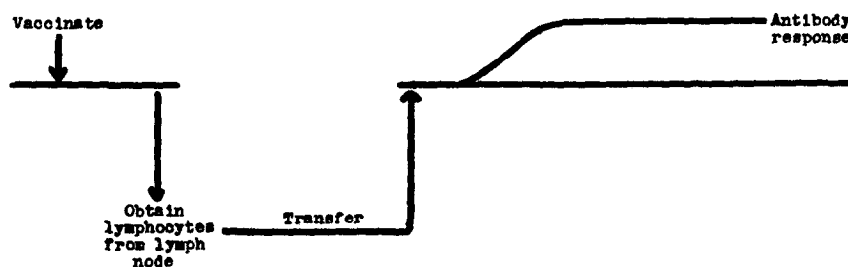


Fig. 1.—Evidence for lymphocyte origin of humoral antibody.

cytes teased from nodes of vaccinated animals can transfer to an irradiated recipient the ability to develop antibodies after an appropriate period (Fig. 1).²⁹⁻³⁸ On the other hand, it is difficult to regard the lymphocyte as the ultimate cell concerned in antibody formation for several reasons: (1) because direct examinations of tissues of vaccinated animals by tracer techniques show the antibody to be in plasma cells,¹⁶⁻¹⁹ (2) because patients with agammaglobulinemia who are unable to form antibodies are entirely lacking in plasma cells, even in lymph nodes regional to sites of vaccine injection³⁹ (Fig. 2), and (3) because of the extensive experiments with x-irradiation carried out during the past few years. These have revealed that, although total body irradiation applied in advance of an antigenic stimulus can be completely suppressive to the antibody response, there is a period of grace for some hours after irradiation during which administration of antigen can still be effective in eliciting almost the normal response (Fig. 3).⁴⁰⁻⁴⁸ This is impressive in view of the general agreement among pathologists that the lymphocytes are among the earliest cells destroyed by irradiation, within hours after its application. It would appear, from this, that lymphocytes and antigens may need to be together in the body for a short period only, and that subsequently antibodies

may continue to be produced by some radio-resistant cell (possibly the plasma cell) at a time when almost all lymphocytes have been destroyed. Robertson⁴⁹ has observed in rabbit ear chamber preparations that cells resembling lymphocytes may take up soluble antigen in the first few hours after its administration, but lymphoid cells with ingested antigen were not seen after the first day. Other observations also indicate that protein antigens reside in lymphocytes only transiently and to a limited extent.^{49a, and b}

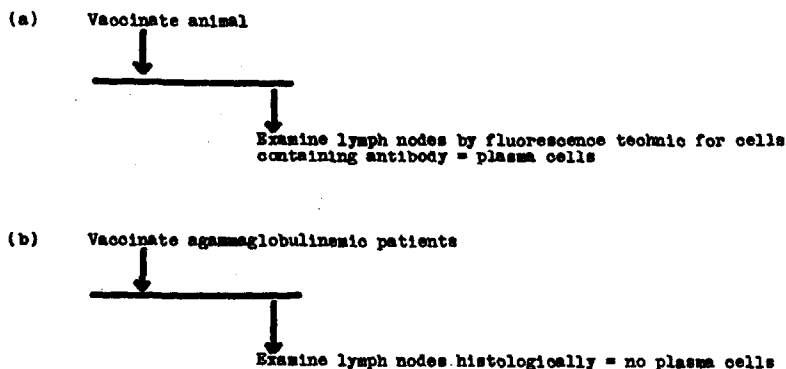


Fig. 2.—Evidence for plasma cell origin or humoral antibody.

The essence of researches so far carried out indicates, then, that plasma cells must be involved in antibody production, and that lymphocytes also must be concerned in the process in some fashion, possibly at an early stage in the reaction between antigen and the tissues of the responding animal. On this tentative basis, we can proceed to examine the question of origin of bacterial hypersensitivity.

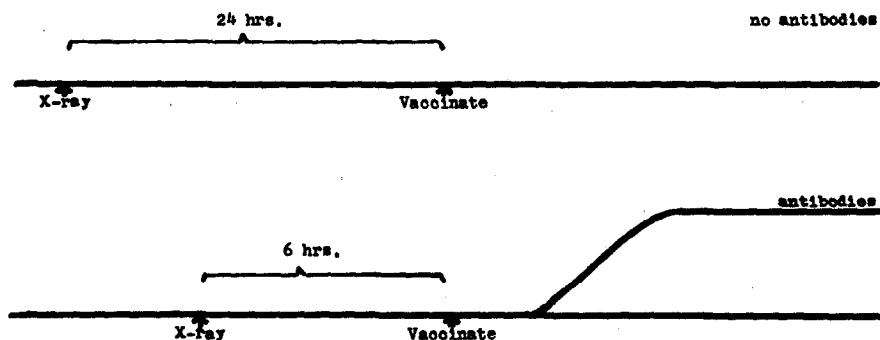


Fig. 3.—Evidence for possible preliminary role of lymphocyte in origin of humoral antibody.

A humoral antibody in bacterial hypersensitivity: For a good many years now, it has been the general opinion that the existence of bacterial hypersensitivity is not related to humoral antibody. There has been equally general agreement that features of this hypersensitivity—the period required for its induction, its specificity, and the occurrence of anamnesis—are sufficiently akin to features of humoral antibody development that some kind of cellular

antibody must be involved in this situation. Recently, Cole and Favour⁵⁰ reported that guinea pigs sensitized by killed tubercle bacilli possess an antibody which occurs in the alpha globulin of the plasma, and which can transfer to normal animals reactivity to tuberculin. They account for the failure of previous transfer studies with whole serum by the finding that the presence of gamma globulin, which contains antibodies of the "conventional" type to tuberculopolysaccharide, in some way inhibits the ability of the alpha fraction to transmit hypersensitivity. There is some precedent for the inhibition or masking of antibody activity by plasma components.^{51, 52} If Cole and Favour's observations prove to be confirmable, they could in one sense settle the issue of origin of bacterial hypersensitivity by relegating this to the same cells which manufacture other humoral antibodies; on the other hand, the fact that the sensitizing antibody resides in an unusual chemical portion of the plasma could well mean that its origin is not the same as that of antibodies of gamma globulin composition. For the present, at least, the observations of Cole and Favour cannot supply direct evidence upon the point in question. Other avenues, followed above in discussing the origin of humoral antibody, have been investigated also in relation to bacterial hypersensitivity.

Passive transfer: Turning now to studies of passive transfer of hypersensitivity by cells, we can compare what has been found here with observations made in the case of humoral antibodies. It has been known for a number of years, since early work of Bail⁵³ and later, more definitive studies by Chase⁵⁴ and others,⁵⁵⁻⁵⁷ that cells obtained from subjects with bacterial hypersensitivity can transmit this reactive state to normal recipients. In more recent work, cells teased from lymph nodes and consisting mainly of lymphocytes have been found to transmit the sensitivity, just as is true of humoral antibody.⁵⁸ On the surface, this coincidence seems to point directly to the conclusion that humoral antibodies and bacterial hypersensitivity must have a common cellular origin. However, certain observations do not permit so direct a conclusion.

Keeping in mind the tenuous state of knowledge about the lymphocyte's role in serum antibody production to begin with, several considerations give pause to acceptance of the idea that bacterial hypersensitivity arises from the same cells, or even via the same pathways, as do plasma antibodies.

In the first place, there may be fundamental differences between the transfer by lymphocytes of a potential ability to produce antibodies and of bacterial hypersensitivity. In the former instance, various studies referred to previously indicate that the transfer is not a direct passive one of antibody already existent in the cells but, rather, of a potential ability. That is, once cells have been planted in the recipient, there follows a *developing curve* of concentration of antibody in the plasma, a process akin to active production.^{29-38, 59} In the case of transfer of bacterial hypersensitivity, on the other hand, there is no real evidence of a similar progressive development in the recipient. Hypersensitivity appears rapidly and in toto, remains for its evanescent period, and disappears.⁶⁰ (Lawrence⁶¹ has found in human beings

that hypersensitivity to tuberculin and streptococcal products may be transferred by leukocytes, and that the reactivity in recipients arises late and may persist for months. This is in contrast to observations made in experimental animals, and has yet to be interpreted in this respect.) This contrast is graphically suggested by Fig. 4. This could mean that in the case of bacterial hypersensitivity the transferred cells simply bring over to the recipient their own already existing sensitization, and themselves react with the antigen employed to test the recipient. Information concerning the life span and the distribution in the recipient of transferred cells is consonant with this possibility.⁶⁰ If this is the case, the lymphocytes may represent simply one kind of sensitized cells of the allergic donor, rather than necessarily an origin of the hypersensitive state.

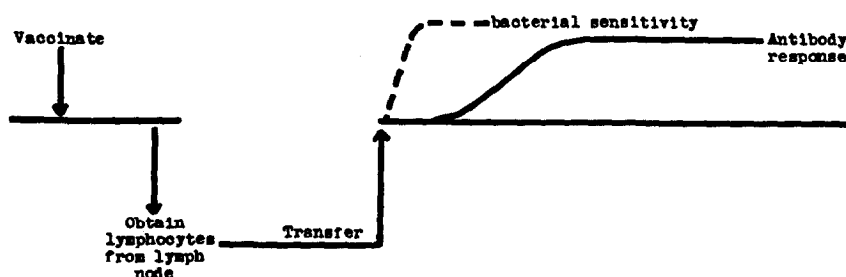


Fig. 4.—Evidence for lymphocyte origin of bacterial hypersensitivity.

If transferred bacterial hypersensitivity represents merely reactivity of the passaged cells in a new individual, one would expect that other sensitive tissues and cells might function like lymphocytes in this respect. There have been few trials of this point—Chase and his associates⁵⁸ state that monocytes collected from the peritoneal cavity probably lack the ability to transfer delayed hypersensitivity, and Kirchheimer and associates⁶² have failed also with granulocytes in guinea pigs. However, Lawrence^{61, 63} has successfully employed blood leukocytes for the purpose, and Schlange⁶⁴ has reported the transmission of tuberculin sensitivity via transfusions, in both cases in human beings. Obviously, lymphocytes were included among the cells transferred in these latter instances, but as minority constituents.

That some essential difference may exist between the cellular transfer of humoral antibody synthesis and of bacterial hypersensitivity is suggested also by the experiments of Good and Varco⁶⁵ in human subjects. The transfer of white cells from typhoid-paratyphoid-vaccinated normal donors to patients with agammaglobulinemia failed to induce in the recipients any circulating antibodies to these bacteria, while, on the other hand, the recipients did develop the bacterial hypersensitivity to streptococcal antigens which the donors had also possessed. This again implies that, in the case of bacterial hypersensitivity, cells may transfer an already existing state to a recipient who, because of lack of elements essential for completing the synthesis of humoral antibodies, is incapable of carrying forward this process.

Related to Good and Varco's experiment in the sense of revealing that the phenomena transmitted by cells to a recipient may be dissociable are the observations of Chase^{58, 59} in guinea pigs. If animals are sensitized with picryl chloride contained in an oily mixture in which killed tubercle bacilli are incorporated, they develop antibodies, anaphylactic sensitivity, and contact sensitivity to the picryl chloride, as shown in Fig. 5. (Contact sensitivity is generally considered an analogue of bacterial hypersensitivity.) The lymphocytes of these animals transfer to normal recipients all three of these properties. If, on the other hand, animals are given picryl chloride conjugated with protein, without the presence of tubercle bacilli in the sensitizing mixture, only the antibody and anaphylactic responses develop, as is well known. Lymphocytes from these animals transfer only these two kinds of reactivity to normal donors. In both experiments the donor animals are engaged in

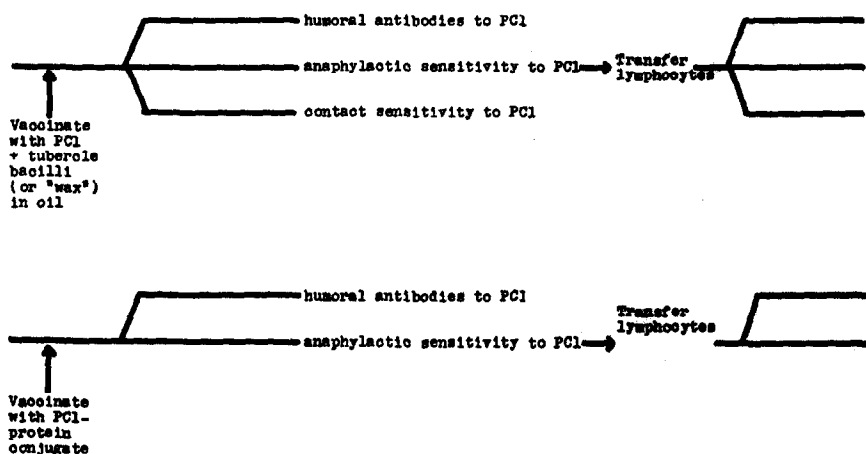


Fig. 5.

responding immunologically to a single chemical antigenic determinant; if in both cases the same cellular elements take part in the process, it is difficult to understand why, on transfer to recipients, these cells persist in transmitting only those responses of which the donors are capable. There must be some qualitative difference in the roles of these cells in the two instances.

Agammaglobulinemia: Studies of agammaglobulinemic patients have been mentioned in respect to passive transfer of bacterial hypersensitivity, but there is another aspect of origin to which data on such subjects may contribute. Since these patients are unable to produce antibodies, at least of the "conventional" kind (apparently no studies have been made of their ability to manufacture atopic reagins, which occur chiefly in the beta globulins⁶⁶⁻⁷⁰), it would be very pertinent to this discussion to inquire whether they are able to develop bacterial hypersensitivity. If they can do this in the absence of the ability to acquire plasma antibodies, the evidence would be strong for a dissociation of origin of these two entities.

The subjects studied by Good and Varco³⁹ were subjected to skin tests for hypersensitivity to the streptococcus, and the reactivity which is expected to occur in 80 per cent of normal subjects was absent in the agammaglobulinemic patients. In the case of tuberculin testing, however, the results were not so conclusively negative. Of seven patients tested, one developed erythema persisting for seventy-two hours after even a 1:10,000 dilution of Old Tuberculin, but this reaction was not accompanied by induration. These investigators decided, in view of the absence of reactivity to the streptococcus and of the atypical character of the tuberculin reaction in the responding patient, that agammaglobulinemic subjects fail to develop bacterial hypersensitivity. Again it would seem wise, for the present, to leave the decision open pending more information for, although there is undoubtedly a decreased incidence of hypersensitive states in these patients, these may occur nevertheless. I have learned recently of two other instances of positive reactivity to tuberculin in agammaglobulinemic subjects—one in a 35-year-old man observed by Drs. H. H. Zinneman and W. H. Hall of the Veterans Hospital in Minneapolis, and a second in a child studied by Drs. Edith Lincoln and Herbert Porter at Bellevue Hospital. Zinneman and Hall's patient lacked gamma globulin and all humoral antibodies, as indicated by the absence of isohemagglutinins. The child studied by Lincoln and Porter was not completely lacking in gamma globulins but its concentration was less than 1 per cent of the normal value. In this case, vaccination with BCG was followed after ten weeks by a positive reaction to Old Tuberculin in 1:10,000 dilution.

Suppressors of immunologic responses: A final line of evidence which bears upon the question of the origin of delayed hypersensitivity comes from studies of the influence of various suppressive agents, including x-irradiation, nitrogen mustard, and cortisone, upon immunologic responses. It seems clear, from the extensive work referred to earlier, that the exposure of animals to total body irradiation at appropriate periods before exposure to antigens may completely suppress the humoral antibody response (Fig. 3). Similarly, Lennox and co-workers⁷¹ have found that irradiation of rabbits just before inoculation of tubercle bacilli postpones the occurrence of tuberculin sensitivity. From such information, one might conclude that irradiation affects a process common to the elaboration of bacterial hypersensitivity as well as humoral antibody, but once again there is cause for question. In addition to the effect described, these investigators noted an influence of irradiation upon hypersensitivity which is not seen in the case of serum antibodies, namely, that exposure of animals to x-rays *after* tuberculin sensitivity had developed resulted in the suppression of visible reactivity to the test antigen. (Surprisingly, histologic sections of tuberculin-tested areas revealed inflammatory responses which could not be differentiated in intensity from those appearing under ordinary conditions.) Recent work with guinea pigs⁷² also demonstrates that tuberculin reactivity is diminished in irradiated animals receiving cells from actively sensitized donors. In both instances, loss of the dermal manifestations of bacterial

hypersensitivity occurs in circumstances which do not interfere with the appearance of serum antibodies. One may question, then, whether the suppressive influence of prior irradiation upon the development of bacterial hypersensitivity may be due to some effect other than immunologic interference of the kind exerted upon serum antibody synthesis. Whatever the nature of this effect, Lennox and associates⁷¹ demonstrated that it is not direct radiation injury to the skin.

Like x-irradiation, nitrogen mustard has been shown by Orris and Eisen⁷³ to interfere with the development of tuberculin hypersensitivity, and the partially suppressive influence of cortisone in this respect is well known. Whether one or multiple aspects of immunologic responses are affected by such agents or whether effects upon nonimmunologic mechanisms (for example, the general anti-inflammatory activity of cortisone) accounts for such observations is not yet known.

In my opinion, these five facets of evidence bearing upon the origin of bacterial hypersensitivity do not necessarily disprove the contention that the cellular origin and development of bacterial hypersensitivity is equatable with that of humoral antibodies. In each instance, however, there are seen to be factors contradictory to such an equation, and these must be clarified before the general question can be settled in either direction.

3. Tissue Reactivity in Bacterial Hypersensitivity.—The final problem to be considered is that of extent of generalization of cellular reactivity in bacterial hypersensitivity. The status of this situation is, unfortunately, also sufficiently unsettled now as to permit only a recounting of existing evidence and an expression of personal opinion. The question as to which cells of the sensitized body are reactive to antigen is, in one respect, closely bound to that of the cellular origin of the hypersensitive state, for if it should eventuate that only one cell type is responsive to antigen, as one viewpoint proposes with respect to the lymphocyte, this would constitute strong evidence that this is also the cell in which hypersensitivity has its nascency. The latter consideration, however, will not be dealt with again here; this section will be concerned only with evidence regarding the hypersensitive reactivity of various tissues.

For some years, and especially since the writings of Rich,¹ it has been widely held that there is a general reactivity of tissues in the tuberculin type of hypersensitivity, with virtually all cells susceptible to injury upon exposure to antigen. This feature, in fact, has been considered one of the main points of distinction between the delayed and immediate types of reactivity, for in the latter more specialized "shock tissues" are involved. More recently evidence has appeared to question this viewpoint.

The work which led to the belief in generalized reactivity was carried out, for the most part, by exposing explanted cells of sensitive animals in

tissue culture to quantities of tuberculin or other appropriate antigen shown to be harmless to normal cells, and gauging the results in terms of cell migration and injury. A number of experimenters demonstrated, in addition, that cells from animals with immediate hypersensitivity to the same antigen were not injured under the same experimental conditions. For many of these tests, portions of hematopoietic tissue were used, commonly bone marrow or spleen. More recent affirmations of these results have been made with leukocytes and splenic tissue of guinea pigs,^{74, 75} with liver cells,^{76, 77} and with macrophages⁷⁸ and leukocytes⁷⁹ from tuberculous human beings. It bears mentioning, in this connection, that another type of test adds testimony to the concept that various cells of the hypersensitive body may be reactive to antigen. Antigen injected into the cornea, a tissue without blood supply and composed of specialized cell types, evokes distinct reactions in animals with bacterial hypersensitivity, but not in those having only serum antibodies directed against the same antigenic substance.^{1, 6, 12, 15}

The opposing viewpoint—that hypersensitive reactivity is limited in its cellular distribution—supposes, of necessity, that the special cell type which does become sensitized lends its reactivity to other tissues. This would explain, for example, how dermal reactions can occur even though only lymphocytes are responsive to antigen. In some quarters lymphocytes and, in others, cells of mesenchymal origin are thought to partake in sensitization.^{80, 81} The process by which such cells are supposed to provide reactivity to other tissues is either through liberation of contained antibody or, by virtue of their potential ubiquity, by themselves reacting with antigen in whatever area a test injection may be deposited.

The experimental evidence supporting this viewpoint is more varied in nature than that on the other side of the question. Although direct tissue culture tests have been employed here also, with negative findings in the case of bone marrow⁸² and epithelial cells of liver and kidney,^{83, 84} other modes of study have included determinations of the effect of antigen upon the respiratory rates of sensitized and normal dermal cells *in vitro*,^{80, 81} assays of release of lysozyme from leukocytes as a measure of injury,⁸⁵ and visual as well as respirometric and glycolytic observations of cells from pleural exudates induced by injections of Old Tuberculin into sensitized and normal animals.⁸⁶ In all these cases little or no difference could be found as between cells from sensitive or normal donors.

Clearly, discussion of this problem at this time can do no more than bring to the surface the difficulties involved in arriving at conclusions. As is always the case when results of a negative nature are under consideration, the burden of proof remains with those who have failed to find a clear explanation in cytologic studies for the phenomenon of general tissue reactivity elicitable in the intact animal.

SUMMARY

In general résumé, the induction of one form of bacterial hypersensitivity, that to the tubercle bacillus, appears to depend upon the simultaneous activity of two bacillary constituents—the protein antigen and a fatty acid ester. In some as yet unknown way, these substances evoke in the normal subject a response to the antigen which we recognize as the bacterial type of hypersensitivity.

The avenue of immunologic response in this case probably will not turn out to be the same as that which leads to the appearance of humoral antibodies. It seems reasonable to believe that in the latter case lymphocytes may be involved in a preliminary stage of the response, with plasma cells later fabricating the finished product. In the case of bacterial hypersensitivity certain experiments, such as those involving passive transfer by cells, suppression of response by x-irradiation and other agents, and observations of agammaglobulinemic patients, suggest that the process may be the same, but in all these instances close inspection discloses sufficient contradictory information to hinder acceptance of this viewpoint.

Finally, the extent of involvement of various tissue and cell types in the reactive state is not clear. The fact that hypersensitive subjects respond locally as well as systemically to antigen in the absence of circulating antibodies gave rise quite naturally to the view that a widespread reactivity of cells is a characteristic of bacterial hypersensitivity. Pointed studies of this possibility in isolated tissue preparations have supported this viewpoint in the past, but recent contradictory experiments bring it into question. Considerable study will be required for the clarification of this and related questions.

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