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THE RELATION OF ALLERGY TO IMMUNITY.

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INTRODUCTORY.

IMMUNITY in the course of disease is a specific protection, either partial or absolute, which the host develops as a result of its experience in fighting an infection. In tuberculosis this shows as an ability to ward off bacillary reinfection entirely; or successfully to combat larger numbers of or more virulent bacilli; or to withstand a wider spread of the disease.

The term "allergy" is used to express the inflammatory reaction which takes place when bacillary protein is brought in contact with the cells of the body of an immunised host which previously have been sensitised in the course of natural infection or as a result of the artificial injection of living or dead bacilli.

Allergy develops coincident with immunity and remains as a potential reaction as long as infection exists in the body of the host.

THE EFFECT AND PURPOSE OF ALLERGY.

Any one who has administered the tuberculin test or who has had the opportunity of carefully observing cases of clinical tuberculosis has noted the exudative phenomena which are described under the term allergy. Allergy develops gradually after the primary infection, more promptly on reinoculation and remains as a factor throughout the course of the disease. Some students look upon allergy as primarily protective but under certain conditions harmful. A few, however, consider it first, last and all the time harmful and something to be avoided altogether.

A very important discussion of allergy has centred about the relationship which it bears to immunity. For many years it was taken for granted that allergy is a part of the specific defence which the host develops to combat infection; but recently the harmful effects which under certain circumstances may attend it have so impressed certain investigators as to make them doubt that it should be considered in any respect a protective mechanism. Anything that will add to the solution of this question should be welcomed.

FACTS ABOUT ALLERGY IN TUBERCULOSIS.

I believe that we can make progress in our discussion by holding in mind those features of the reaction which are self-evident.

We undoubtedly are on solid ground when we state that every

infectious disease has the property of stimulating the body of the host to the production of a specific defence or immunity, which may be either complete or relative. We further are sound, immunologically, when we state that during the incubation period of infectious diseases the host is not ill; but, that illness makes its appearance coincident with and is caused by the complex reactions of the host which are called out as he specifically opposes the infection. This statement does not ignore the fact that immunity may be produced in some instances in which the host reacts so feebly as not to disturb body functions nor to cause illness. In the conflict which goes on following infection the bacteria injure the tissues and the tissues react in protecting themselves and in injuring the bacteria. Certain limitations on the action of bacilli and certain injurious effects upon them have been assigned to allergy. No matter what opinion is held as to its purpose it is one of the specific reactions which develop in the presence of infection.

I would catalogue the following features of allergy in tuberculosis as being among those assigned to it by various observers:—

(1) Allergy develops coincident with specific defence.

(2) Allergy is a phenomenon which does not permanently disappear so long as tuberculous infection is unhealed. It may, however, become lowered or abolished temporarily during certain intercurrent diseases or conditions which are met during the life of the infected individual. It has been observed to disappear when the disease heals and on the excision of an experimental focus.

Liebermeister and his followers show that bacillæmia is common in tuberculosis and that it may occur at any time from the establishment of first infection in the tissues until the death of the patient; and suggest further that it may be the particular condition which keeps up the sensitisation of the cells when it has once been established. Furthermore, they suggest that reinoculations which take place by way of the blood stream are probably responsible for producing the more complete specific defence of the host which is developed during the long course of latency of the infection.

(3) Allergy is not a stable and fixed reaction but one which varies from time to time, even disappearing coincident with certain infections and cachexias.

(4) The allergic reaction is strongest as a rule during those periods when bacilli are multiplying and the tuberculous lesions are most active, provided the infection is not so severe as to overcome the resistance of the patient. Particularly is it marked with the primary complex and early metastases; but it also appears with later metastases. However, after the activity caused by the metastases has ceased, a certain degree of desensitisation appears; and, as a rule, advanced disease requires larger amounts of bacillary protein to bring about a given degree of reaction than the active stage of early lesions.

(5) Coincident with the allergic reaction certain definite, specific protective phenomena appear. Such are: a more rapid tissue reaction; a

derivation of protective cells to the site of infection; an increased phagocytosis; a dilution of toxins by the serous exudate; a partial exclusion of oxygen from the bacilli in the tissues brought about by the atelectasis and exudation present; an ability to ward off reinfection entirely, to cause new implantations of bacilli to become abortive, or to cause the lesion to be less serious should implantation occur; and a fixing of bacilli in situ or at least a retardation of their passage through the tissues.

(6) In diseases in which a permanent immunity is conveyed to the host, such as smallpox, a degree of cell sensitisation remains permanently and calls forth a feeble but accelerated reaction to revaccination, although the individual is insusceptible to marked response. We assume that he is usually protected against further infection.

Discussion.

The fact that allergy develops so early in the course of tuberculosis, appearing from one to three weeks after the implantation of bacilli; that it appears when dead bacilli are injected and when non-virulent bacilli are implanted, as well as when virulent bacilli cause the infection; that it decreases relatively as the volume of the disease increases; that it is due to a functional hypersensitivity of cells and hastens and magnifies the body's response to further invading bacilli or bacillary protein; that the patient shows an increased power to resist and limit infection when it is present; that the reaction as we produce it with tuberculin used therapeutically, as may be seen in such visible lesions as those of the eye and ulcerations of the tongue and larynx, is followed by improvement and healing; that it fixes the bacilli in situ where local abscesses are formed with discharge of bacilli; and that it stimulates open foci and causes them to throw off bacilli, thus aiding the host in ridding himself of bacilli, would seem to suggest that it is a phase of the protective mechanism. The fact that it may break down tissue, particularly when it is severe, is also evident; but when these other effects are taken into consideration, is there any justification for classifying it wholly as an undesirable and dangerous reaction?

A Comparison of Allergy as Manifested in Preponderantly Proliferative and Preponderantly Exudative Tuberculosis.—A discussion of the difference in reaction of preponderantly proliferative as compared with preponderantly exudative tuberculosis may throw some light on the problem, because allergy seems to play a very different rôle in these two pathologic pictures.

Preponderantly proliferative lesions are caused by bacilli in relatively small numbers and of relatively low virulence. While they sensitise the cells of the body and make them capable of reacting to bacillary protein with an exudative response, bacillary protein is produced in amounts so small that only a mild allergic inflammatory reaction is called forth; and, an immunity is developed which is so slight that it is wholly incompetent to protect the host against the repeated mild metastases which take place. The proliferative lesions, as the name implies, consist largely of a structural response. The bacilli are possibly protected to a certain degree by the

monocytes and their congeners, the epithelioid cells, as has been suggested by Sabin and her co-workers.

This form of tuberculosis is mild until metastases are produced by a larger number of bacilli than usual, possibly also bacilli of greater virulence; then larger quantities of bacillary substances are formed in the foci, more severe reactions follow, and the lesions assume characteristics of an exudative and even destructive nature. Although up to this time the lesion has been mild, yet it has lacked the "something" which is necessary to bring about a halt in its progress. Conspicuously absent have been both allergic response and specific defence.

In spite of mildness, proliferative tuberculosis shows a greater tendency to extension than to self-limitation. It also heals with difficulty. The fact that it is favourably influenced by therapeutic doses of tuberculin bears upon the question of whether or not allergy is a favourable or unfavourable reaction; for this response to tuberculin is a response to the protein which produces the allergic reaction and at the same time stimulates the immunising mechanism.

Predominantly proliferative lesions require a longer time for healing than do predominantly exudative processes of equal extent, even though the latter are more acute and are accompanied by more serious symptoms.

The response of the tissues in exudative tuberculosis also shows structural changes in the form of tubercles and other proliferative phenomena, but exudation both in and near the foci of disease, and often in tissues distant from them, dominates the pathological picture. The contents of caseous foci, including bacilli and substances which result both from bacillary metabolism and bacillary destruction, as well as products of tissue destruction, are liberated in larger amounts.

In pulmonary tuberculosis predominantly exudative lesions as well as proliferative lesions, which have taken on marked exudative characteristics, form metastases more often through bronchogenic spread than is the case in the more purely proliferative disease, particularly in its early stages, the bacilli which are responsible for the new implantations often being held in situ by the infecting mass obstructing a bronchus. The destructive effects are dependent largely upon the fact that large numbers of bacilli cause the new implantation.

In preponderantly exudative tuberculosis the infection is not co-extensive with the exudation, as is so nearly the case in the preponderantly proliferative lesion, and resolution of the exudate clears most of the pulmonary field. The lesion has less structural changes and apparently develops a more efficient defensive mechanism with the result that bacilli are destroyed more readily and bacillary substances are released in larger quantities. Hence, while the lesion shows greater inflammatory reaction and the symptoms are more acute, it may heal more completely and in a shorter period of time. While the lesion is accompanied by a greater degree of allergy it also seems to be accompanied by greater specific defence, for extension is held in check more successfully than is the case in the milder proliferative lesions. The relative absence or mildness of symptoms in preponderantly proliferative tuberculosis, as compared with the exudative

form, seems to mean, or at least is accompanied by, an absence of an adequate amount of the nonstructural elements in specific protection.

A study of predominantly proliferative and predominantly exudative lesions in relationship to extent of disease gives important information. The former may become widespread before a metastasis sufficiently severe to produce symptoms of acuteness appears; but no matter when it appears, it is due to the fact that in some focus or some foci within the infected area an unusual number of bacilli have become active and are multiplying and causing the usual destructive tissue effects as a result of which an increased quantity of focal substances escape into adjacent tissues and gain access to the circulation. An allergic response develops which corresponds with the degree of cell sensitisation and the amount of focal substances (protein) present. While the reaction shows a certain amount of destructive changes, it also possesses phases which mean increased specific protection, or at least which are accompanied by increased specific protection. In the early period of increased activity in proliferative lesions, destruction of tissue, as a rule, is limited to small foci, but later it may involve large areas, for, when destruction once starts greater numbers of bacilli become involved and larger quantities of bacillary protein and other focal products are engendered and widespread effects, even of a caseo-pneumonic type, may appear. The proliferative process now manifests phenomena similar to those which the predominantly exudative lesion manifests from the start.

Should activity quiet down and the destructive process be checked then these two types of tuberculosis would assume much the same status, except that the one shows destruction in the midst of a primarily proliferative process, the other, destruction in an area which was marked from the beginning as an exudative process. The body cells in both instances, for a time thereafter, would probably show a decreased sensitisation to bacillary protein and the patient would possess a relatively heightened specific defence.

The Double Aspects of Allergy.—After following the differences in these two predominating types of tuberculosis are we warranted in considering the allergic reaction as primarily and fundamentally harmful and apart from the immunity mechanism, or does it not seem more reasonable to look upon it as an integral and necessary part of specific defence, which, while beneficial in its milder form, may be injurious in its severe form? Is it not possible, too, that some of the harmful and destructive phenomena which accompany severe focal inflammation may be at least partly due to substances other than the allergic producing substances, for it must be remembered that caseation quickly follows epithelioid cell formation before allergy has been established. Again, may not the destructive action be conservative in that it prevents the bacilli from spreading through the tissues and causes them to form a local abscess which on rupturing rids the host of large quantities of bacilli and bacillary substances that otherwise might prove injurious? Does the caseation and necrosis of tissue which take place in tuberculosis differ in any way in principle from the caseation and rupture of the localised streptococcic abscess, or abscesses due to other micro-organisms? Angevine has recently shown that hæmolytic

streptococci, when injected into the skin of sensitised animals, produce a quicker inflammatory reaction, which results in necrosis and fixing of the micro-organisms in situ. He also points out that in the previously infected animal they multiply faster, which we would expect because of the larger numbers being held at the site of injection. In the normal animal, on the other hand, they quickly spread to the lymph glands and enter the blood-stream ; so a smaller number remain to multiply at the point of implantation.

As tuberculosis extends there is no doubt that the allergic response to a given amount of bacillary protein becomes relatively less severe, and further there is no doubt that the host becomes more resistant to infection and more able to withstand larger numbers of bacilli. This is true whether the infection heals or not. Every episode of infection through which the host passes, no matter what its nature, causes the body cells to be influenced for a time—sometimes permanently. Circulating antibodies may disappear soon after the disease has healed, but those fixed to the tissue cells may persist and even maintain the condition of sensitisation permanently.

Abortive implantations are frequently met in such visible organs as the eyes, glands and testicles, and also are frequently present, although determined with greater difficulty, in the lung. These temporary implantations are caused by relatively small numbers of bacilli in the tissues of an immunised host. They are accompanied by allergic phenomena, but not regularly followed by destruction. Are we wrong in assuming that sensitisation of the cells and the resultant allergic reaction are important factors in keeping these lesions from assuming aspects of severity and causing some of them to become abortive in character? There is doubt whether in the course of active disease reinfection of tissues and organs may ever occur without calling out some degree of allergy; and further, there is little evidence that any such reactions, except those caused by large numbers of bacilli, cause destruction of tissue.

Instances are reported in which the tuberculin tests may become negative after healing has occurred, but we have no absolute data to show that this was not simply a marked desensitisation and that a positive reaction would not have occurred had larger doses been administered, nor have we any data to show the status of such individuals as regards reinfection, whether they revert to a condition of absence of specific defence the same as prior to primary infection, or whether as a result of their experience they possess an increased resistance which is advantageous to them in fighting further infection. It is reported that Koch responded with a general reaction to 50 mg. of tuberculin, although he had failed to respond to 10 mg.

Certain experimental work has been carried out which shows that a certain degree of immunity can be produced in animals without a sufficient degree of sensitisation of the cells to produce allergy, and experimental animals have been desensitised by tuberculin so completely as to remove the sensitisation of the cells without interfering with immunity.

While it is very important that immunity has been produced without

allergy and that allergy has been removed without interfering with immunity, yet these facts do not definitely prove that there is no relationship between the allergic reaction and immunity. The relation of allergy to healing, as shown in the administration of tuberculin, seems to me definitely to show that allergy has a protective significance. While there may be a difference between allergy and the final stages of immunity, nevertheless there is very definite evidence that the allergic reaction has protective qualities.

When large reinoculations take place in the lungs of a tuberculous patient they are apt to cause cavities, but we do not regularly see extensive destruction caused by bacillary protein take place except in the foci where it is produced. In the Pottenger Sanatorium Laboratory we have made several thousand observations of the length of bacilli, in reference to activity and quiescence of lesions, and we have been able to show that an increase in the numbers of short as compared with the longer forms accompanies acute caseation and cavitation. The sputum at the time of these destructive effects teems with young bacilli, suggesting at least that the destruction is due to activity primarily within the focus, and presumably caused by the focal contents and not by circulating bacillary substances.

In order to understand sensitisation as we meet it in testing groups of people with tuberculin, or as we see it at the site of injection when tuberculin is used therapeutically, or as we follow it in the varying pathologic lesions of active tuberculosis, we must think of it as an ever-changing force. Because of the failure to recognise its variability much difference of opinion has come into our interpretation of the meaning of the reaction as exhibited in administering the tuberculin test.

It is a common observation among clinicians that a cavity of considerable dimensions may follow early reinfection and that thereafter reinoculation after reinoculation may take place over long periods of time without further large cavities forming. If we may draw any conclusion at all from this observation, it is that, as the disease progresses the patient becomes more highly immunised and the cells become desensitised to bacilli and bacillary protein ; for we cannot assume that the numbers of reinoculating bacilli grow less. This fact cannot be interpreted as meaning that allergy is harmful, but rather that as immunity becomes greater the allergic phenomena become less marked and probably less necessary for the host's protection. It indicates a very close association between allergy and immunity.

The allergic reaction met in tuberculosis cannot be compared with the exudative phenomena met in the so-called allergic diseases. There is a prompt skin response noted after intradermal injections of tuberculin, which quickly clears away and which Zinsser has likened to the immediate anaphylactic response to antigens shown by the asthmatic or hay-fever patient ; but the main allergic response in tuberculosis comes on later and does not clear away so quickly ; in fact, the allergic phenomena which appear during the clinical course of tuberculosis may last for weeks or months. There is no parallel between the allergy in asthma which may be relieved almost instantly by an injection of adrenalin and the allergy in tuberculosis which persists for weeks and months, regardless of any

remedy that we know. The former is largely serous; the latter, serous, cellular and fibrinous.

The number of instances in which a child or adult reacts with symptoms to a reinoculation of bacilli must be compared with the number of instances in which they overcome the infection without symptoms following. How often the latter occurs we have no way of knowing, but we are undoubtedly safe in assuming that it occurs often, because of the number of lesions found without the patient's knowledge. The frequency with which bacilli are found in the blood-stream of tuberculous patients without infection taking place, and the frequency with which infection follows without inciting symptoms is sufficient to indicate that allergy in itself is not injurious to the host, for some degree of allergy is probably a part of every reaction to reinfection. The fact that predominantly proliferative tuberculosis fails to show any marked allergic reaction and continues to spread in spite of its mildness, and the further fact that the allergic response brought about by tuberculin administered therapeutically is favourable to healing indicates that mild allergy is not harmful but favourable to the host.

While the allergic reaction produces symptoms which are characteristic of active disease, yet I fail to find any evidence to support the thesis that one who has developed cell sensitisation as a result of a tuberculous infection is thereby rendered more susceptible to reinfection or more prone to develop a progressive tuberculosis when reasonable numbers of bacilli again become implanted in his tissues. On the other hand, allergy gives information that the individual has attained an increased resistance to bacilli and hastens his specific reaction against them.

In the assumption on the part of certain students of tuberculosis that the primary infection heals but leaves the patient sensitised and particularly susceptible to superinfections of exogenous origin, is there not a confusion of the recognised fact that allergy, if sufficiently marked, produces symptoms, with an unproved fact that allergy is responsible for disease?

That the primary lesion heals so constantly, as is often assumed, is not borne out by facts; and that superinfection is so frequently of exogenous origin, as is assumed, is not proved. Pathologists who have given special attention to the subject have shown that many primary lesions are still in an unhealed state at the time of the death of the individual, even though years have elapsed since infection occurred.

We furthermore are warranted in assuming that incomplete healing in childhood is frequent. So we must always remember that from childhood henceforth an unhealed primary focus may be present as a source of reinfection. An unhealed lung focus or a lymph node with caseous contents offers a real threat to the individual any time after infection has occurred, and furnishes a more logical explanation for many superinfections than the assumption of a new infection from without. Allergy may attend reinfection in either case, but it seems more logical that larger quantities of bacilli should be given off into the bronchi from open lesions within the chest than that infecting doses of bacilli could readily be introduced from without. No one denies, however, that exogenous infection is a real source of disease.

In considering the probable source of reinfecting bacilli one must consider the ease with which bacilli, coming from within, may be carried by the blood-stream, or, mixed with focal débris, may be discharged in large numbers into the air passages where they may cling to the bronchial walls or even plug a bronchus and maintain contact sufficiently long for infection to take place. On the other hand, one must consider the difficulties which would be encountered by bacilli of exogenous origin. They would likely be fewer in number and be able to gain access to the air passages with greater difficulty than those of endogenous origin and then be obliged to enter the tissues against the normal as well as specific resistance which has been developed as a result of previous infection.

It is a condition precedent for bacilli readily to enter the tissues of those already infected that there must be a special aid such as a narrowed vessel, or a time contact, as in case of the larynx and intestinal tract, or a narrowing or closure of a bronchus. Clinical experience shows that the air passages and other surfaces of the tuberculous patient strongly resist the re-entry of bacilli, otherwise how can one explain the relative infrequency of infection of the bronchi, trachea, larynx and intestines in advanced disease where literally millions of bacilli come in contact with these surfaces daily? In spite of this fact, not only does reinfection and disease of these structures not take place commonly, but the patient may go on to healing, which could not be if the risk were so great as is assumed by those who teach that there is great danger of reinfection taking place because of the patient's ability to react allergically.

Summary.

(1) The phenomena which are recognised as belonging to allergy are shown to have protective characteristics, although when severe they may produce destructive effects.

(2) Preponderantly proliferative tuberculosis is shown to be largely a cellular response in which allergy is mild and immunity is inadequate.

(3) The therapeutic use of tuberculin in preponderantly proliferative tuberculosis causes mild allergy, checks the spread of the disease, and hastens healing, creating at the same time an immunity sufficient to overcome the disease.

(4) Preponderantly exudative tuberculosis, while more severe shows a more marked allergic response, appears to develop a greater specific defence and heals more satisfactorily.

(5) As tuberculosis advances the patient becomes less sensitive to bacillary protein, which makes it appear that allergy is of greatest service as a defensive mechanism during the early stages of infection prior to the time when the specific ability to resist bacilli which we designate as immunity has become more definitely established.

(6) The comparative ease with which endogenous reinfection can take place, as compared with the difficulties which bacilli of exogenous source encounter in gaining entrance to immune tissues, is discussed.

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