Reprinted from THE AMERICAN REVIEW OF TUBERCULOSIS
Vol. XLV, No. 6, JUNE, 1942

IMMUNITY IN TUBERCULOSIS

Clinical Considerations

F. M. POTTENGER[1]

THE NATURE OF IMMUNITY

Of the many valuable contributions to our knowledge of tuberculosis which were made by Allen Krause, those relating to immunity are of outstanding interest. So it is fitting to discuss the subject in this Memorial Issue.

It may be said truly that the tuberculous patient cures himself or kills himself by his own infection, meaning that each reinoculation which is within his capacity to defend himself increases his total resistance, and each reinoculation which is too large for him to counteract lowers his total resistance. Cure depends upon developing an increase in resistance or immunity to bacilli and bacillary substances. What will happen depends upon the character of the infection, that is, the number and virulence of the bacilli and the state of the host at the time. There is no chance of healing taking place if immunity fails, for immunity alone is able to protect against the multiplication of bacilli and their spread in the tissues and to bring about healing of the lesion. This may be understood by comparing primary infection produced by a sufficiently large number of bacilli to cause a disease which spreads rapidly and produces early death, with a chronic advanced disease in which the numbers of bacilli in the tissues are equally large and the opportunity for metastases forming is continuously great, and yet the disease advances slowly, if at all; in fact, may heal.

It is necessary that we attempt to understand of what this increased protection consists, how it is developed and how it performs its service. The fact that our opinions are confused calls for careful discussion rather than discouragement.

Koch made the first observation of the immunity mechanism at work in tuberculosis when he noted the difference between the local reaction caused by an inoculation of bacilli into a healthy and into an infected guinea pig. In the healthy pig he noted that the inoculation was followed at first by little more than the trauma caused by the injection, but that this enlarged to a fair-sized nodule in one, two or three weeks, according to the number of bacilli in the inoculum, after which it went on as a progressive process. In the tuberculous pig he also noted that an inflammatory reaction appeared at the site of infection, but this came on quickly in a few hours after inoculation and increased in severity; and, like that in the healthy pig, became nodular in about two weeks' time, but thereafter the course differed—it became retrogressive.

The important thing to stress in these observations is that in the nontuberculous pig the reaction is slow in appearing but the disease progresses, while in the tuberculous pig the reaction develops quickly but comes to a standstill and then

[1] Monrovia, California.

proceeds to retrogress. This shows that a change is brought about by the first inoculation which increases resistance. The mechanism responsible for this difference is recognized as immunity. It is a mechanism of many phases, affecting many tissues and involving many functions.

While immunity in tuberculosis is only relative, it is far from being a negligible mechanism. Clinicians, as a rule, give insufficient attention to it, for it is the most important factor in determining the character and course of the disease and a necessary one in healing. Experiments such as those of Koch, von Behring, Römer, Hamburger, Bartel, Wolff-Eisner, Löwenstein, Wright, Raw, Trudeau, Gilliland, Webb, von Ruck, Krause, Willis, Rich, Opie, Sewall, Menkin, Sabin, Lurie and many others, should be carefully studied by every one who treats tuberculosis, for they elucidate the basic facts of defense and healing. While many of these experiments can be criticized as having been carried out with inoculations of bacilli in which the numbers were far too large, thus failing to approach conditions of natural infection, yet they indicate how the host reacts to his disease.

Attempts have been made to separate the various phases of immunity; but this, from my understanding of the subject, is not only impossible but regrettable. It causes much confusion. Allergy has been associated largely with the inflammatory exudative reaction and, because of the violence of the reaction at times, there are those who see in it only harm to the host. Some speak of allergy in contradistinction to immunity. This is illogical. It perhaps would have saved confusion had the term "allergy" not been injected into our conception. We must understand it as being only one phase of tissue sensitization, while immunity includes all specific protective phenomena. In immunity we must consider that tissues, in the widest sense, body fluids, wandering cells as well as fixed cells, are sensitized to the invading microörganisms so that their action may be rendered more effective in protecting the host. If we define immunity in infection as an altered reaction of the host necessary to protect it from invading bacteria, we cannot help seeing that it is not only an inflammatory, exudative phenomenon caused by allergen-antibody reaction, but that it includes other altered reactions which exert an antibacillary effect and an inhibiting effect upon the multiplication of bacilli, and a favorable effect upon the production of tubercles; in fact, it is the whole defense picture.

It seems to me to clarify our ideas if we look upon the preponderantly exudative process, which is usually termed allergic, as a less complete, early phase of immunity; and look upon total specific defense as a later and more effective immunity. If one will analyze all known factors in immunity, he will see that they are all evidence of quickened and enhanced physiological functions brought about to meet the particular phase of infection present at the time. The thing that reinoculation does to the reaction is to hasten it and increase its efficiency. Immunity is always a protective and healing process, without which probably no tuberculous infection could heal, but a process the efficiency of which must be built up *pari passu* with the infection against which it protects.

HOW IS IMMUNITY PRODUCED?

If we attempt to understand the difference in reaction of the normal and the tuberculous animal to bacilli and bacillary products, we shall find the answer in the entire category of intimate phenomena called out to resist infection.

When bacilli enter the the tissues they attempt to destroy the local cells and convert them into pabulum to serve their needs during multiplication and growth. The cells of the body, on the other hand, attempt to destroy the bacilli and to check their development and growth. First infection meets less opposition than reinfection. As a result of this tissue-bacillus struggle, bacilli are destroyed and bacillary fractions in increasing amounts are set free into the tissues which they sensitize to further contact with bacillary products. Thereafter, when contacted by bacilli or bacillary proteins, the cells respond quickly with inflammation and exudation. If the same protein which sensitizes continues, in amounts which are not too large, to act upon the cells, it may cause desensitization and other phenomena such as a slower multiplication and an increased destruction of bacilli, and a more rapid and extensive tubercle formation, which indicate that the resistance of the host has been substantially increased. These are all phases of the increased resistance which we call immunity.

Man's normal physiological response may be sufficient to protect him against slight stimuli of various kinds; but, when stimuli are greater, an abnormal response is required to make the protective mechanism effective. This is true no matter what the nature of the stimulus.

The relation of physiological response to the type of force making the attack is shown in comparing protection against such diversified dangers as an approaching enemy and an infection. The reaction which prepares for defense or flight in case of the former is primarily an emotional response which is expressed through both the voluntary and involuntary nervous systems, through the glands of internal secretion and the electrolytic system. It is primarily an exaggeration of normal emotional reactions and accordingly initiates abnormal physiological response.

The reaction against bacteria in disease-producing numbers likewise consists of an increase in intensity of physiological response. It consists of increased cellular, nervous, hormonal and electrolytic reactions. It is an intensification of those functions of the body by which it normally is able to digest, destroy or retard growth and movement of bacteria and various fractions of bacteria should they gain entrance to the tissues in small amounts.

The important point is that ordinary defense is a normal physiological process, and immunity a heightening of these same physiological forces. They depart from normal activity because they are required to do so in order to be able to meet new and unusual stimuli.

The body, under normal conditions, is able to digest a limited amount of protein—either of bacterial or nonbacterial origin—which may gain access to the tissues. Each cell that enters into the structure of complex organisms car-

ries with it, as it evolves from lower life, a digestive function similar to that possessed by the simple unicellular amoeba. This comes into use in protecting it against bacteria or injurious foreign protein which gains access to the tissues. In case of infection probably the chief manner in which tissue digestion differs from normal cellular digestion is in the ever increasing amount of protein which it is obliged to destroy. Immunity against infectious disease, then, may be said to consist of the processes which the host marshals to digest, destroy or protect itself against bacteria and bacterial products which gain access to the tissues in amounts which, if not destroyed, would injure or threaten the life of the individual.

Immunity in tuberculosis starts to develop as soon as the infecting bacilli begin to multiply and the bacillary products in minute quantities begin to make their escape into the tissues. Our conception here includes not only solid tissues but the fluids of the body as well.

EFFECT OF IMMUNITY IN TUBERCULOSIS

What is the effect of the altered physiological reaction which we call immunity in tuberculous disease?

By comparing the phenomena which attend primary experimental infection with those of reinfection, certain facts may be noted which show that the two conditions differ in important features. In primary infection there seems to be a very inadequate protection and bacilli quickly pass to the regional lymph nodes; and, furthermore, if the number of microörganisms is large, they readily pass beyond these barriers and make a circuit of the body, infecting the viscera. On the other hand, in infection produced by reinoculating a tuberculous animal with similar numbers of bacilli a greater degree of protection is shown for the microörganisms are fixed and detained at the point of inoculation. They do not find ready passage through the tissues. Only slowly and in comparatively small numbers do they gain access to the regional lymph nodes, and still more slowly do they make the circuit of the body and infect the viscera. This was shown by Krause. He infected animals with a bacillus of known low virulence and later reinoculated certain groups of them, as well as groups of normal animals, with a strain of greater virulence. The two strains were so different that the latter could be readily differentiated from those which caused the primary infection. The more virulent bacilli spread rapidly and in great numbers to the viscera of the normal animals, but the viscera of the infected animals were involved tardily and showed evidence only of mild infection, thus proving that the primary infection had produced a marked protection.

In a tuberculous host, whenever bacilli or bacillary protein (tuberculin) comes in contact with the sensitized fixed cells, reaction occurs. This reaction is an antigen-antibody reaction taking place with the antibody while attached to the cell. It is evidence of protection. At first the reaction consists of inflammation with exudation and an outpouring of wandering cells; but it is also accompanied by proliferation. However, as immunity increases, the cells become less sensitive and the inflammatory exudative elements of the reaction

become less prominent, while the bacilli are inhibited in their multiplication and growth and proliferation becomes more evident.

The allergic, inflammatory, exudative reaction takes place when the cells are highly sensitized. In clinical practice it is particularly the lesion of adolescence and young adult life. It appears when reinfection is caused by comparatively large numbers of bacilli, before the host has developed relative desensitization and the marked ability to inhibit growth and multiplication of bacilli and the increased power to destroy bacilli, which it develops after it has had many reinoculations of small numbers of bacilli. In this relatively early type of lesion the chief factor in defense is the seizing and anchoring of bacilli by inflammation and tubercle formation and interfering with their spreading in the tissues. Thus the host is protected from what, without it, might be an extensive invasion.

While the inflammatory reaction may detain relatively small numbers of bacilli in the foci of infection, there is nothing that will explain the survival of a patient with active wide-spread tuberculosis, except a highly developed power of the body tissues to protect the individual from a constantly increasing number of bacilli. If the patient is to survive, multiplication and spread of bacilli must be inhibited and an increased ability to destroy them, as well as an increased ability to wall them in by tubercle formation, must be developed. Without this greater protection no individual could survive after bacilli once gain access to his tissues in large numbers; for, unhindered, they would multiply and spread in great numbers.

If many bacilli gain access to the lower air passages of normal individuals, infection will readily take place. We have observed this in animal experimentation and in the early primary infections that we meet in children. When a patient has advanced ulcerative tuberculosis, on the other hand, millions of bacilli may pass over the mucous membranes of the same air passages daily and be forced into the finer air passages by cough without further infection taking place and with the disease healing. Furthermore, in advanced tuberculosis we must assume that, frequently, great numbers of bacilli gain access to the blood stream without infection following; so they must be restrained from forming new foci by some effective mechanism which is not competent in the noninfected. This increased protection also explains the fact that visceral infection is not common in tuberculous patients except as the end of life approaches and the immunity is rapidly vanishing.

Further clinical proof of increased resistance or immunity is furnished by the fact that, while chronic tuberculosis is a series of episodes of reinfection, some with few, others with many bacilli, if the new foci are not caused by too many bacilli they are usually relatively mild and many of them prove to be abortive. This is particularly true of the metastases which occur in patients who are treated according to modern physiological principles by which the protective body functions are kept at a high point of efficiency.

That there is a difference in the mechanism required to protect the host in early and late tuberculosis is self-evident; for, if the body cells remained as

highly sensitized to bacilli and bacillary substances throughout the course of advanced tuberculosis as they are in the period of early infection, the reaction to the many bacilli which form metastases would destroy the patient. In fact, there would be no chronic tuberculosis. It would be an acute, rapidly destructive disease.

Still further evidence of the protective influence of a tuberculous infection is provided in case a patient has tuberculosis of some particular organ, for example, the lung, kidney or bone. If later another organ becomes infected, the disease is apt to be mild in character. An exception to this is found, as mentioned above, in the late stages of severe pulmonary tuberculosis when immunity is markedly depressed and the host is losing his power of resistance. Under these circumstances it is not uncommon to have the larynx and intestines involved.

Healing results when the immunity mechanism becomes so competent that bacilli no longer multiply and spread, when the products of exudation and necrosis have been removed from the diseased area and when all remaining bacilli and bacillary products have been killed or walled in by living cells. The patient dies of his tuberculosis when his immunity mechanism has been so overtaxed that it is no longer able to respond to the specific stimuli which originate in the foci of disease.

IMMUNITY AND COMPENSATION IN HEALING

Immunity alone will not cure all cases of tuberculosis any more than the knife will cure all cases of appendicitis. However, during the time of early invasion if immunity could be raised to a high efficiency, cure would usually be brought about. But clinicians as a rule do not have the choice of treating early invasion. They are devoting their time and directing their skill largely toward overcoming the ravages of advanced and advancing disease, which injects many problems which do not belong to the early stage of the disease.

We are apt to have a wrong conception of what constitutes curable tuberculosis. Extent of lesion and cavity are given too much attention in forming a prognosis. There are certain types of cavity which make their appearance early and heal readily and certain extensive lesions which are favorable for cure, if only we will aid the patient physiologically to react efficiently.

Compensation is also an important factor in healing. It is only second to immunity in importance. The more extensive and the more destructive the process, either in tissue elasticity or tissue volume, the greater the compensation which must take place. Compensation in early invasion is simple and consists largely of reduced movement, mild emphysema of the tissues adjoining the infiltration and an almost insignificant contraction of the bony cage. In advanced, destructive lesions, on the other hand, marked emphysematous changes may take place, enlarging the lung volume; intercostal spaces may narrow, making the thoracic cage smaller; the contralateral lung may enlarge and the mediastinum may shift from its central position toward the affected side; the diaphragm may become elevated—all for the purpose of maintaining an equi-

librium between the lung volume and the size of the bony thorax. In certain instances, regardless of these attempts at adjustment, compensation may be insufficient to overcome the tension on the tissues and to permit the walls of cavities, large and small, to approximate so that the patient's healing power may act efficiently. In many instances in which natural compensation is insufficient, aid may be brought to the patient artificially in the form of therapeutic pneumothorax, operations on the phrenic nerve, severing adhesions and thoracoplasty. These are now universally recognized as valuable and necessary aids in such instances.

Healing of tuberculosis, as we meet it in clinical practice, is, when accurately analyzed, a combination of immunity and compensation. Immunity depending upon physiological processes is enhanced by all measures which will improve the general condition of the patient. Compensation is a mechanical process and may be aided either by such measures as will relax or compress the diseased lung tissue or diminish the capacity of the bony cage. In practice, it is too often forgotten that, no matter what mechanical assistance is given, measures which improve physiological stability and enhance those particular physiological processes which are utilized in creating immunity are necessary in order to bring about healing. The reverse is equally true. No matter how high the immunity, tissues that cannot relax or contract, especially if cavitation is present, heal with difficulty or do not heal at all.

TUBERCULIN AND IMMUNITY

If a tuberculous infection produces changes in the reaction of the tissues of the body so that it heals itself by bringing about immunity, and if the principal fractions of the bacillus which are active in creating immunity and in increasing it when created are bacillary proteins, then it seems reasonable that these proteins should have value when administered therapeutically.

It is particularly significant that an animal's resistance can be increased by the use of dead bacilli. While there may be other fractions than the proteins which are necessary in order to bring about the fullest measure of immunity, studies so far do not indicate what they are. Whole bacilli, dead or alive, will produce sensitization, and their reinoculation in doses which are not too large will produce desensitization and a more complete immunity. This is in line with the experience of desensitizing cells in the so-called allergic diseases by using the specific allergen. Desensitization is an important factor in defense in chronic tuberculosis. It is associated with resistance and healing.

Contrary to usual opinion, tuberculin may be used advantageously in acute exudative tuberculosis. I have noted in many extensive exudative lesions what seems to be a more rapid desensitization of the tissues, a more rapid absorption of the exudate and a more rapid fibrosis than occurs without its use. It has generally been recognized that tuberculin is of value in the treatment of chronic advanced lesions which are more or less quiescent but fail to heal. Its value seems to be in its ability to increase fibrosis and to clear the field of the products of exudation.

With a knowledge of tuberculosis and a knowledge of the immunity reactions one is able to administer tuberculin with a confidence of being able to control reactions so as not to cause stimulation beyond that which is desired.

There is often great fear that tuberculin will reactivate quiescent lesions. This is usually expressed by those who have had little or no experience in its use. I have seen none of the disasters that so many fear; on the contrary, I have seen great benefit result from its use. While it is not a perfect immunizing product it comes nearest to having the immunizing properties of viable bacilli of any remedy that we possess. No remedy is perfect or sufficient in the treatment of tuberculosis. None will heal the lesions quickly; but each one should be used for what it is able to contribute to cure. Tuberculin is the only remedy that we have which imitates the stimulation which bacilli, themselves, produce, and has the advantage of being under the control of the physician.

SUMMARY

1. The tuberculous patient cures himself or kills himself by his own infection. Infrequent small reinoculations bring about fibrosis and healing. Frequent large reinoculations cause destruction and spreading of the disease.

2. Allergy is discussed as being an intimate part of the total immunity reaction.

3. Man's normal physiological response may be sufficient to protect him against mild invasions, but a quickening and a heightening of physiological response is necessary to protect against more serious infection.

4. The effect of immunity in tuberculosis is to lessen the danger of reinoculation and to make the reaction of the body more favorable to healing in case infection occurs.

5. Immunity checks the spread of bacilli in the body, interferes with the multiplication of bacilli, increases the host's power to destroy bacilli, hastens tubercle formation and increases fibrosis.

6. Immunity is essential to healing but cannot produce the result unless a proper compensation can take place between the pulmonary tissues and the thoracic cage. This compensation may be brought about naturally by: (*1*) emphysema developing in the pulmonary tissues, (*2*) shifting of the mediastinum, (*3*) elevation of the diaphragm and (*4*) contraction of the bony cage. The purpose of all these compensatory measures is to restore equilibrium between the lung volume and the thoracic space.

7. In cases where compensation cannot be produced naturally, it may be aided by pneumothorax, operations on the phrenic nerve, the severing of adhesions, and thoracoplasty; but immunity must still heal the lesion.

8. The action of living bacilli in creating immunity and stimulating healing may be imitated by dead bacilli. Bacillary proteins (tuberculin) are recognized as the active factors in producing these effects. Tuberculin will not produce all of the reactions of the tubercle bacillus, but when used therapeutically will produce many of the effects which are necessary to healing. It has a logical basis for use, though it is not a perfect immunizing agent.

SUMARIO

1. El tuberculoso se cura o se mata con su propia infección. Las pequeñas y raras reinoculaciones provocan fibrosis y cicatrización, mientras que las frecuentes y grandes producen destrucción y difusión de la enfermedad.

2. Discútese la alergia como parte íntima de la reacción total de inmunidad.

3. La respuesta normofisiológica del hombre puede bastar para protegerlo contra las invasiones leves, pero para resguardar contra una infección más grave se necesita la avivación y realce de la respuesta fisiológica.

4. El efecto de la inmunidad en la tuberculosis es mermar el peligro de la reinoculación, y hacer la reacción orgánica más favorable a la curación en caso de que sobrevenga infección.

5. La inmunidad cohibe la propagación de bacilos en el organismo, impide su multiplicación, refuerza la facultad del huésped para destruirlos, acelera la tuberculogenia y acrecienta la fibrosis.

6. La inmunidad es esencial para la curación, pero no puede producir tal resultado a menos que tenga lugar la debida compensación entre los tejidos pulmonares y la caja torácica. Esta compensación puede obtenerse naturalmente por: (*1*) formación de enfisema en los tejidos pulmonares; (*2*) desviación del mediastino; (*3*) elevación del diafragma; y (*4*), contracción de la caja ósea. El fin de todas estas medidas compensatorias es restablecer el equilibrio entre el volumen pulmonar y el espacio torácico.

7. En los casos en que no puede producirse naturalmente compensación, puede ayudarse con el neumotórax, las operaciones en el nervio frénico, la resección de las adherencias y la toracoplastia, pero a la inmunidad le corresponde todavía la curación de la lesión.

8. La acción de los bacilos vivos en la creación de inmunidad y estímulo de la cicatrización puede ser imitada por los muertos. En la producción de estos efectos las proteínas bacilares (tuberculina) están reconocidas como los factores activos. La tuberculina no producirá todas las reacciones del bacilo tuberculoso, pero empleada terapéuticamente sí producirá muchos de los efectos necesarios para la curación. Hay, pues, base lágica para su empleo, aunque no constituye un perfecto elemento immunizante.