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The Relationship of the Immunity Mechanism to Pathologic Changes, Clinical Symptoms, and Therapeutic Measures in Tuberculosis[1]

In the treatment of tuberculosis one should take into consideration all of the complex pathologic conditions which are to be influenced by therapy. It has long been known that early, and even many advanced, lesions may heal as a result of the action of the patient's own natural and specific protective mechanisms. More recently measures have been added which are capable of greatly increasing therapeutic results, and it is necessary to understand in what manner they exert their favorable effects and also to know wherein they are deficient, because no perfect remedy has yet been found.

The pathologic conditions which present range from those found in mild lesions with fibrosis; acute lesions, with exudation, with or without destruction and cavity; to widespread chronic fibrosis, with or without exudation, caseation, and cavity. The prognosis differs with the extent and nature of the lesion, its location, and the reactive capacity of the patient.

In primary tuberculosis the body's reaction is similar to that toward any particulate matter. It is usually symptomless. But when infection has been once established and the individual's immunity mechanism awakened, the changes with which reinoculation is met are the result of the reaction between the bacilli and their products and the natural and awakened specific protective forces of the patient. This reaction is inflammatory and accompanied by symptoms.

Fifty years ago tuberculosis to most people meant certain death. To a few it meant life and suggested rest, eggs and milk, and living in the open air as measures necessary for its cure, because patients were regaining health under such treatment. The explanation for this was not known. Today, however, it is recognized that man's native resistance is best and his immune mechanisms most competent when his resistance is high.

In the years intervening since the early attempts at therapy, increased pathologic, bacteriologic, and immunologic knowledge have made it possible to understand the disease better. Nevertheless, there is a strong tendency to think of tuberculosis more in terms of therapeutic measures, such as hygienic living with rest and good food, compression, surgery, and antimicrobial drugs, than in terms of the fundamental reactions which should determine when and why these various therapeutic measures should be used.

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Fundamental to an understanding of the therapeutic problems is an appreciation of the manner in which the host protects himself and a recognition of the evidence of such protection.

[1] Presented in part before the Medical Session, as part of the symposium on the *Medical Aspects of Tuberculosis*, at the annual meeting of the National Tuberculosis Association, Los Angeles, California, May 18, 1953.

Clinical tuberculosis must be recognized as a struggle between the tubercle bacillus and the tissues of an immunized host. It may be described as a metastasizing, inflammatory, destructive, and curative process. The patient kills himself or cures himself according to the metastases which take place, the number and virulence of the bacilli which cause them, and the state of his resistance, natural and immunologic, at the time the metastases form or that he is able to develop in response to their stimulation. While the immunity reaction is the cause of destruction of tissues, at the same time it is the most important aid in the cure of the disease and one without which there would be no recovery.

We recognize the following as evidences of immunity which are met regularly in patients who suffer from clinical tuberculosis:

1. The entrance of bacilli into the tissues of the immunized host is antagonized, and their movement through the tissues is retarded.

2. Hundreds of millions of bacilli may be poured out into the air passages daily and pass over the bronchial mucous membranes of patients who suffer from destructive pulmonary disease without producing new metastases of clinical significance. The same is true of the intestines although large numbers of bacilli are swallowed daily. These facts should be sufficient to convince the most skeptical that the patient is endowed with strong protection.

3. Bacilli gain access to the blood stream frequently during the disease and may produce small foci in other organs such as the liver, kidney, spleen, bones, and joints, but rarely produce an advancing lesion.

These clinical experiences have many animal experiments, such as the following, upon which their explanation may be based.

Koch[2] observed that bacilli injected subcutaneously in a normal guinea pig ulcerate and remain ulcerated until the death of the animal, while bacilli injected in a pig which has been infected a few weeks previously also produce ulceration but go on to healing.

Webb and Williams[3] proved that the resisting power of animals could be increased specifically by injecting a single bacillus and then gradually increasing the number. In this manner animals were made to withstand 150,000 virulent bacilli without producing active disease.

Krause and Willis[4] showed that bacilli quickly pass from the primary focus to the regional lymph nodes in noninfected animals and make the circuit of the body in a few days; but in infected animals the passage is markedly retarded, requiring many days for the bacilli to reach distant organs.

Lurie[5] has shown that tubercle bacilli may live within leukocytes of a normal animal but die rapidly when the animal has been immunized by previous infection.

Manwaring and Bonfrenbrener[6] showed that 90 per cent of bacilli injected

[2] Koch, R.: Deutsche med. Wchnschr., 1891, *17*, 101.

[3] Webb, G., and Williams, W. W.: Tr. International Congress on Tuberculosis, Washington, D. C., 1908, vol. I, part 1, p. 174.

[4] Krause, A. K.: Am. Rev. Tuberc., 1924, *9*, 83.

[5] Lurie, M. B.: J. Exper. Med., 1942, *75*, 247.

[6] Manwaring, W. H., and Bonfrenbrener, J.: J. Exper. Med., 1913, *18*, 601.

intraperitoneally in guinea pigs previously infected were destroyed within one hour, while in a noninfected pig they produced infection.

Aside from the natural and specific protective powers of the body, mechanical changes take place which afford further aid in healing. An infiltrated lung contracts and becomes smaller; so does the bony cage; and the respiratory movement lessens. It readily may be seen that these changes are favorable to healing.

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Hygienic measures in the early years of treatment proved to be rational and successful sometimes in advanced cases. But advanced and destructive pathology with cavitation furnished special problems. Pneumothorax was introduced and was successful in many instances but still was not the perfect remedy hoped for. Pneumoperitoneum, thoracoplasty, and minor surgical measures were added. All of these compress the lung and lessen its movement, and so have become helpful measures.

Surgeons have now perfected their technique and offer aid in the way of resecting infected areas, cavities, lobes, and lungs, aid which was not thought possible but a short time ago.

Pneumothorax is now being displaced by pneumoperitoneum and surgery, partly because of the many failures and the complications which so often arise following its use. However, much of this injury may be avoided by using less pressure and stopping the refills when the desired result has been attained or when it has been reasonably determined that it will not be successful.

In advising surgery one must always bear in mind that there are many foci of infection in the lung outside the area which is chiefly involved. Such a thing as completely removing the infection is rare, and this fact must always be borne in mind. But patients may be prepared for the operation and be fairly well protected from activation afterwards by building up their physical strength and by the proper use of antimicrobial therapy.

Any form of treatment which reduces the functional capacity of the lung to any great extent must be considered carefully before it is employed. Patients who survive tuberculosis will often live for years, many to advanced age, and will now and then develop other respiratory diseases, such as pneumonia, acute or chronic bronchitis, bronchiectasis, asthma, emphysema, and a rigidity of the thorax. These make extra demands on the respiratory mechanism and, if its function has already been lowered by our therapeutic measures, the patient may be greatly incapacitated.

While chemotherapy has now come to the aid of the therapist, it is necessary to understand that it is an aid, not a cure. The chief function of our present antimicrobials is to prevent the multiplication of bacilli. Although one of our greatest therapeutic assets, it is not enough. We must still depend upon the patient's own protective forces—natural and acquired—for the destruction of the bacilli and healing of the lesion. Chemotherapy is of special value in preventing metastases from forming and, should they form, in checking their progression. It is in the acute types of the disease that it is most useful. Extensive, advanced, fibrotic lesions with destruction and cavity offer the greatest obstacles to its successful

action. This is also true of the patient's own natural and immunologic protective factors.

Jacobs and Kulms[7] have recently examined lungs removed by excision and shown that marked destruction and obliteration of the blood vessels take place. To overcome this effect they suggested that such remedies as the iodides and tuberculin be used. It has long been known that tuberculin produces a focal hyperemia. This makes it possible for the antitoxins, as well as the patient's own natural and immunologic protective substances, to come in more intimate contact with the bacilli in the tissues. In the treatment of tuberculous meningitis, tuberculin has been used intrathecally with reported advantage.

Bacilli sooner or later become resistant to antimicrobials but, by combining them, the time of the appearance of resistant strains may be postponed or prevented, and treatment may be carried on much longer than when they are used individually.

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There is no dependable cure in any single therapeutic measure for all of the many pathologic conditions met in the patient who suffers from advanced tuberculosis; but, if those we have are used understandingly, each for what it is capable of doing and properly reinforced by others, the treatment of tuberculosis may be remarkably successful. However, there has never been a time when it was more necessary than it is now to have accurate knowledge of the host, the disease, and the curative measures in order to treat patients intelligently and effectively. Research in the fundamentals of tuberculosis must go on. The better we understand the patient and his physiologic, bacteriologic, pathologic and immunologic reactions, the more successfully will the clinical problems be met.

It can be seen that anything which will improve the patient's resistance is indicated in all instances. While exudation and cavity will yield to the dietetic-open air-rest regimen, they can often be treated more successfully when collapse measures or surgery and antimicrobials are added. Antimicrobials have a special value in the presence of cavity because they act upon the disease in the bronchus, so favoring respiratory exchange and drainage.

No one who has been active in the treatment of tuberculosis during the past fifty years can fail to note the changes which have taken place in the clinical picture. The symptoms of the disease are less severe. Acute, so-called "galloping consumption" is now rarely met. Complications such as meningitis and tuberculosis of the larynx and intestines occur rarely, and the "good chronic" is a common rather than an occasional type. Resistance has lowered the susceptibility to infection, caused a decrease in the number of metastases in the infected, decreased the number of complications, and lowered the mortality rate. At the same time it has produced more chronics and prevented the morbidity rate from falling in proportion. This has been brought about, not by therapy alone, but also by the improved economic and social status of the people. Today, patients show more resistance to the disease and live longer with or without treatment.

[7] Jacobs, E. C., and Kulms, D. W.: Dis. of Chest, 1952, *22*, 523.

This is shown in the entire Western world as compared with the nations with a lower standard of living, where tuberculosis is still rampant in its acute forms.

If improved conditions in the economic and social status of the people will cause a reduction in the severity of the disease, reduce serious complications, increase the life span, and lower the death rate, this should be ample proof that the hygienic-dietetic-open air-rest regimen, which has for its purpose the making of the patient more resistant, is a true basis for therapy, no matter what other measures are used. In all instances the patient must cure himself.

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