THE NEED FOR FUNDAMENTAL RESEARCH IN TUBERCULOSIS

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Does current attitude reflect the relative importance of the various phases of the tuberculosis problem? Is it not too much colored by a desire for a short cut to prevention and cure? We are avoiding the discussion of some of the most fundamental problems in phthisogenesis, the understanding of which would make our approach to both prevention and treatment more intelligent. That we are winning the fight is gratifying, but not a satisfying answer. Knowledge is always better than ignorance.

In therapy we seem to be depending on a hope that some chemical or antibiotic alone, or combined with surgery, will be the answer that we have been hoping for. In this we are losing sight of the fundamental fact that tuberculosis consists of multiple foci of infection in varying phases of pathologic change which the patient opposes by creating a specific defense which is variable in its degree of efficiency. No matter what therapeutic measures are used the patient must still cure himself by keeping his defensive forces at a high level so that the live bacilli which lie in the tissues will remain encased; or, if they should escape from their imprisonment, will be destroyed. We must not lose sight of the fact that while tuberculosis has a tendency to metastasize it also has a tendency to heal and must seek to know those factors which aid in healing.

We assume that the best method of preventing infection is by breaking contacts. This is true in the primary infection of childhood but not necessarily in the disease of adults. But we make no distinction. We fail to take into consideration that most adult patients suffering from active tuberculosis do not give a history of direct contact. Whence do the infecting bacilli come and how do they enter the body? We fail properly to consider the fact that when once infected continued association rarely produces multiple primary lesions, and in the great majority of instances fails to cause an immediate clinical pulmonary disease. Does this not suggest that infection protects as well as destroys? Was this not shown in the Lubeck disaster?

The disease which so often kills during the early years of childhood is blood-borne. Its fatal forms are often due to foci in the meninges or general dissemination causing miliary disease. Foci in other organs such as bones, joints, and the apices of the lungs produce immediate disease much less frequently. Pulmonary disease causes some deaths but not so many as would be expected.

Are we not at this time, in spite of the fact that primary infection is so common in the lung, justified in explaining the rarity of pulmonary disease as meaning that primary infection is followed by a degree of protection which increases as the bacilli multiply and which is capable of keeping the infection localized? Is this not sufficiently evident to make it the part of wisdom to accept this as a fundamental fact in our program for prevention and healing?

That infection produces increased resistance was shown by Koch when he first produced tuberculin. He

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showed that the specific effect of an infection when well established is to localize the bacilli of reinfection and produce healing of the resulting focus. The Lubeck disaster showed localization in about 70 per cent of patients although the number of bacilli engaged in the infection was much larger than could ever be expected to produce a normal primary lesion. Furthermore, a high degree of protection is demonstrated every day in the clinic. Whereas a few (we do not know how many) bacilli will produce an infection in a normal individual, millions and billions may pass over the bronchial mucous membranes of those suffering from active tuberculosis daily and be forced into the finer air spaces through cough without new infection occurring and without preventing the disease from healing. Should these facts not stimulate the inquiring mind for a better understanding of this acquired resistance?

In spite of the fact that most individuals who suffer from active disease have also had primary foci in which bacilli remain alive for long periods of time, our programs of prevention are based largely on the acceptance of the idea that exogenous reinfection is the chief cause of clinical tuberculosis. This is accepted without definite proof. Unless it can be explained why exogenous reinfection, regardless of the specific protection produced by first infection, is able to localize almost with regularity in the upper portion of the lung, while exogenous primary infection localizes predominantly in the lower and central portions, we are compelled to at least suspect that the source of infection in these two instances may be different. Would not the specific resistance created by primary infection make it more difficult for bacilli coming from without to cause reinfection, and particularly to cause a spreading disease?

Furthermore, there are reasons which seem to be quite convincing for believing that bacilli of reinfection may be largely endogenous. In early primary infection bacilli escape from the primary focus and enter the lymphatic system and gain access to the regional glands. While doing this bacilli are also carried to other parts of the lung and to other organs such as the kidney, the bones, the joints, the meninges—through the blood stream. Pathologists have called attention to the number of small metastatic lesions found postmortem at or near the apex of the lung in which the bacilli were carried by the blood stream. Why does this early blood-borne infection cause so little immediate pulmonary disease, and why does pulmonary disease predominate later with so little involvement in other organs? The number of bacilli causing disease must either be greater or the conditions for establishing foci be more favorable, or both.

An explanation has been given for these pulmonary foci which should be explored. When the child assumes the erect posture the anterior portion of the ribs drop from the horizontal position at birth to an increasingly acute angle as age progresses. The result is a progressive compression of the air spaces, lymph spaces and vessels in the upper part of the lung, and a minimal movement in and near the apex. This facilitates the screening out and localizing of bacilli at or near the apex when they circulate in the blood, as they often do. Here they may die or remain viable.

It is interesting that those who survive death in childhood have an increased resistance to the disease until puberty. This puberal form of the disease is usually a rather extensive active lesion frequently exudative in character with tendency to destruction and cavitation, which would indicate that it is caused by large numbers of virulent bacilli, or that conditions for their growth are extra favorable.

There are certain conditions in puberty which make this period particularly favorable for the spread of infection. First, the lung doubles in size during the puberal years. Naturally pathologic foci can not grow, so growth of the surrounding tissues would be expected to weaken the walls which envelop the viable bacilli. Second, puberty is an age when extra physiological and physical demands are made on the patient. These conditions have a tendency to disturb the bacilli and favor their escape, on the one hand, and to lower the resistance of the individual and make him more susceptible to infection, on the other.

Whence could the bacilli which cause these massive infections during and following puberty come so readily as from the primary lesions, or metastases from them? From their vantage point of being already within the tissues not only their ability to multiply but to produce metastases is much greater than that of bacilli which must gain access to the tissues from without.

It is reasonable that with unhealed lesions present in the body bacillemia will now and then occur and bacilli will also now and then escape into the bronchi as a result of the strain and vicissitudes of an ordinary life. We find this in patients whom we have followed over a period of many years.

In re-examining at intervals patients discharged from the Pottenger Sanatorium with an apparently arrested tuberculosis, we have nearly always found their sputa to remain negative for bacilli to the most efficient methods of examination except when they have acute respiratory infections or have lowered their resistance by overwork or bad living conditions. Then those who have previously had destructive lesions will frequently have positive sputum for a time. One case is particularly interesting. The patient had been discharged in 1904. He remained well, lived an active life, and raised a splendid family. In 1944 he had an acute pneumonia, and many bacilli were found in his sputum. Shortly after his recovery the sputum became negative and has remained so. The primary complex and metastases from it may take the same course, yet this is rarely followed as we follow our clinical cases. This is a field for investigation that might give valuable information. It is not uncommon to find an active lesion sometimes with cavity adjoining the lymphatic component of the primary complex which seems to be a direct extension.

The chief factor on which these patients rely is their natural and acquired defense which may or may not be adequate. But it is more apt to be adequate when intelligent action is used on the part of the individual. Patients who are trained properly during treatment usually live carefully after arrestment has been attained and respect respiratory infections and give themselves more rest and recover without serious harm to themselves or associates. But those

who are careless or ignorant of their infection and its seriousness are more apt to suffer reactivation and endanger others. It is not uncommon to have some bacilli last for several weeks following these acute infections. This brings up the question: How dangerous are rare bacilli? How many bacilli are dangerous to the patient, and how many will contaminate an environment sufficiently to make it dangerous to others? Will a few hundred or a few thousand per day contaminate the air of a well ventilated room?

The relative importance of endogenous and exogenous sources of bacilli of reinfection is one of the most important of all tuberculosis problems to be explored. A rational program for treatment and prevention depends on the correct answer.

If the source is largely endogenous, then primary infection becomes the ultimate cause of most tuberculous disease and calls for its prevention or, in case it has taken place, for its healing.

If infection has not taken place, it should be prevented or be reduced in frequency. This may be accomplished by substituting a non-virulent bacillus such as BCG, which will cause protection without danger of producing metastases. This may not be a complete answer, but it is a logical approach. Suppose it will offer only a partial protection, can one think of any other measure that will do as well? Moreover, if immunity stimulated by BCG is not permanent, is there any reason why vaccination can not be repeated with another elevation of the individual's resistance, the same as occurs by small repeated metastases in the course of natural disease? Suppose the patient would react with symptoms, they could not produce disease because BCG is a non-virulent bacillus, and the reactions would not be as dangerous as tuberculin reactions that we now and then see when using tuberculin therapeutically because the infection is non-virulent. I have never seen harm result from tuberculin although I have given thousands of injections during the past fifty years.

When an infection occurs it is our duty to see that the child develops normally. Attention to hygiene and supplementary food for undernourished children might prevent many metastases in later life.

Is it not probable that we pay too little attention to the primary complex? We accept its benignity without considering its future possibilities. Is it not in many cases a bomb with an unextinguished fuse which might be rendered harmless with attention to the diet and hygiene of the individual until healing occurs; or would it not be better to supplement a non-virulent for a virulent infection?

Why should from five to seven times as many people be allowed to break down with active tuberculosis in those of low economic and social level as those who live on a higher plane? How may this be prevented? Is not vaccination and a regimen for building up resistance of the infected individual a reasonable answer?