The Pathogenesis of Tuberculosis

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Introduction

There are many unanswered questions concerning the pathogenesis of tuberculosis. However, this complex subject is made more complicated by lack of uniform terminology, failure to recognize many events that may occur regardless of any difference of opinion in regard to their origin, failure to recognize fully the factors modifying the development of tuberculous disease under different conditions and in different localities, and lack of adequate control observations.

Some Basic Terms

Recognition of the terms to be employed is paramount in any discussion. A primary focus is the lesion produced in any tissue where the first infection with tubercle bacilli occurs. The primary complex includes the primary focus and the involved efferent lymphatic vessels and nodes. A progressive primary lesion is one which results from direct or contiguous extension of disease from a primary focus, with or without a period of comparative inactivity. Endogenous exacerbation refers to a reactivation of a disease locus that has remained dormant for a variable period of time. Exogenous reinfection indicates a new infection from without which occurs in an individual who has a healed tuberculous infection. Superinfection (if it exists) consists of infection from an external source which is superimposed upon an unhealed tuberculous lesion. Miliary tuberculosis refers to numerous “millet-sized” lesions uniformly distributed through an organ or throughout the body, and implies a hematogenous dissemination of infection. A tuberculoma is an isolated lesion of variable size which contains a caseous center and tends to be encapsulated. This lesion may be entirely replaced by fibrous tissue. It is seen in the liver or brain as a result of hematogenous dissemination, but in the lung it may result from bronchogenic spread (round foci). Miliary endobronchial metastases are small lesions initiated by secondary extension through the bronchi, and lack the homogenous distribution of a hematogenous spread. Phthisis indicates a “wasting” or progres-

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sive disease, more or less limited to an organ system, and is usually used in connection with lung disease.

**Portals of Entry**

In countries where pasteurization of milk is extensively practiced the portal of entry is via the respiratory tract in well over 90 per cent of the cases. Occasionally there is infection via the oral cavity with a primary focus in the tonsil or in the gastro-intestinal tract. The skin has been mentioned as a portal of entry in ritual circumcision and rarely at other sites of trauma. Transmission through the placenta is rare, but is reported. One portal of entry, for example the tonsil, may not preclude a later portal of entry in another tissue such as the lung.

**Modes of Spread**

Tuberculous infection may be propagated by contiguous spread, via lymphatics or blood stream, by lymph-hematogenous spread (e.g., thoracic duct to left subclavian vein), through the bronchial tree (bronchogenic spread), or by intracanalicular spread (e.g., bronchi to trachea to larynx to gastrointestinal tract).

**Basic Pattern of Tuberculous Infection**

The individual is unaware of the entrance of tubercle bacilli into the body for some time. The primary focus of infection in the lungs may be located in any lobe, usually subpleurally. After an incubation period of three to eight weeks (average four to six weeks), the tuberculin reaction can be elicited and the primary focus or primary complex may or may not be visible upon x-ray examination. Levine found 16 children who had lesions demonstrable by roentgenogram before the development of tuberculin reaction. However, in most cases the reverse may be true. Usually the roentgen signs, when present, may be demonstrated within 10 to 16 weeks after infection occurs. Indeed, the tuberculin reaction may be the only indication of infection, or the period of initial invasion may be accompanied by symptoms and signs. These include fever, malaise, anorexia, weight loss, cough, wheezing, increased erythrocyte sedimentation rate, neutrophilic leukocytosis followed by monocytosis or lymphocytosis, phlyctenular conjunctivitis and erythema nodosum. The last-mentioned is quite common in the Scandinavian countries, but is uncommon in the United States. The subsequent course of events may be modified by factors of individual resistance, age, sex, race, socio-economic factors, etc. The period of initial invasion is especially dangerous in the ages of birth to three years and from 15 to 35 years, which Wallgren designates as the first and second danger periods. It is like-
wise dangerous in the Negro and in some social groups, and seems to be influenced by geographic variations (e.g., less dangerous in Minnesota than in the Scandinavian countries).

During the stage of initial invasion there is usually a "first hematogenous spread." By this is meant that in most cases tubercle bacilli are disseminated throughout the body by the blood stream, probably before the tuberculin reaction is in evidence. Subsequent lesions tend to be localized by the Koch phenomenon when allergy develops. However, generalized hematogenous miliary tuberculosis or meningitis may result at this time, or the foci may tend to heal only to reactivate at a later date.

After four to six months (but sometimes longer) the initial complex tends to stabilize, and to heal by fibrosis, calcification and/or resolution. The patient may thus have completed the triad depicted in figure 1, and yet fully 75 per cent may not show evidence of disease on the roentgenogram. On the other hand, the primary lesion may proceed directly or after a variable latent period to a more advanced disease process, or even to a wasting phthisis, with extensive involvement of the contiguous pulmonary tissue (figure 2). Also, a non-caseating or serous pneumonia may develop in the surrounding area, and bronchial compression or invasion may lead to obstructive emphysema, including formation of cyst-like blebs or bullae, and atelectasis. These latter conditions were previously designated as "epituberculosis" to designate that the entire roentgenographic picture did not consist of caseous or tuberculous inflammatory tissue, and could resolve in a few months, leaving at times only a small fibrous or calcific nodule as evidence of disease. This atelectasis may result in bronchiectasis in a high percentage of cases, however, if it doesn't resolve within 9 to 12 months.

Since the primary lesion is usually located subpleurally, only

![FIGURE 1: Basic Pattern of Infection.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21191/)
minimal extension is required to reach the pleural surface, and pneumothorax or pleural effusion may result.

If the primary lesion appears to be controlled, an endogenous exacerbation or exogenous reinfection may lead to bronchogenic dissemination of disease. This quite commonly results in the sub-clavicular minimal infiltrate, single or multiple tuberculomata (round foci) or milia prevent bronchial metastases. Apico-caudal extension may then produce moderately advanced or even far advanced lesions. At any time during this progression the bacilli may enter the blood stream for a secondary hematogenous dissemination, or a small focus of disease in some other organ may reactivate, progress and invade the blood stream.

Superinfection, occurring in the presence of unhealed lesions, may be a factor, but this still awaits definite proof. It is included only for completeness.

Thus, phthisis or wasting of the lung tissue may result from the progression of the primary lesion, endogenous exacerbation, exogenous reinfection, or from any one of the three plus the possible superinfection, if the balance of bacillary virulence and host resistance is disturbed. This progressive disease may occur in organs or systems other than the lungs. At any stage of disease in any organ a lesion may progress to produce local phthisis or to invade the blood stream.

**What Happens to Involved Regional Nodes? (figure 3)**

We have already discussed the various consequences of the primary focus. The nodal lesions may likewise heal or proceed to
caseation. The caseous node may perforate a bronchus, leading to positive sputum, and the bacilli may take the intracanicular route to the larynx and gastro-intestinal tract. Bronchial compression or invasion leads to manifestations of obstructive emphysema or atelectasis. Discharge of a large caseous mass may result in a complete blockage of the rima glottis with sudden death. The caseous node may perforate the thoracic duct and the bacilli are then conducted to the subclavian vein to initiate a hematogenous dissemination. Rupture of caseous material into the pericardium may cause tuberculous pericarditis. Calcified hilar nodes may produce bronchostenosis, leading to future difficulties such as recurrent pneumonias and atelectasis, which may in turn lead to bronchiectasis.

**What Happens to the Progressive Primary Lesion?**

In figure 4 the progressive primary lesion and its subsequent possibilities are shown. Briefly, it may heal, spread through the surrounding tissue, involve the bronchial tree, or invade the blood stream.

**What Happens to the First Hematogenous Spread? (figure 5)**

A transient bacilluria may be the only demonstrable evidence of the first hematogenous spread. This may occur in the absence of any other urinary findings, and some even believe that the tubercle bacilli go through the intact glomerulus. This is difficult to prove. Hematogenous miliary tuberculosis or meningitis may

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**FIGURE 3: What Happens to Involved Regional Nodes?**
occur. More often the disseminated foci remain quiescent, but may reactivate after a period of a few months or years, giving rise to progressive organ disease and at times to a secondary hematogenous spread. Thus, a chest roentgenogram may reveal an active lesion, an apparently healed lesion, or nothing at all, while a progressive tuberculous lesion is present in the skeletal system or kidney.

Bone tuberculosis frequently starts in the metaphysis, less fre-
quently in the epiphysis. The lesions may penetrate the joints, slowly destroying the cartilage.\textsuperscript{14} Poncet’s rheumatism is an “allergic” type of joint swelling which may disappear in two to three weeks, and does not indicate the presence of tubercle bacilli in the joint space. Rarely, cyst-like lesions appear in the diaphyses of the long bones and the phalanges (spina ventosa), simulating lesions seen in sarcoid and coccidiodomycosis. Tuberculosis of the spine is the most frequent type of bone tuberculosis; this may lead to the formation of paravertebral abscess, and thus be responsible for the development of meningitis or pleural effusion.

In the brain solitary or multiple tuberculomata may form. Large areas of involvement in the mid-brain may lead to ventricular block, and cortical lesions may rupture into the subarachnoid space\textsuperscript{2} to produce meningitis. Meningitis may be “bacillary” (with demonstrable bacilli) or “serous” (without demonstrable bacilli).

In the liver, spleen and kidneys single or multiple foci may either heal and calcify or form progressive lesions. Renal tuberculosis\textsuperscript{15} spreads inward from the cortex to the renal pelvis and thence by intracanalicular spread downward. Tuberculous salpingitis may spread to involve the ovaries or uterus. Lesions of the uveal tract and choroid of the eye may be noted in some cases. Involvement of the adrenals may produce Addison’s disease, and the rare pancreatic tuberculosis may lead to signs of pancreatic insufficiency and skin pigmentation.

\textit{Pathogenesis of Phthisiogenic Infiltrates}

From the preceding discussion and in figure 6 it is seen that a wasting phthisis may occur in any organ in which any tuberculous lesion may progress by spreading through the contiguous tissue. Thus, this possibility must be kept in mind from the time of the appearance of the primary focus until the death of the patient. This would seem to indicate that the therapy of the patient should depend upon the pathological process present, and not be limited by the designation of a lesion as primary or other form of tuberculosis.

\textit{The Secondary Hematogenous Spread}

The secondary hematogenous spread is a term used in this paper to indicate any hematogenous dissemination of disease that occurs after the first hematogenous spread. It may occur in patients who have a progressive primary lesion in the lung as well as in those who have lesions that have spread to other parts of the lungs. It may be initiated in an area of infection that has been previously established by the first hematogenous dissemination. At post-mortem one may find a hematogenous miliary tuberculosis or
tuberculous meningitis and after thorough search find only a small caseous process in bone, kidney, prostate, etc., that has produced the overwhelming infection by invading the blood stream. Any unhealed lesion in any organ may progress and invade the blood stream.

Effect of Non-Specific Diseases

In children incidental disease such as non-tuberculous pneumonia, upper respiratory infections, etc., may result in visible progression of disease. In adults, on the other hand, the sputum may temporarily turn positive, but demonstrable progression or extension of disease is less likely to occur. Necrotizing pneumonia is most potent in activating tuberculous lesions. Satisfactory collapse usually prevents spread.

The presence of incidental infections may also lead to the false conclusion that tuberculous disease has progressed. Certainly in reading chest roentgenograms, the possibility of viral and non-tuberculous bacterial pneumonias, Loeffler's eosinophilic infiltration, lipiodal reactions after bronchograms and pleural effusions such as occur in disseminated lupus erythematosus must be kept in mind.

The Negative Tuberculin

Failure to react to tuberculin may signify that the individual has never sustained tuberculous infection or is in the preallergic incubation period. A small percentage of patients heal their infec-

![Pathogenesis of Phthisis Diagram]

FIGURE 6: Pathogenesis of Phthisis.
tion and the allergy subsequently disappears. The tuberculin test may become negative temporarily as a result of an incidental infectious disease such as measles, in the late stages of generalized miliary tuberculosis or meningitis, or after an overwhelming seeding of the pleural space following rupture of a subpleural focus. Inadequate technique is not an uncommon factor. Some patients apparently never or only intermittently have skin allergy even in the presence of active disease.

Whether sensitivity to tuberculin without active disease protects the individual has been discussed widely for many years. This status may be attained in persons who have controlled a first infection, and the proponents of BCG vaccination state that they produce the tuberculin reaction without harm to the individual.

**FIGURE 7:** Composite Pattern of Possibilities.
Cellular transfer of tuberculin sensitivity has also been reported. Although allergy and immunity appear to be due to separate factors they usually co-exist to some degree. Some say that allergy is dangerous, while others claim that the protective immunity that co-exists with the allergy more than offsets this danger. Many studies discussing this problem have been inadequately controlled, but it is hoped that in a few years more scientific conclusions may be drawn. Regardless of the results, other tried and proved methods of control must not be neglected. Further discussion of this problem is beyond the scope of this paper.

Discussion

The study of tuberculosis has many interesting facets. The diagnosis alone is often difficult to establish, and Garland lists 89 conditions that have caused confusion in chest roentgenograms alone. Beyond this each case poses an individual problem of management, and public health control aspects form grounds for endless discussion. Many physicians find themselves lost in the controversial opinions expressed in the literature. However, it seems logical that the adoption of uniform terminology and the recognition of a unified conception of the development of tuberculous lesions as depicted in figure 7 may form a basis of thought to aid one in the study of tuberculosis in its various aspects.

SUMMARY AND CONCLUSIONS

The basic pattern of tuberculous infection has been discussed. Various theories of the mechanisms involved have been purposely omitted in many instances, and indeed, many are unsolved. It is hoped that further research and clinical observations will serve to clarify further the evolution of this disease. Although we may not be able to state dogmatically that a given lesion is a progressive primary lesion or is the result of endogenous exacerbation or exogenous reinfection, a unified concept of the pathogenesis of tuberculosis will aid in the interpretation and management of each individual case.

RESUMEN Y CONCLUSIONES

Las formas básicas de la infección tuberculosa se discuten. Varias teorías de los mecanismos que se ponen en juego se han omitido intencionalmente y desde luego muchos mecanismos no están aclarados. Se espera que estudios ulteriores y la observación clínica servirán para aclarar la evolución de la enfermedad.

Aunque estamos incapacitados para asentar dogmatically si una lesión es primaria progresiva o es resultado de una infección exógena, una unificación del concepto patogénico de la tuber-
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REFERENCES