AN OUTLINE OF THE PRINCIPAL FORMS OF TUBERCULOSIS IN MAN

Primary, Disseminated and Bronchogenic Tuberculosis

By WALTER PAGEL

Department of Morbid Anatomy and Histology, Central Middlesex Hospital, Park Royal, London, N.W.10

Introduction

In about 50 per cent. of the population in most parts of Europe and North America, tuberculous infection occurs before the age of 16 to 20 years. The infection usually remains latent but sometimes, either soon after the infection or later, clinical disease develops. Infection itself has, however, a long lasting effect on the body, for the response of the tissues to tubercle bacilli differs from that evoked when the bacillus is first introduced. This altered response (allergy) is found even in those who have never shown clinical symptoms or signs of tuberculous disease. It is recognized in two ways: (1) By long persistence of the property of reacting positively to the tuberculin test, and (2) by the fact that the anatomical character of post-primary lesions differs from those of the primary lesion. The latter remains recognizable as such even in a late stage by the characteristic picture of a caseous (calcified or ossified) focus in the lung, associated with a similar caseous (calcified or ossified) focus in the regional lymph node.

Tuberculosis has been classified anatomically in several ways. Three only deserve discussion here.

1. *Childhood and adult forms.* The distinction between childhood and adult tuberculosis has no place in pathology. Primary infection with its sequel—disseminated tuberculosis—was regarded as the childhood manifestation and pulmonary consumption as the adult form of tuberculosis. But primary tuberculosis is not limited to childhood; the percentage of primary infections in adults is considerable and anatomically the lesion is no different from that found in childhood. The factor that does vary with age is the severity of the disease. The physical and chemical conditions of the tissues, the metabolism of the body and the endocrine activity, these are the factors upon which variation in severity depend and these vary with age. Such age differences underlie the comparatively severe course of tuberculosis in early infancy, in puberty and in elderly people after 50 years and probably its benign course in children

of school age. Dissemination of the disease to several organs occurs at any age and has no preference to any one age group.

2. *Acute and chronic forms.* These two clinical forms are observed at every age in individuals of widely differing types and races and may appear in the course of disseminated tuberculosis as well as in forms limited to the lungs.

3. *Forms depending upon the effect of the specific response of the whole body.* There exist three fundamental anatomical types of tuberculosis which are due to a specific response of the whole body and are independent of constitutional factors, viz.:

(a) Primary infection.

(b) Haematogenous dissemination.

(c) Lesions limited to the lungs (bronchogenic tuberculosis, so termed because it tends to spread by the bronchi).

The Primary Infection

Tubercle bacilli usually invade the body either by the lung or by the intestine. Other portals such as the skin, tonsils, conjunctiva, nose, middle ear and genitals are rare. When the bacillus enters the lung a small patch of caseous bronchopneumonia develops and later encapsulates. This is the *primary focus*, often and unjustifiably called the Ghon focus. It was described by Parrot in 1876, by Küss in 1898 and by Ghon in 1912. Before the primary focus is fully developed, a similar caseous lesion appears in one of the regional lymph nodes. The lymph nodal component plus the primary focus together constitute the *primary complex* (Ranke, 1928) (Fig. 1). The lymph nodes beyond the regional nodes first affected may become involved by lymphatic spread both upwards towards the neck and downwards towards the abdomen. In primary intestinal tuberculosis, mucosal ulcers constitute the primary focus; the mesenteric lymph nodes become caseous, enlarge and soon become more conspicuous than the mucosal component (Fig. 2).

Situation. In the lung the primary focus is usually in the lower part of the upper lobe or in the upper part of the lower lobe, chiefly in the right upper lobe and not infrequently near the base (Fig. 1). It is seldom found in the apex. It is mostly situated near the pleura.

Size. The size of the primary focus varies. As a rule it is no bigger than a hazel nut and remains smaller than the corresponding focus in the regional lymph node, a correlation which may be reversed in adult primary infection (Pagel, 1942).

The Fate of the Primary Complex

1. **Healing.** The encapsulated area of lobular and caseous pneumonia that is the primary focus usually becomes quiescent and calcifies. Ossification occurs in about 40 per cent. of the calcified lesions. Retraction of the calcified focus affects the surrounding parenchyma and bronchiectasis (Fig. 5) and bronchial stenosis are common sequels to old primary infection (Brock, 1950).

FIG. 1.—To demonstrate a typical, fairly fresh *primary complex* in the lung. The age of the changes is about three months. They consist of:

P.F.: The primary focus in the medial corner of the right lower lobe, in a subpleural position, just above the base. This was followed by caseation of the lymph nodes.

L.N.: The lymph node change typically exceeds in size the primary focus. In addition, there are scattered miliary nodules due to early haematogenous spread probably from the lymph nodes.

Boy, aged one year. Central Middlesex Hospital. Post-mortem No. 43/287. Death from meningitis.

2. **Local Extension: Primary Infiltration and Epituberculosis.** Non-caseating and resorbing tuberculous infiltrations are known as epituberculosis. They may be found at any time during primary or post-primary tuberculosis but are most common in connection with a primary focus. Hence the various anatomical changes concerned with epituberculosis can be conveniently described here, *viz.*:

(a) A 'perifocal infiltration' may be seen when a small bacillary focus is surrounded by a large area of toxic oedema or gelatinous infiltration

FIG. 2.—A primary complex in the gut, several months old. It shows, as an equivalent of the primary focus, the ulcerated appendix (P.A.). Primary ulceration of coecum not shown. The regional mesenteric lymph nodes are grossly enlarged and caseous (P.M.).

Bottom: The lungs, showing a miliary spread and no caseous foci, the hilar lymph nodes being small and free.

Boy, aged seven. C.M.H. P.-M. 48/342.

attributable to a hypersensitive response of the tissue towards tuberculo-proteins. This is often the basis of a large shadow of infiltration in a radiograph.

(b) Tuberculous pneumonia may occur without any tendency to caseation and therefore may resorb.

(c) Innumerable tuberculoid granulomata with Langhans giant cells but without tubercle bacilli and caseation may be found at the site of an 'epituberculous' infiltration. This may occur together with segmental collapse and is found when a tuberculous—usually primary—focus extends into the segmental bronchi. Presumably, it thereby provides a source of aspiration of material containing dead bacilli and tuberculo-protein. This explains the picture of multiple tuberculoid granulomata in the absence of caseation and tubercle bacilli—a picture that is reminiscent of the change at the site of a positive tuberculin reaction.

Segmental collapse in primary tuberculosis. In the causation of segmental collapse, pressure on the bronchus by a lymph node or its eruption into it (Figs. 3 and 4) has been rightly emphasized as the common cause. However, it is not the only cause. Another important incident causing segmental collapse is extension of the primary focus via the bronchi with obstruction thereof (Pagel, 1952).

Collapse alone is not epituberculosis. We cannot endorse the view that transient 'infiltrative' shadows in the radiographs of the tuberculous are always due to collapse.

Primary Cavity. It is a common fallacy to believe that the primary focus must be small and become quiescent and eventually calcify. It may reach several centimetres in diameter and, as a caseous lobular pneumonia, it is subject to all possible developments of a caseous focus. One such development is softening and its sequela—cavitation—which is becoming increasingly important as a source of bronchogenic tuberculosis (*vide infra* and Fig. 10).

Post Primary Tuberculosis: Haematogenous Disseminated Tuberculosis

Haematogenous dissemination can be mild and comparatively benign or may cause severe and fatal illness. All intermediate stages are observed between the most acute tuberculous septicaemia on one hand and clinically latent discrete nodules on the other. It is not known what factors decide the development of one or other form, though the number of bacilli reaching the blood stream and multiplying in the tissues is the main condition. The 'virulence' of the bacilli is of doubtful

importance, as is the type; both bovine and human strains may cause acute tuberculous septicaemia.

The Morbid Anatomy of Dissemination. We may divide the lesions into the following types

1. Acute tuberculous septicaemia.
2. Miliary tuberculosis.
3. Chronic disseminated tuberculosis.

1. *Acute ('Fulminant') Tuberculous septicaemia.*

The most malignant form is the so-called *sepsis tuberculosa gravissima*. This causes a clinically obscure picture of acute pyrexia with leucopenia resembling typhoid fever or virus pneumonia. As a rule, its tubercular origin is not recognized before post-mortem examination, although an early clinical diagnosis is particularly desirable, since chemotherapy may be effective (Ball, Jules and Pagel, 1951). The condition seems to be a sequel to a severe primary infection acquired in middle-aged or even elderly persons. At post-mortem the spleen and liver are usually (but not invariably) enlarged and studded with small, ill-defined necrotic foci (Fig. 6). Histologically, no definite tuberculous structures are seen, but the necrotic

FIG. 3.—To demonstrate, in the region of a fresh primary complex, a block in a major bronchus probably due to eruption of a liquefied caseous lymph node or possibly to aspiration of material from the liquefying primary focus.

P.L.: A caseous block in the lumen of a major bronchus.

P.C.: The large primary focus.

L.N.: Lymph node component of the primary complex.

Girl, aged seven months. C.M.H. P.-M. 47/1.

FIG. 4.—To demonstrate communication of an old caseous lymph node at the bifurcation of the trachea with the lumen of the main bronchus by a fistulous track. A: Shows a survey of the lungs, with the primary focus (P.F.) in a subpleural situation in the left mid-zone. The bifurcation lymph node is enlarged old caseous, and the arrow points to the fistulous track. B: Close-up of the primary focus. C: Close-up of bifurcation lymph node with fistulous track. D: A deeper section through the same lymph node. Male, aged 27. Death from purulent meningitis, probably due to mixed infection of the fistulous track in the bifurcation lymph node. C.M.H. P.-M. 50/173.

areas contain innumerable acid-fast bacilli. In some cases no naked eye changes are seen apart from trivial 'septicaemic' changes (Pagel and Woolf, 1949).

2. *Miliary tuberculosis* is characterized by the simultaneous formation of foci equal in size and with identical anatomical features. Its course may be acute or chronic, persisting for years or even healing.

FIG. 5.—To demonstrate the late sequelae of scarring due to multiple calcified foci in the area of an old primary complex.

Top: The apical region of the lung with extensive bronchiectasis in a scar field with multiple calcified foci (C.F.).

Male, aged 78. C.M.H. P.-M. 50/64.

Bottom: A similar case. Specimen radiograph showing gross emphysema and multiple calcified foci (black).

Male, aged 57. C.M.H. P.-M. 48/384.

FIG. 6.—Fulminating tuberculous septicaemia.

Spleen: Irregular patches of necrosis containing innumerable tubercle bacilli (human strain).

Male, aged 55. C.M.H. P.-M. 46/140.

Acute miliary tuberculosis is caused by repeated transmission of large numbers of tubercle bacilli into the blood stream. This may follow the curettage of a tuberculous endometrium or the massage of a tuberculous joint. However, most cases are accounted for by the erosion of a vessel by an extra-vascular focus, or by the liquefaction of caseous foci (Weigert's foci), which can be seen in the intima usually of the large veins, sometimes of the thoracic duct and rarely in the arterial system. The foci in acute miliary dissemination vary in character, chiefly with the duration of the process, but they are not essentially different in character from foci observed in other forms of tuberculosis.

3. *Chronic disseminated tuberculosis*. This condition has no anatomical difference from acute miliary dissemination but often takes a protracted course, the chronicity being due to the small number of bacilli injected, classically in cases of tuberculosis of bones, joints, uro-genital system, meninges, eyes (Brooks *et al.*, 1940) etc. The foci are quite different from acute miliary tubercles. The latter are poorly defined nodules with a tendency to confluence and with exudation and hyperaemia in the surrounding lung tissue. In chronic disseminated tuberculosis the small individual foci and groups of foci are sharply defined and connected with one another by fine, barely visible, fibrotic strands (Figs. 7, 8 and 9). Histologically, fibrotic proliferation predominates, caseation, if present, being confined to small areas (Fig. 9).

This definite fibrotic character of the foci accounts for a dilatation of the alveoli and small bronchi in the neighbourhood of the shrinking nodules. Thus small, emphysematous bullae alternate with fibrous miliary nodules, the so-called *disseminated emphysematous tuberculosis* (Fig. 7).

In chronic disseminated tuberculosis the miliary nodules are not evenly distributed through the lungs but show predilection for the apical areas or the subpleural tissue (*corticopleural dissemination* (Fig. 8).

Cavities are sometimes found in chronic disseminated tuberculosis. Caseation is not conspicuous in their walls and the radiograph suggests that holes have been 'punched' out of the pulmonary parenchyma.

Tuberculous bacteraemia is found only occasionally in acute and chronic dissemination. The presence of serum substances preventing the general growth of tubercle bacilli *in vitro* (Pagel, 1940) may account for this. Emmart and Seibert (1945) have shown a globulin to be responsible for the bacteriostatic action of certain sera. Lysozyme may also play a part (Myrwick and Weiser, 1951).

FIG. 7.—Chronic disseminated tuberculosis. Two typical X-ray appearances.

Right: Bilateral symmetrical dissemination of hard, super-miliary nodules.

Male, aged 55. Death from meningitis. C.M.H. P.-M. 47/92.

Left: Haematogenous emphysematous tuberculosis, i.e. spread of fibrosing nodules with alternate emphysematous bullae.

Male, aged 63. Death from tuberculous meningitis. C.M.H. P.-M. 47/136.

FIG. 8.—Chronic miliary tuberculosis showing the so-called cortico-pleural type. Dissemination of well-defined, fibrosing nodules in the apical and subpleural parts in a bilateral symmetrical distribution. Near the base the right lung shows caseous pleurisy.

Male, aged 30. Duration of disease three years, chiefly in a picture of repeated and bilateral pleurisy. Death from tuberculous meningitis.

FIG. 9.—Demonstrating apical miliary dissemination with typical histological appearances. The latter show a tubercle with epithelioid cells and a giant cell surrounded by thickened septal tissue and also simple thickening of peri-vascular connective tissue which 'lymphangitic' form is characteristic of completely fibrosed tubercular changes.

Age. There is no relationship between the distribution of chronic disseminated tuberculosis and age; 54 per cent. of cases are found between the ages of 25 and 45, compared with bronchogenic phthisis, 58 per cent. of cases of which occur between these age limits.

Post-Primary tuberculosis: Bronchogenic Tuberculosis

Bronchogenic tuberculosis differs from primary tuberculosis in that the regional lymph nodes, though they may show some non-specific reactive changes and transitory swelling, remain devoid of appreciable caseation. It differs from disseminated tuberculosis in that it is restricted to the lungs and the sputum draining channels (larynx and gut); further, the lesions are asymmetrical and have a marked tendency to caseation and cavitation. As the condition progresses it is characterized by gradual destruction of the lungs by caseous and liquefying lesions produced by transmission of the bacilli along the bronchi.

These lesions may eventually prove fatal or death may follow laryngeal or intestinal tuberculosis, usually caused by gross aspiration of bacilli and their implantation in the mucous membranes.

The 'early' infiltrate (Assmann's focus) which leads to progressive bronchogenic tuberculosis may be found in an infraclavicular area, or in the apical and subapical regions of the upper lobe or in the apex of the lower lobe. Any of these areas, but particularly the infraclavicular one, may become the source of bronchogenic disease.

The early infiltrate itself may arise from:

1. *The primary focus.* The primary cavity, mentioned above, can be seen in adults (Fig. 10) as well as children, and is a potential or actual source of phthisis. Nassau and Pagel (1951) report 11 out of 23 primary lesions in surgical lobectomy specimens which show cavitation of a large primary focus. The average age of this group is 23.5 years. These figures emphasize that the primary cavity often provides the breeding ground and the source for coarse bronchogenic transmission of tuberculosis.

When in a solid state such foci as examined by Nassau and Pagel are often called *tuberculomata*. This term does not represent a specific entity but embraces any large caseous focus with fibrotic capsule. Such foci are either slowly progressing primary (Fig. 11), or re-infection foci, or inspissated cavities (Fig. 12) or haematogenous foci.

2. *Genuine reinfection.* This means a second primary complex which occurs but rarely because most individuals retain their sensitivity to tuberculin.

3. *Superinfection.* This term implies bacillary invasion of a primarily infected person in whom

there is still acquired ('allergic') resistance sufficient to prevent a further primary complex from developing. Instead, a new focus is supposed to form at the site of entry of the bacillus without affecting the hilar lymph nodes but progressing by local extension, cavitation and bronchogenic spread. Superinfection does not lend itself to anatomical or experimental investigation. It may explain cases of tuberculosis in primarily infected persons in close and prolonged contact with heavy bacillary doses.

4. *'Endogenous development.'* This implies the setting up from *within* by the bronchial or haemic route of the early post-primary focus which, by its cavitation and bronchial spread, actually leads to bronchogenic phthisis. Such endogenous development may give rise to an early infiltrate. This can be due to the confluence of small haematogenous foci or to recrudescence of any pre-existing focus (haematogenous or bronchogenic). Such pictures of recrudescence are seen in conditions weakening resistance, such as diabetes, pregnancy, carcinoma and starvation. It is recognizable by the picture of 'pultaceous liquefaction' (Fig. 13), i.e. of liquefaction occurring in a calcified focus (Pagel, 1952). A calcified lesion may contain viable tubercle bacilli which may become re-activated in suitable circumstances.

Summary

The following possibilities in the evolution of tuberculosis in man may be envisaged:

1. The progressive or regressive primary complex with or without abortive dissemination.
2. Disseminated tuberculosis fully developed.
3. Abortive dissemination followed by bronchogenic tuberculosis.
4. Fully developed disseminated tuberculosis but healed and followed by bronchogenic tuberculosis.
5. Fully developed disseminated tuberculosis with subsequent bronchogenic tuberculosis.
6. Fully developed bronchogenic tuberculosis followed by fully developing disseminated tuberculosis.

Extensive post-mortem and X-ray investigations (Pagel, 1933; Reisner, 1934; Tepper and Jacobson, 1943) have shown that the majority of cases fall into groups 1 to 4. Instances belonging to groups 5 and 6 do occur but are much less common.

7. *Bronchogenic tuberculosis* either develops from a primary lesion within a short interval or after a protracted period of latency. In the former case, it either emerges from a cavitating primary focus by local extension or endobronchial spread, or else from 'sub-primary' (probably haematogenous) nodules, some in the apical and posterior segments of the upper lobes. The rapid evolution

FIG. 10.—A primary cavity in an adult (P.C.) in the lower parts of the right upper lobe. The enlarged and caseous paratracheal lymph nodes (L.N.).

Inset: The chest radiograph showing the cavitating primary focus (P.C.).

Male, aged 18. C.M.H. P.-M. 44/257. Death from tuberculous meningitis.

FIG. 11.—A primary tuberculoma. Lobectomy specimen. A large, encapsulated, partly calcified, partly cavitating primary focus.

Upper inset: Shows the caseous and calcifying regional lymph nodes.

Lower inset: A specimen radiograph showing the small, calcified nucleus of the tuberculoma and calcification of regional lymph nodes.

FIG. 12.—To demonstrate a pseudo-tuberculoma which is, in reality, a healed cavity. Chest radiograph showing the cavity still patent. Specimen: An inspissated, caseous, calcifying focus at the former site of the cavity and inspissating caseous bronchitis leading to it.

FIG. 13.—To demonstrate pultaceous liquefaction. Left: P.L.—A partly old caseous, chalky, partly cavitating focus near the apex. C.F.—Disseminated calcified foci.

Right: Histological appearances of pultaceous liquefaction. P.M.—liquefying material. T.B.—Large clumps of acid-fast bacilli indicating large clumps of tubercle bacilli. The intimate mixture of liquefying areas with abundant tubercle bacilli indicates recrudescence of an old focus, which is thereby converted into a source of bronchogenic tuberculosis.

of bronchogenic tuberculosis from a primary infection is seen typically in young adults. If bronchogenic tuberculosis is separated from primary infection by a long interval, the picture of recrudescence may be observed either in the old primary lesion or in old post-primary foci—a development not infrequently seen in middle-aged or elderly people.

In this view primary and bronchogenic tuberculosis appear to be connected with each other, the latter being interpreted as a manifestation of tuberculosis developing from 'within,' rather than from superinfection.

This interpretation of bronchogenic tuberculosis as an 'endogenous' development in no way interferes with the demand for eradication of sources of infection, for it is an exogenous, *i.e.* the primary, infection which will lead to phthisis, if contracted at a time when natural or acquired resistance is low, for example at puberty or in periods of economic stress, intervening diseases, or with malnutrition. Although possibly a few tubercle bacilli may be capable of setting up primary infection when brought into contact with the lung in the experimental animal, in human adults such seeding will be more likely when there is a source productive of massive bacillary doses ('the full

sputum mug') and that protracted exposure which gives the bacillus an opportunity to reach its victim at a moment when resistance is low.

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