THE NATURAL HISTORY OF PULMONARY TUBERCULOSIS

Dr William Harris, Professor of Clinical Medicine of New York University, School of Medicine describes, in this series of slides, the natural history of pulmonary tuberculosis and the importance of early diagnosis and treatment in achieving cure.

The World Health Organization and other agencies have developed guidelines for the diagnosis and treatment of tuberculosis. Throughout the world where these recommendations are used, the cure rate of TB cases has increased, and control of the disease within communities has improved. However, in addition to using these guidelines appropriately, physicians need to be familiar with the natural history of pulmonary tuberculosis and its varied clinical manifestations, in order to understand events that may occur in their patients.

Slide 1 shows an unconcentrated sputum specimen stained with Ziehl-Neelsen stain, demonstrating the typical appearance of acid-fast bacilli.

Slide 2 shows a similar specimen stained with auramine and examined with a fluorescence microscope. This technique is used in many laboratories because it permits more rapid reading. Both methods detect various species of mycobacteria, but *M. tuberculosis* is, by far, the most common cause for positive acid-fast stains among patients with pulmonary disease.
Slide 3 illustrates colonies of *M. tuberculosis* growing on laboratory media. Other species, such as *M. avium* may appear similar, but can be distinguished by specific chemical and other tests.

Although the disease tuberculosis was known for many centuries to be a major cause of an illness called consumption and death, its cause was unknown. The specific cause was first proved in 1882 by Robert Koch, (slide 4), who recognized the germs in stained sputum from patients with the disease.
We turn now to Miss EB, a healthy 19 year old woman who entered nursing training in 1940. A tuberculin skin test (TST) was negative, indicating that she had never become infected with the tubercle bacillus. Sometime during the course of her duties in the hospital, she was exposed to a patient with infectious TB who coughed and disseminated small droplets containing tubercle bacilli into the air (slide 5). These tiny droplet nuclei float in air; the fluid evaporates, and the living tubercle bacillus may remain airborne for long periods. Another individual who inhales the organism may become infected.

Initially, there is a rapid inflammation with polymorphonuclear leukocytes at the alveolar site where the tubercle bacillus is deposited. This inflammatory reaction does not usually curtail the growth of the organism, however, and it proliferates and extends the local reaction. Tubercle bacilli drain via lung lymphatics to the hilar lymph nodes, to the thoracic duct and ultimately may gain entry to the systemic venous circulation. From there, they recirculate to the lungs and can cause additional local foci of infection.

Organisms may escape from lung capillaries to the systemic arterial circulation and become deposited in various organs throughout the body. Such extra pulmonary foci may progress promptly, but more often, they remain dormant throughout life, or may exacerbate many years after the initial infection.

After a period of 6-12 weeks following the initial infection, cellular immunity directed to the tubercle bacillus develops. Stimulated by antigens from the organism, T-lymphocytes become specifically sensitized and activated; these in turn activate macrophages that become capable of antibacterial action against the tubercle bacillus. The cellular immune reaction provides the basis for the tuberculin skin test, and for the characteristic pathologic lesion, the granuloma, that is typical of tuberculous infection.
Six months later, Miss EB received another tuberculin skin test which was positive, indicating that she had become infected with the tubercle bacillus.

**Slide 6** shows the technique for the intradermal injection of "purified-protein derivative" (PPD) antigens derived from tubercle bacilli.

**Slide 7** demonstrates a positive reaction measuring 25 mm of induration when examined 48 hours after injection.

The bovine strain of mycobacteria used for BCG vaccination also induces a cellular immune reaction that responds to PPD as well as to the bovine antigen. This cross reaction diminishes the specificity and generally reduces the accuracy of the TST in countries where BCG is widely used.
As is the case with most individuals during the early period of infection by TB, EB remained completely free of symptoms. A chest radiograph (slide 8), obtained to determine if she had developed a radiologically visible lung lesion, was normal.

However, at some site in her lung parenchyma there was, likely, a tiny granuloma as shown in slide 9.

The lesion is composed of a roughly spherical collection of lymphocytes, macrophages and epithelioid cells with a small area of central caseation necrosis, a granuloma typical of TB.

Slide 10 shows the microscopic appearance of a similar granuloma in the liver where a tubercle bacillus was deposited subsequent to "post-primary" dissemination.
In the great majority of individuals who become infected with the tubercle bacillus, possibly 90%, these small granulomas remain localized and quiescent, become encapsulated with fibrous tissue, and may ultimately demonstrate calcification of the central caseum.

Slide 11 shows the chest radiograph of a TST positive patient with a tiny calcified granuloma in the right mid lung field.

About 10% of infected individuals develop tuberculous disease, due either to progression of the lesion as a continuous process within a year or so after infection, or years later after a long dormant period.

Miss E.B. remained completely well for about a year, but then developed an acute episode of right pleuritic chest pain, fever and dyspnea. A chest radiograph (slide 12) demonstrated a large right pleural effusion. A thoracentesis yielded straw-colored fluid with elevated protein and lymphocytic cellular predominance, findings typical of tuberculous pleuritis. At some site in the right lung, a small TB focus located under the visceral pleura eroded into the pleural space and spilled organisms there. These, in turn, implanted on the pleural surfaces causing multiple granulomas and an outpouring of inflammatory fluid into the pleura.

Pleural biopsies were not used in 1941, but modern techniques of pleural needle biopsy frequently demonstrate caseating or noncaseating granulomas.
Slide 13 shows such a lesion in the pleura, a mononuclear cellular reaction with an area of caseous necrosis.

Antituberculous chemotherapy was not available in 1941, but the patient received bed rest therapy for several months while the fluid resorbed, the typical course of most tuberculous pleural effusions, even without specific treatment.

Slide 14 shows complete clearing of the pleural effusion within a four month period. Her physician, realizing that she was now at greater risk of developing active TB in the lung, and having no anti-tuberculosis treatment to offer in 1941, obtained chest radiographs every three months.

Slide 15, a chest radiograph taken 6 months later, demonstrates a new rounded shadow in the right upper lobe.
If this lesion could be examined pathologically it would likely appear as shown in slide 16. This is a typical tuberculous nodule, the lower portion of which contains a mononuclear cellular reaction, and the upper zone, a homogenous, acellular area of caseation necrosis.

The future of such an individual, with respect to tuberculous infection, depends largely upon the subsequent behavior of the caseous component of such a lesion. In most subjects, the lesion becomes surrounded by fibrous tissue, and the caseum calcifies, leading to a stable encapsulated tuberculoma.

In other subjects, for reasons that are not clearly understood, the caseous material undergoes liquefaction, tubercle bacilli proliferate and produce more antigen at the site, which causes a greater cellular immune response, and the lesion enlarges. Ultimately, the necrotic zone may rupture into a neighbouring bronchus, the liquid caseum drains into the bronchus, and the site is replaced by air, resulting in a small tuberculous cavity.

Miss EB was treated again with bed rest with the hope that the focus would become quiescent. A repeated chest radiograph (slide 18) after 6 months showed no enlargement or other change, and she was permitted to return to school.
About three months later, she developed a chronic cough with scant sputum but no other symptoms. A repeat chest radiograph (slide 19) showed a new irregular, hazy shadow above the rounded lesion. Examination of her sputum was positive for acid-fast bacilli, and sputum cultures grew *M. tuberculosis*.

What was the basis for this progressive lung infection? Instead of inspissating and becoming encapsulated, the caseous tissue liquefied, the local lesion extended and ruptured into a bronchus. The fluid draining from the resulting cavity contained viable tubercle bacilli that were aspirated into the neighbouring pulmonary parenchyma, where they implanted and evoked further cellular inflammatory reaction, the basis for the new shadows seen on chest radiograph.

Slide 20, a chest radiograph of another patient, shows more distinctively an X-ray visible air-containing cavity within the inflammatory tissue.
The process of bronchial drainage from the cavity, and progressive inflammatory lesions due to bronchial dissemination is further illustrated in slide 21 where the lesion is more extensive.

Slide 22 demonstrates the gross appearance of a large tuberculous cavity. The cavity is ventilated by atmospheric air which offers an ideal oxygen tension for the proliferation of the organisms. The surface of the cavity wall contains a high concentration of tubercle bacilli that spread via the bronchial system to even more remote areas in the lung parenchyma, including the contralateral lung.

The surface wall of such cavities has a polymorphonuclear cellular reaction rather than the typical cellular immune pathology. Slide 23 shows the microscopic appearance of such a cavity wall, with polymorphonuclear leukocytes extruded into the cavity resulting in what is essentially a lung abscess due to *M. tuberculosis*. This exudate is the source of purulent sputum in patients with advanced cavitary pulmonary TB.
Despite all therapy efforts, the disease in Miss EB progressed to involve both lungs (Slide 24).

Slide 25 demonstrates the pathologic appearance of such extensive inflammation, a pneumonia-like pattern of alveolar consolidation due to *M. tuberculosis*.

Slide 26 illustrates the basis for progressive extension of the TB lesions because of bronchogenic dissemination. New caseous lesions lead to new cavities which produce airborne infected particles in the bronchi. These are in turn aspirated into remote areas of the lung parenchyma.
Miss EB’s pulmonary tuberculosis progressed inexorably over the next several years. She suffered persistent fever, severe night sweats, chronic cough with sputum production and occasional bouts of hemoptysis. She was one of the earliest patients in New York City to receive streptomycin (SM) when it became available. Initially, there was a reduction in the number of tubercle bacilli in the sputum, but this improvement was short-lived as the *M. tuberculosis* rapidly developed resistance to the drug.

**Slide 27** demonstrates how SM resistant tubercle bacilli emerge when the drug is given alone. Before treatment, the *M. tuberculosis* population, present predominantly in cavities, consists of one SM resistant bacillus to every million SM susceptible organisms. SM rapidly kills the susceptible but does not effect the resistant bacilli. As the number of SM susceptible bacilli diminishes, they are replaced by SM resistant ones that become the predominant *M. tuberculosis* in cavities and contained in the sputum. When two effective agents are administered concomittantly, each drug kills the cells that are resistant to the companion drug and prevents the emergency of resistance to the other.

**Slide 28** shows EB’s chest radiograph a few months before she died of the disease. This shows multiple cavities replacing and destroying most of the lung parenchyma.

This patient had progressive tuberculous disease almost from the beginning of the infection. Other patients develop active TB many years after the initial infection when tubercle bacilli in a long dormant lesion in the lung begin to multiply, and the basic cycle of TB progression, illustrated in **slide 26**, ensues.
Slide 29 is a chest radiograph of a 55-year-old male, a long time resident in a psychiatric hospital, which shows a small, densely calcified TB focus in the right lower lung field. This lesion had been visible on serial chest radiographs's for more than 10 years.

Slide 30 is of a routine chest radiograph taken one year later. Close inspection reveals a new linear shadow just medial to the calcified focus. The patient was completely free of respiratory symptoms at the time and no diagnostic investigation or treatment was undertaken.

A repeat chest radiograph (slide 31) shows extensive, confluent tuberculous lesions in both lungs. In retrospect, the changes in the chest radiograph shown in slide 30 were the walls of a thin-walled tuberculous cavity that had developed near the calcified focus from an old, previously quiescent, caseous granuloma in the lung. The new infiltrates seen in Slide 31 developed in parenchymal sites of bronchogenic dissemination of tubercle bacilli from the thin-walled cavity.
We will now consider how TB lesions heal, either spontaneously or following appropriate chemotherapy. It is important to recognize that the lesions that develop in tissue infected with tubercle bacilli, as seen in histologic sections, or as shadows on a chest radiograph, are caused by the reaction of the host's cellular defense to the presence of antigens from the tubercle bacillus. If tubercle bacilli die, or become dormant, the cellular reaction subsides as the concentration of antigen lessens.

Slide 32 depicts schematically the usual mode of healing of various types of lesions. Cellular, exudative lesions may completely resorb leaving no residual in the lung parenchyma, or they may lead to a fibrous scar. Caseous lesions usually do not resorb, but can inspissate and, surrounded by a fibrous capsule, become a typical tuberculoma. Liquefied caseum, if it does not rupture into a bronchus, may also inspissate and evolve into a tuberculoma.

Active tuberculous cavities can also heal if the bronchocavitary junction becomes obstructed; intracavitary air is absorbed, and the space filled with liquid exudate that ultimately inspissates. The attempt to achieve this series of changes prompted the use of collapse therapy before antibiotics were available to treat tuberculosis.

With chemotherapy, cavities may heal in the same fashion, leaving a "filled-in" cavity that ultimately is encapsulated with fibrous tissue as a tuberculoma. Slide 33 shows a chest radiograph with a large spherical density in the RUL.

Slide 34 shows a resected lobe that contains a large, homogenous caseous mass, the end result of a tuberculous cavity that inspissated and encapsulated.
With chemotherapy most large cavities undergo "open" healing. The bronchocavitary junction remains patent, the cavity is ventilated by the entering bronchus, but most or all the caseous material is extruded, and the cellular reaction resorbed. The remaining cystic space is composed of a fibrous wall that may be virtually free of cellular reaction.

*Slide 35* is of a chest radiograph demonstrating advanced pulmonary TB with a large cavity in the left upper lobe.

*Slide 36* is a chest radiograph taken after successful therapy, and shows a persistent thin-walled cavity and a markedly contracted LUL due to the fibrous healing of the extensive tuberculous lesions.

Without chemotherapy, pulmonary cavities due to TB must be assumed to represent active tuberculous disease, since spontaneous "open" healing rarely, if ever, occurs. With appropriate therapy, however, such as that recommended by WHO guidelines, the relapse rate following therapy is very low, even if large "open" healed cavities remain.

We have reviewed only two individuals from the past who had pulmonary tuberculosis but have not touched on the importance of the disease today.
Slide 37 shows the worldwide rates of tuberculosis estimated for the year 1997 represented by colour code. The estimated number of cases in 1999 was 7.9 million. The DOTS strategy cures 85%.

Slide 38 What is DOTS? It is more than observing TB drug treatment. It is a government commitment to a country-wide network of diagnostic sputum smear microscopy labs, uninterrupted drug supply to every district, recording and reporting and outcome evaluation, and government commitment to resourcing the programme. But only less than 25% of patients receive DOTS and therefore many go undiagnosed and untreated. An estimated 1.8 million people died of TB in 1997.

Slide 39 shows the projection for TB case rates with current programmes, compared with more rapid increase in the delivery of DOTS. The medical practitioner is critical to the control of TB for suspecting a case in a person coughing more than three weeks and referring them to the laboratory for sputum smear microscopy.