Tuberculosis and Respiratory Disease
□ **Review** □

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Transition in Mode of Onset and Progression of Tuberculosis

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According to the classical theory for pathogenesis of tuberculosis, the disease was divided into two types: primary tuberculosis of so-called child type and secondary tuberculosis of adult type. Primary tuberculosis, which develops following a primary infection and is characterized by a lymph-hemic spread of tubercle bacilli, was further divided into the following subtypes: 1. hilar lymph node tuberculosis, 2. early dissemination, 3. so-called idiopathic pleurisy, 4. perforation of the hilar lymph node lesion into the bronchial lumen with subsuquent aspiration pneumonia, and 5. cavitation of primary lung lesion. In contrast, secondary tuberculosis which develops many years after the primary infection, shows characteristic features of isolated organ tuberculosis, cavity formation and canalicular spread of bacilli. However, these pathogenetic patterns are insidiously going to change or be modified, along with a decrease of tuberculosis, probably in any country.

Changing Pattern of Primary Tuberculosis

1. Hilar Lymph Node Tuberculosis

According to age distribution, the registered cases of hilar lymph node tuberculosis in 1990 in Japan peaked in the age group of less than 5 years old, whereas around one fourth of the cases were found in those of 30 years old and more, up to over 70. This may be explained partly by a yearly decrease of infection rate in the whole country which resulted in an increasing percentage of non-infected people

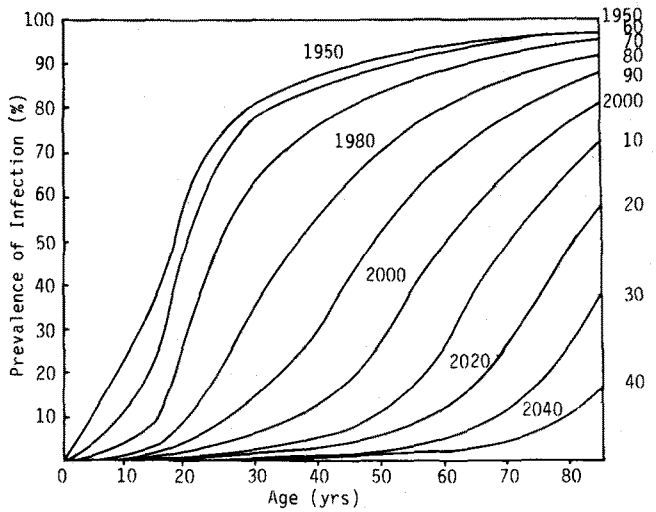

Fig. 1. Trend of infection rate by age[2].

among the older people (Fig. 1) and retardation of primary infection age towards higher ages. At the same time, it must be noted that, especially among aged people, there is a possibility that an incompletely healed primary lymph node lesion relapses due to immunological impairment, leading to reccurence of lymph node tuberculosis. The bacteriological studies in the past which revealed positive cultures on calcified lymph node lesions at substantial percentages, supported a possibility of such re-aggravation. We have to recognize that a calcified lesion does not always mean a healed change, and that tubercle bacilli may survive very long in these non-treated inactive lesion.

2. Miliary Tuberculosis

Pathological examination on 28 autopsy cases of miliary tuberculosis revealed a presence of four patterns in the disease: a) progression subsequent to primary complex (early dissemination) in 2 cases, b) dissemination from an active lesion in secondary tuberculosis (late dissemination) in 16 cases, c) dissemination from relapsed primary lymph node lesions in 7 cases, and d) progression from secondary complex in 2 cases which were seen in the cases of over 60 years of age. The age distribution of registered clinical cases of miliary tuberculosis in 1989 in Japan showed a small peak in children which probably corresponds to early dissemination, and another high peak in seventies corresponding to any of b), c) and d) patterns as described above. Miliary tuberculosis with meningitis which was a representative cause of death in tuberculous infants has decreased markedly and miliary tuberculosis in now coming to be a disease in aged peoples whose immunity is reduced.

3. Idiopathic Pleurisy

So-called "idiopathic" pleurisy has been presumed to occur through a spread of tubercle bacilli from a primary lung or hilar lymph node lesion to the pleural surface and was observed mostly in young peoples. However, we recently experienced an autopsy case of pleurisy in an 84 year old female. She died suddenly on the second day of admission, and the cause of her death was detected on autopsy to be fresh myocardial infarction. A re-activated, calcified primary lung lesion was noted beneath the pleura, and active inflammatory change continued from the lung lesion to the pleural surface. Recurrence of an old tuberculous focus may partially explain the way of onset of "idiopathic" pleurisy in the aged.

Metamorphosis of Tubercle Bacilli

Acid-fast rods are the typical feature of tubercle bacilli growing vividly on culture media, on cavity walls, and hence, in sputum. However, tubercle bacilli can transform into short, granular appearance with non-acid fastness in caseous necrosis where oxygen supply for the bacilli is insufficient, and many caseous lesions show negative stain by Ziel-Neelsen staining. When these unstainable bacilli

Table 1. Effect of Nyka's Fixation

Specimen No.	4% Formalin	Nyka method
1309	−	++
1327 − 1	−	++
− 2	−	+
1370 − 3	+	+++
− 4	−	+
− 6	−	−
1681	−	+
1683	+	++
2821 − 1	−	−
− 2	−	++++
x	+	++
1589 − 4	−	−
− 5	−	−
1644 − 2	−	+
− 6	−	++++
1651 − 7	−	+
1658	−	+

in the lesions were stained with ordinal Ziel-Neelsen stain after the Nyka's fixative treatment which includes strong oxidative procedures, various sized acid-fast bacilli were demonstrated in these necrotic areas (Table 1).

In order to follow this metamorphosis of tubercle bacilli in the in vitro system, we cultured tubercle bacilli in Sauton's media and sealed the culture media with a thick layer of liquid paraffin after tubercle bacilli had grown forming a thick membrane on the surface of the liquid media. The first culture was carried out in 1964, and the bottles were preserved in an incubator at 37°C for over 20 years. During this long periods, the culture media changed the color from clear yellow to dark brown and turbid, and the bacillary membranes on the surface were going to sink and be disintegrated.

Recently, we have taken these culture bottles out of the incubator and examined the nature of the tubercle bacilli preserved for a long time in an hypoxemic environment. Ziel-Neelsen staining for the flocculate in the culture media showed numerous, non-acid fast cords of bacilli, but acid-fastness was recovered after Nyka' oxidative treatment. Electron microscopical observation of the culture media revealed two types of change, a loosing of cytoplasm remaining bacillary cell wall, and a shortening of bacilli which were voluminous in shape and contained surfur and phosphur.

Next, we innoculated several ml of the preserved culture media on fresh culture media of several kinds. As shown in Table 2, living tubercle bacilli were recovered from these long-preserved, hypoxemic liquid media. It was also noticed that all of the virulent strains and some of the low virulent strains, but none of the avirulent strains showed positive results. Then, the size of these surviving bacilli was examined by using milipore filters. Not a few number of living bacilli of less than 5 μm in length and a small number of bacilli of less than 0.65 and over 0.45 μm could be recovered, but no bacilli of 0.45 μm or less in size was demonstrated, indicating that tubercle bacilli may transform up to approximately 0.5 μm in length in a certain condition (Table 3).

Table 2. Recovery of Viable Tubercle from Long-Stored Culture

Strain	No. tested	No. of positive culture
M. tuberculosis		
H37RV	25	25
Kurono	5	5
Aoyama B	3	1
M. bovis		
B.C.G.	5	0

Table 3. Recovery of Viable M. Tuberculosis, H37RV from Long-Stored Culture

Bottle No.	No. of viable tubercle bacilli recovered from			
	Total hemogenate	Filtrate with 5 μm	0.65 μm	0.45 μm
17	ca. 3,000	198	35	0
23	ca. 2,000	78	2	0
35	ca. 5,000	223	0	0

These morphologic changes may represent an adaptation of tubercle bacilli to an unfavorable environment, probably accompanying a low metabolic condition by which they can survive even in an anaerobic situation. These so-called dormant bacilli might be the cause of relapse in tuberculosis after a long latent period, which is, clinically, the characteristic feature of tuberculosis.

Problems in the Pathogenesis of Secondary Tuberculosis

Concerning the onset of secondary tuberculosis, the exogenous re-infection theory and the endogenous re-activation theory have been discussed in the past. At present, we consider that the former is a possible but minor one and the latter is a believable and predominat way. For re-activation of an ante-

cedent tuberculous lesion, dormant tubercle bacilli in closed lesions, as described above, may be a necessary condition on one hand, while a high age may be another considerable factor relating to a relapse of old tuberculous lesions. Histology of the cavity wall in aged tuberculous patients shows atrophic epithelioid cell granulations with scarce lymphocytyc infiltration and reduced fibrogenesis as compared to those in young patients. Experimental observation on the extent of lung lesions and number of recovered tubercle bacilli from the lungs or spleens in the infected mice, revealed a wider area of pneumonia and a larger number of recovered bacilli in old mice when compared to those in young mice (Fig. 2). It has been reported that when a small number of bacilli was inhaled in young mice, bacilli in the lung increased to a certain number, then maintained its number until 18 months of age, and again began to multiply thereafter, relating to decreased immune response by age. Similarly, in aged humans, a reduction of many signs of cellular immunity, eg. reduced tuberculin skin reaction, a smaller number of helper T cells or IL-2 receptor positive cells, suppressed proliferative response to mitogens or IL-2 producing ability have been reported. Low albuminemia seen in these aged patients has been suspected to relate to the suppressed immunity.

Diagram of Tuberculosis Epidemic

There are two kinds of populations, non-infected and infected ones. The disease develops partly from primary lesions in the non-infected people, most commonly from a relapse of old lesions in the infected-healthy people, and in a few cases from reinfected individuals among the infected-healthy population, or rarely from the secondary complexes of the people whose immunological memory of primary infection was lost. Most of the diseased people return to the infected-healthy population after an effective treatment, but some of them die and fall out of the objective population (Fig. 2). The ratio of non-infected to infected populations varies according to the situation of the tuberculosis epidemic in each country, reflecting the natural infection rate in each age group.

With a gradual decrease in infection rate in the whole country, a gradual shift of the age distribution of the disease, and simultanous transition of the mode of onset of disease may happen in any country. Such changes seen in Japan during these 30 years were shown in Fig. 3.

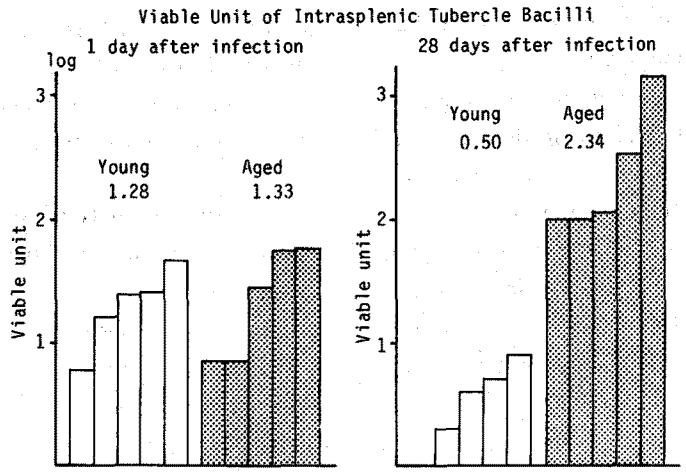

Fig. 2. No. of tubercle bacilli recovered from the spleens of young and old mice, 1 and 28 days after infection.

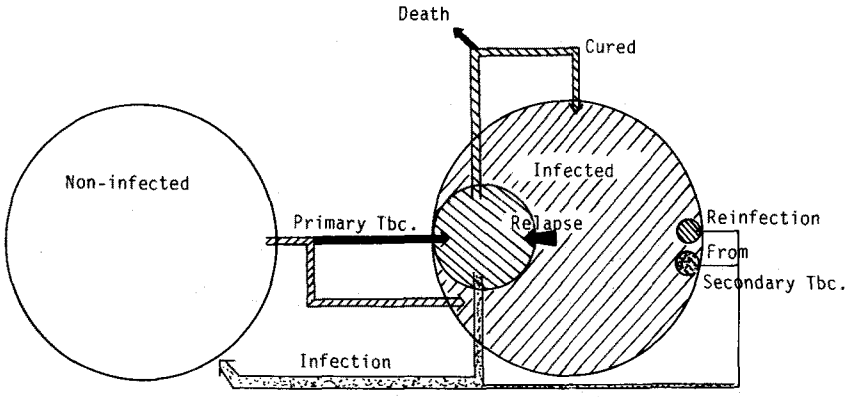

Fig. 3. Diagram of tuberculosis epidemic.

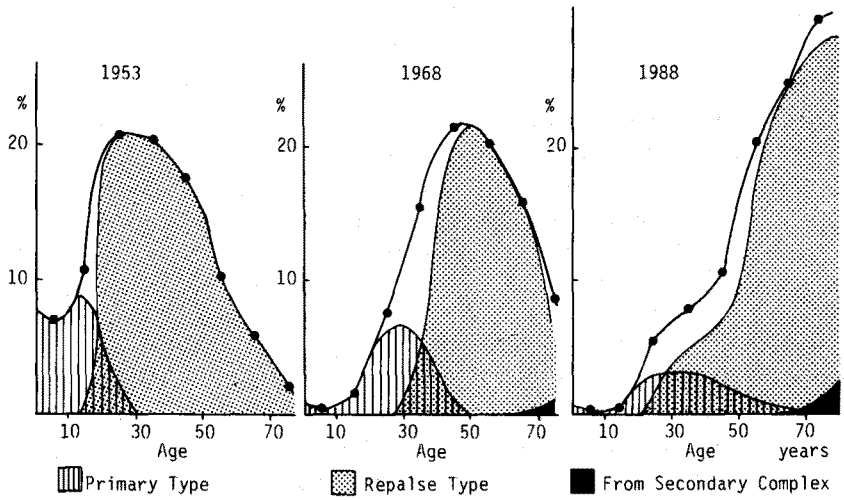

Fig. 4. Transition in onset and progression of tuberculosis.

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