Prognosis and Treatment of Tuberculosis Among Children*

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Children now constitute approximately one-third of the world's population of nearly three billion people. According to the 1960 census, there were in the United States 179,323,175 persons of whom 20,320,901 were under the age of five years, 18,691,780 from five to nine, 16,773,492 from 10 to 14 and 13,219,243 from 15 to 19 years. Thus, nearly 70 million of our citizens were 19 years old or younger.

Prevalence of Primary Tuberculosis

With rare exceptions, these children were born free from tubercle bacilli. In fact, at birth, and immediately after, has been and is the only time the people of any generation in the United States have been free from infections with this organism. In no generation in the history of this nation have even all of the newborn children been protected against tubercle bacilli. Some have been invaded with these organisms during the first few hours after birth. Obviously the infections which occurred at this time and subsequently were dependent upon persons (usually adults) with contagious tuberculosis who were permitted to associate with children, as well as the bovine type of tubercle bacilli in the diets of children.

Until the opening of the 20th century, almost nothing had been done to protect children from individuals with contagious tuberculosis, most of whom died in their homes and communities after prolonged periods in the consumptive state. Moreover, children were not protected against the bovine type of tubercle bacillus. Hence, a preponderance of girls and boys were invaded with mammalian type bacilli by the time they attained adulthood. This situation carried well over into the 20th century. However, with the advent of the National Tuberculosis Association and its component state and county organizations, information was disseminated among our citizenry everywhere and effort was begun to protect children from persons with contagious tuberculosis. The sanatorium building movement which was initiated in the latter part of the 19th century and reached its height during the second decade of the 20th century played a tremendous role. Of immense importance also were pasteurization ordinances in the cities, the flash method in villages and on farms, and finally the movement of eradication of tuberculosis among animals, particularly cattle. These procedures with continuous dissemination of information about tuberculosis began to result in freedom from tubercle bacilli of the mammalian type in the environments of enough children to cause questioning of the often repeated statement that by the age of 15 years, 90 to 95 per cent had been invaded. In 1915, Veeder and Johnston1 found in testing more than 1,300 children of 12 and 13 years in St. Louis, only 48 per cent reacted. In 1924, Slater2 startled the tuberculosis world by reporting that in testing of more than 1,600 grade school children in a rich farming area, only 10 per cent reacted. However, he observed that among those with known cases of contagious tuberculosis in their homes, 80 per cent were infected. In Minneapolis, Harrington and Myers' reported that 47 per cent of grade school children reacted in 1926. In the same county, Mattil and Fenger3 found that 22.5 per cent of rural grade school children reacted. Chadwick and Zacks4 (1929) tested more than 42,000 school children in Massachusetts and stated that 28 per cent were sensitive to tuberculin. The same year, McCain5 tested over 25,000 school children in North

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Carolina of whom 22.7 per cent of the white and 27.34 per cent of the Negro children reacted.

In the third of a century or more following these and other similar reports, there was intensification of the tuberculosis eradication activities among cattle, the isolation of adults with contagious disease, introduction of extensive epidemiologic work, dissemination of more and more information by tuberculosis associations, increased interest and activity of medical and nursing organizations and of numerous physicians in private practice. Thus, there was ever increasing protection of children with sharp declines reported in the percentages of tuberculin reactor children.

Harrington and Myers' and Myers and co-workers' tested city grade school children in the same schools approximately every ten years with gratifying results from about 47 per cent reactors in 1926, 19 per cent in 1936, 8 per cent in 1944 and 4 per cent in 1954. In this study, among the children tested in 1926, more than 20 per cent of those of six years reacted whereas in 1954 only 1.7 per cent reacted. This decline of infections among children has continued, and in many places it is now difficult to find more than 2 per cent reactors in grade schools and 3 to 4 per cent in high schools. Testing of 14,164 first grade children in Boston6 in 1962 revealed only 77 (0.6 per cent) infected. Jordan7 reported finding no tuberculin reactors among 3900 children in rural and village schools in western Minnesota. Pronounced reductions in invasions of tubercle bacilli have occurred among children in other countries, including Scandinavian nations, the Netherlands and Canada, which used good isolation facilities for contagious cases of tuberculosis and have controlled tuberculosis among domestic animals.

The fact that such large numbers of girls and boys were entering adulthood uninfected with tubercle bacilli a few decades ago was difficult for many persons to accept. When Lees and Myers8 tested the entering students at the University of Minnesota in 1928 and found that only 33.14 per cent reacted, many believed errors had occurred with reference to such items as deterioration of tuberculin and method of administration. However, in testing the entering class the next year, making sure of compliance with critics' suggestions, only 31.08 per cent reacted. When Heimbeck,9 in Oslo, tested students on admission to a school of nursing in 1928 and found only 48 per cent reactors, he had difficulty in believing the results. He then tested medical students and military recruits of approximately the same age with about the same outcome. This was contrary to the statement that had been parroted so long around the world to the effect that approximately 100 per cent of young adults were infected with tubercle bacilli. The fact that had been overlooked in Oslo, as in many other parts of the world, was that previous effort to protect children had borne fruit and what was then observed among young adults was to have been expected.

As such large numbers of young adults having escaped infection were more generally observed, great fear was expressed about their future. Many physicians believed that if humans first became infected in adulthood, they would develop rapidly progressive, fatal tuberculosis. Therefore, they thought an error had been made by protecting these persons from tubercle bacilli in childhood. However, since this had occurred, many believed that with great promptness living tubercle bacilli of "reduced virulence" should be introduced into their bodies to make up for the "deficiency."

**Pathogenesis**

The early pathogenesis of primary tuberculosis was established experimentally by Vorwald10 who showed that within an hour after the invasion of tubercle bacilli, multiple lesions have begun to develop and their evolution was observed hour by hour. It is well known that bacilli of first invasions are focalized in many places and in various organs. From the original points of focalization, some bacilli pass to regional
lymph nodes where similar lesions are produced. These, along with an original lesion, constitute a primary tuberculosis complex.

The early reaction of the body's defense mechanism to tubercle bacilli is non-specific, not differing from the reaction to inanimate particulate material such as silicon dioxide. Usually the lesions of the primary complexes harboring tubercle bacilli are walled off, first with columns of white blood cells, then fibrous tissue, then lime, and often bone.

**Diagnosis of Primary Tuberculosis**

Inasmuch as early observations revealed that a great preponderance of the tuberculin reactor children and young adults appeared in normal health and x-ray films of their chests were unrevealing except for evidence of calcific deposits in approximately 25 per cent of them, several theories evolved. One was that these individuals were infected but did not have the disease. Another was that in controlling the infection, immunity had been acquired so there was no likelihood of subsequent development of clinical disease. However, in 1912, Ghon had reported on meticuous post-mortem examinations of the bodies of 184 children who died from nontuberculous conditions, but during life had no evidence of tuberculosis except sensitivity to tuberculin. In 177, lesions were found in lungs or regional lymph nodes or both. The lesions were so small in some cases that he returned and took a second look because of the previous tuberculin reaction. In five bodies, lesions were not found in the chest, but were located extrathoracically. In the remaining two bodies, no lesion was found, but in one of them, two guineapigs was injected with tissue prepared from the deep medial cervical and upper and lower tracheobronchial lymph nodes. The animals died from tuberculosis. In the remaining case, animals were not inoculated and tuberculosis was not diagnosed. Concerning this study, Ghon said, "From the point of view of a pathologist, I can therefore state on the basis of my own studies, which not only refer to all the cases quoted in the monograph, that I am completely in accord with those who strongly believe in the specificity of the tuberculin reaction."

Twenty years before Ghon's report and ever since the veterinary profession found lesions with such frequency in the carcasses of cattle which were apparently healthy but were slaughtered because of sensitivity to tuberculin, this test continues to be accepted as diagnostic in the periodic testing of the 99,500,000 cattle of the United States and in most other parts of the world. The magnitude of the work done by veterinarians of this country justifies their conclusion. For example, between July 1, 1917 and June 30, 1962 they administered the tuberculin test to cattle 433,321,837 times and examined at post-mortem the 4,146,577 reactors.

As primary lesions are evolving, the protein of the tubercle bacillus is liberated in such amounts as to sensitize the individual's tissues. This sensitivity starts in a slight undetectable way except by microscopic study of cells as demonstrated by Dienes and Mallory, but gradually increases until within three to seven weeks if tuberculo-protein is brought in contact with the inner layers of the skin, a demonstrable and significant reaction results which identifies the reactor as one harboring tubercle bacilli. At that time, the lesions are small and vascular. Therefore, the tuberculin reaction is the earliest diagnostic criterion and with well known exceptions justifies the diagnosis of primary tuberculosis.

Work on primary tuberculosis among children and young adults, which has been continuous since 1920, has shown that when sensitivity to tuberculin can first be elicited, x-ray film inspection of the chest reveals no abnormality in 95 per cent or more of cases except in the occasional case where the hilar shadows may appear enlarged on one or both sides. In 5 per cent or less, primary pulmonary infiltrates are of such size and consistency and are so located as to cast visible shadows on x-ray films. Snijder has recently carefully studied such le-
sions and described them as segmental infiltrations due to bronchial obstruction. The shadows these lesions cast when observed periodically indicate that the infiltrates remain unchanged for several months after which they gradually recede and become non-demonstrable by x-ray film inspection or later, in about one-fourth of such cases, calcific deposits appear at the sites of old primary foci or in hilar regions or both.

When allergy can first be elicited, if symptoms are present, they are usually so mild and fleeting as to be unnoticed or ignored. Therefore, the presence of the disease usually is unknown to the individual or his immediate associates. This type of tuberculosis is probably the most widespread major disease in the human family today. Its benignity has caused it to be overlooked among most of the persons of past generations and of the present peoples of the world.

**Prognosis of Primary Tuberculosis**

The prognosis of primary tuberculosis *per se* in children is excellent. We have observed no significant difference in those whose primary pulmonary infiltrates cast visible shadows or the hilum shadows appear slightly enlarged from those whose x-ray films appear entirely clear. We have seen no one die, nor even have significant prolonged illness, from this type of disease.

In 1959, results of follow-up study were reported on 300 children who had demonstrable tuberculous primary pulmonary infiltrates diagnosed between May, 1921 and November, 1941 of whom 267 were traced and 257 examined. The average age was about five and one-half years when the first examinations were made and about 31.5 years when traced. In no case was evidence found of significant illness or more than minor destruction of tissue having been caused by the primary lesions *per se*. In a recent report on 750 persons, 25 had died from nontuberculous conditions and of the 725 remaining, 611 were traced. These children had reacted to tuberculin at the mean age of three years and averaged 32 years of age when traced. There was no evidence that their primary tuberculosis *per se* had caused significant incapacity.

Observations of 2,266 persons who developed primary tuberculosis in adulthood revealed only 78 who presented demonstrable primary pulmonary infiltrates. The response to primary tuberculosis acquired in adulthood did not differ from that acquired in childhood. Thus, it resulted in no significant destruction of tissues or incapacity.

**Treatment of Primary Tuberculosis**

Despite the fact that the lesions of primary tuberculosis *per se* cause no significant illness, numerous methods of treatment have been employed including hospitalization, collapse therapy, drugs and resection. Equally excellent results have been observed during and following each form of treatment although controls usually were lacking. In 1935, we reported observations on three groups of children with demonstrable primary pulmonary infiltrates. One group was treated in a sanatorium, another in a special school for tuberculous children and the third in their homes. No significant difference was observed in the course of the primary lesions. They all took the same receding course. These observations justified the closing of a special school for treatment of tuberculous children which had been in operation for more than a decade.

We had long lamented the fact that no germicidal drug had been found which could be administered soon after children were invaded so as to destroy all tubercle bacilli. Hope brightened when Feldman *et al.* proved that Disodium p,p' - Sulfonyldianiline-N,N'-diguicoside disulfonate (Promin) is unequivocally effective in suppressing experimental tuberculosis induced by human type of tubercle bacilli. The findings were so promising that in the fall of 1940, we strongly considered administration of Promin to children who had recently converted to tuberculin reactors with or without chest x-ray film manifestations. However, because of its toxicity and later
proved failure as a germicide the proposed program was abandoned.

In 1947, Burns re-emphasized that if an efficacious drug were available, it would be most effective when administered as soon as possible after tubercle bacilli invade the body. Therefore, recent tuberculin converters should have such a drug administered promptly. He outlined a project for periodic testing of nonreactor children in an institution for the mentally ill. When children converted to tuberculin reactors they were to receive a course of streptomycin immediately. He procured a research grant from the United States Public Health Service. However, before the project was started, it was determined that streptomycin is only bacteriostatic. Moreover, it became known that in the presence of streptomycin, resistant tubercle bacilli emerge. Despite his enthusiasm, these facts convinced him that streptomycin was not adequate for his study. Therefore, he withdrew the project. In 1951, we began treating recent tuberculin converters with antituberculosis drugs. However, as time passed it appeared that disadvantages outweighed possible advantages and the project was discontinued.

When streptomycin, aminosalicylic acid and isoniazid were found to be so effective in suppressing tubercle bacilli in progressive clinical disease many physicians hoped they might sterilize lesions of primary complexes. Waring2324 said, "It seems completely illogical not to treat an infectious disease at the earliest possible moment." He urged therefore that "chemotherapy, especially including isoniazid, be used not only for the treatment of primary and minimal tuberculosis, but also as 'preventive therapy' in the treatment of certain 'converters' of the tuberculin test from negative to positive." Waring had hoped that early and continuous administration of drugs over prolonged periods might destroy all tubercle bacilli in the treated individual. Unfortunately, to date no single drug or combination of drugs has been found adequate. Although they are usually good suppressants, there is reason to believe that when drugs have been discontinued even after long periods of administration, the suppressed tubercle bacilli revive to become as dangerous to the subsequent health of the individual as they would have been if the drugs had not been administered. Indeed, they may then be more dangerous for having acquired resistance to drugs. In 1960, Grace21 repeated his previous warnings of the danger of resistant mutants evolving in the course of antimicrobial drug administration.

Chaves et al.22 tested bacilli from 398 ambulatory clinical cases and found 75 per cent harbored drug resistant strains of tubercle bacilli. In another group of 428 previously untreated clinical cases, some degree of isoniazid resistance was found in 13.8 per cent as compared to 6.5 per cent observed in similar tests in 1955. Among men of the skid row variety, 40.8 per cent had organisms which showed some degree of resistance to one of the drugs. In Tokyo, T. Haga et al.23 reported on 873 pulmonary resections on which tubercle bacilli were tested with reference to susceptibility to drugs before surgery. The number of streptomycin resistant cases increased year by year from 6.6 per cent in 1954 to 13.4 per cent in 1955 and 36.1 per cent in 1959.

Meissner24 stated that in eight countries among formerly treated patients readmitted to sanatoriums, resistant bacilli were found in 16 per cent in Holland, 32 per cent in England and Poland, 45 per cent in Germany and Austria, 51 per cent in Belgium and Yugoslavia and 83 per cent in Canada. In the same year, primary resistance among untreated patients was found in 2.7 per cent in Germany and Holland, 4.4 per cent in Belgium, 4.6 per cent in England, 14.0 per cent in Poland, 15.0 per cent in Canada, 17.0 per cent in Austria and 19.0 per cent in Yugoslavia.

Concerning the extensive practice of home treatment of tuberculous adults, Kendig25 called attention to a problem that may prove extremely serious. He said: "One of the factors which has contributed
to the closure of sanatoriums in addition to the lower case rate has been the increase in frequency of home treatment. The introduction of chemotherapy made possible the treatment of an increasing number of patients in this way. It is difficult to speak authoritatively on the advantages and disadvantages of home therapy. But, one thing seems certain—more children are infected in these homes."

In this country, numerous persons, including many in the upper age brackets for whom there was no hope of complete recovery, have received antituberculosis drugs. It is likely that many of them have since transmitted drug resistant tubercle bacilli. It has been estimated that there are now 7,000,000 persons in the United States harboring drug resistant tubercle bacilli and that the number is rapidly increasing. After extensive observations, Chaves et al.35 said, "In spite of all effort, however, the time may come in the years ahead when the majority of organisms isolated from untreated tuberculous patients may be strongly resistant to isoniazid and possibly to streptomycin and PAS as well."

There seems little doubt, therefore, that an appreciable number of tuberculin reactor children of three years and younger, as well as recent converters among older children, have been infected with drug resistant tubercle bacilli. This can be determined from tubercle bacilli recovered from bronchial or gastric washings in 25 per cent or more of recent converters. Gorley36 found acid-fast bacilli in gastric washings of 40 per cent of 210 children studied. In 20 cases examined periodically, the duration of presence of bacilli in gastric contents was five to 12 months in 10, and 12 to 18 months in 10. In the remainder, for the most part, biopsy material would need to be obtained to recover tubercle bacilli for study.

Sight must not be lost of the apparent impossibility of convincing many parents to administer drugs to children for a year or more in whom the only evidence of tuberculosis is the tuberculin reaction. In fact, it is not possible to have correct and precise information as to how regularly such children and recent converters living in their homes take the drugs. Novak21 has commented editorially on a study conducted by Lichenstein on 1257 children under four years of age. It was found that 15 per cent of the eligible children never started to take the prescribed drug. Of those who started, 38 per cent failed to complete a year. Moreover, of the 47 per cent supposed to have finished, many of the parents admitted they did not give the drug regularly. The policy of treating recent converters will be sound only when a dependable and safe germicidal drug becomes available. At the time of conversion, the lesions are small and vascular. Therefore, a germicide in the blood stream could be expected to reach all tubercle bacilli in the multiple lesions in the patient's body and thus cure the disease in the strict sense of the word. How soon lesions lose their blood supply has not been determined. In any event, once it is lost, tubercle bacilli in such avascular areas would most likely be safe from any drug, regardless of its germicidal qualities or its concentration.

It must also be emphasized that resectional surgery for primary tuberculous lesions is not a panacea since it is not possible to remove all lesions of primary complexes.

To date, no method of treating primary tuberculosis, including antituberculosis drug and resection of demonstrable lesions, has changed its excellent prognosis regardless of how much or how little treatment was administered.

Bjerkedal and Palmer37 have recently reported that administration of isoniazid in minute doses to tuberculous guinea pigs over prolonged periods not only resulted in loss of sensitivity to tuberculoprotein, but also prevented the animals from later dying from tuberculosis. Moreover, with these minute doses there was no side effect and no resistant mutant appeared. This report of apparent complete sterilization in animals is exceedingly encouraging in that
this method may prove equally effective in recently infected humans.

Reinfection (Clinical) Type of Tuberculosis in Children

Although primary tuberculosis per se is an extremely benign disease, it sets the stage for all incapacitating and killing clinical forms of tuberculosis. While lesions of primary tuberculosis complexes usually become encapsulated, bacilli may escape from them while this is being accomplished. Moreover, after capsules are well formed they may be resorbed so the bacilli they contain are liberated on allergic tissue thus resulting in endogenous reinfections. Instead of the mild reaction of the tissue to tubercle bacilli of the first invasion, an intense specific reaction now occurs when they are implanted on allergic tissue. This is because tuberculoprotein is destructive to tissue sensitized to it. Although some reinfections are brought under control, at least temporarily, by the natural defense mechanism of the body, others produce continuous or intermittently progressive disease. Both acute and chronic forms of clinical tuberculosis develop in children from endogenous reinfections.

Birth to Four Years

With such high incidence of primary tuberculosis among infants and children before and at the beginning of this century, there were correspondingly high morbidity and mortality rates. Drolet pointed out that in the United States in 1868 tuberculosis mortality among infants was 1,000 per 100,000 living. In 1900, the rate was 311.6 for infants under one year of age and 101.8 for those from one to four years. ('The rate for people of all ages in 1900 was 194.4 per 100,000.)

Many persons expressed the opinion that in infancy and early childhood, the human body has exceedingly high susceptibility and low resistance to tubercle bacilli. Inasmuch as in the early part of this century most of the tuberculosis mortality among children from birth to four years was due to acute highly fatal forms of the disease which usually were ushered in by sudden onsets with no previous manifestation, it was thought that the condition was primary and the term "infantile" tuberculosis was coined. After safe methods of administering tuberculin became available in 1907 and 1908, and it was believed a reaction indicated presence of tuberculous infection, it was thought that any apparently well child who reacted to this test during the first year of life would soon die from "infantile" tuberculosis and that at least half of those who reacted to the test between the ages of one and two years were doomed. However, in 1920, search of the literature revealed that practically all that had been said and written was a matter of opinion since no well documented study was found to justify a conclusion. Reports in the literature already available and many subsequently made were based upon mortality among children with the endogenous reinfection clinical type of tuberculosis. These included such conditions as meningitis, miliary disease and pneumonia, which were nearly always fatal, as well as clinical lesions in peripheral lymph nodes, bones, joints, etc., from which children usually do not die.

In series of cases reported, rarely had there been an attempt to determine how many infants and young children were infected with tubercle bacilli in the areas from which the ill ones originated. Therefore, nothing was known of what percentage of infected infants developed reinfection type of tuberculosis.

For too long, we talked about "high susceptibility" and "low resistance" and theorized about methods of increasing resistance to tubercle bacilli when such factors as intimate contact exposure should have claimed our greatest attention. Infants are often subjected to excessive fondling and kissing by members of the immediate families, as well as by relatives, including grandparents. Elderly neighbors also participate in this activity.

Theories were also extant regarding high susceptibility and lack of resistance in new-
born animals. When it was observed that the adult guinea pig, like the human infant, has a high percentage of lymphocytes, whereas the newborn guinea pig has a low lymphocyte count, similar to that of adult humans, it was thought this might account for the alleged low resistance of young guinea pigs to tubercle bacilli. Various theories and expressions of opinion led Krause to make the following statement in 1925: “Because paper after paper of those appearing on many subjects in tuberculosis avers that young animals are in general inordinately susceptible to tuberculosis and because many an author easily and lightly solves a knotty problem as it arises with the statement of the assumption, it is particularly desirable to point out on how slender a basis of ascertained fact the assumption is based.” This led him to undertake a study of resistance of young and old guinea pigs. His experiments revealed that when young and old guinea pigs are infected intracutaneously with relatively small quantities of virulent tubercle bacilli that are equal for all the animals, there is an earlier appearance and more vigorous development of tubercles at the site of inoculation than in the regional lymph nodes in the old animals. “After infection of this nature and heavy enough to cause generalized tuberculosis in the old animals, both young and old guinea pigs developed essentially the same grade of infection. There was nothing to indicate that the young were more susceptible than the old.”

When he infected subcutaneously with large quantities of virulent tubercle bacilli in equal dosage, a more extensive and progressive involvement resulted in the young than in the old animals. Inasmuch as the young animals received double the quantity of tubercle bacilli per body weight than was sufficient to cause fatal disease in the old animals, he believed the more advanced condition found in the young animals was a result of overdosage.

In 1926, Krause said: “Infection tests performed thus far indicate that on the average, about 10 per cent of the general run of dispensary infants of one year of age react positively. Of course, the number dead or ill from tuberculosis at this age is no where near this proportion and these newer facts of the evidence of infection must surely make us revise our older ideas of extreme gravity of tuberculous infection as such for young infants.” Again he said, “During 1915 to 1920, the tuberculosis death rate for male infants from birth to four years in New York City was 150 per 100,000 alive. The infection incidence was surely as high as 10 per cent or 10,000 per 100,000. On this basis, it would appear that only 1 out of every 66 infected male infants dies from tuberculosis.”

Krause’s estimate of one death in every 66 infected was a revelation which had a profound influence on the thinking of many physicians and led to observations designed to determine facts. As the tuberculin test came into more general use, it was observed that such grave prognosis among the tuberculin reactors was not justified and that the high degree of susceptibility and low degree of resistance to tubercle bacilli thought to exist in this age period had been overestimated. Indeed, infants and young children are endowed with an exceedingly efficacious defense mechanism against first invasions with tubercle bacilli.

In the United States, tuberculosis mortality rate among children under one year declined from 311.6 in 1900 to 24.6 in 1940—a decrease of 92.1 per cent and to 0.5 in 1961 (Fig. 1). Among those from one to four years, the rate dropped from 101.8 in 1900 to 12.3 in 1940— a decrease of 87.9 per cent and to less than 1 in 1961. Among children of five to 14 years the mortality rate was 36.2 per 100,000 in 1900, 5.5 in 1940 and 0.37 in 1961 (Fig. 1).

In Minnesota where our work was done, records were not available prior to 1918. At that time, the mortality rates for infants from birth to four years were approximately the same as those for the United States in 1920 (Fig. 1 and 2). There is reason to believe the rate prior to 1918 was essentially the same as that reported in the United
States inasmuch as for several decades during the last century Minnesota was regarded as a Mecca for consumptives, and tremendous numbers from abroad and from the New England states migrated to that state. The mortality rate among Minnesota children under one year old dropped from 107.2 in 1918 to 10.9 in 1940, a decrease of 89.8 per cent, and to 0 in 1961. Among those from one to four years, the rate decreased from 48.0 in 1918 to 6.5 in 1940, a decrease of 86.5 per cent and to 0 in 1961. During the last ten years, there have been three deaths among babies under one year old and eight among children from one to four years.

Among children from five to 14 years, the mortality rate was 27.3 per 100,000 in 1918, 3.7 in 1940 and 0 in 1961 (Fig. 2). Since 1952, only five children from five to 14 years have died from tuberculosis.

Among our 267 persons traced and reported in 1959 who had demonstrable primary pulmonary infiltrates in childhood, seven (2.6 per cent) had died from acute reinfection type of tuberculosis including meningitis, miliary dissemination and pneumonia before the advent of antituberculosis drugs. Two died from chronic pulmonary tuberculosis, one at the age of 12 and the other at 22 years. Nine others who developed chronic reinfection type of disease were first found to have these lesions at the average age of 18.8 years. They made good recoveries. These 267 individuals were first examined at the mean age of 5.5 years and averaged 31.5 years when traced. They had been followed 6,305 person-years.

### Tuberculosis Mortality Rates
United States 1900 to 1961

- Birth to 1 year
- 1 to 4 years
- 5 to 14 years

**Figure 1**

Drugs introduced
A report on 611 persons who reacted to tuberculin at the average age of three years, between 1921 and 1941, and at the mean age of 32 years with 17,040 person-years of follow-up when recently traced, revealed that clinical disease had not appeared in 556 (90.98 per cent). There were 33 (5.40 per cent) who developed but recovered from clinical disease. Only 18 (2.94 per cent) expired as infants and young children from meningitis and miliary disease then universally fatal conditions and from tuberculous pneumonia which usually killed. The remaining four (0.65 per cent) died from chronic tuberculosis at ages 13, 14, 17 and 37 years.

In the United States from 1900 to 1940, the decrease in tuberculosis mortality among children from birth to four years was entirely due to methods of protecting them against tubercle bacilli. In the early part of this period, isolation of large numbers of persons with contagious disease began and continued. Control of tuberculosis in cattle was well under way between 1892 and 1916. The nationwide eradication project began in 1917 and has since been promoted vigorously. As the infection rate among children tumbled down, there was a corresponding decrease in mortality—92.1 per cent among those under one year and 87.9 per cent among those from one to four years between 1900 and 1940 (Fig. 1). These preventive measures continued to operate and between 1940 and 1961 among infants under one year, the mortality rate decreased 97.9 per cent.

**Figure 2**

*Tuberculosis Mortality Rates*  
*Minnesota 1918 to 1961*
Treatment obviously played no role in the prognosis of clinical tuberculosis among children from birth to four years from 1900 to 1940. Therefore, prognosis was the same throughout this period of 40 years. Preventive measures were continued with the same effectiveness and anti-tuberculosis drugs were added about 1947. This was the first time that prognosis was changed by treatment. With fewer cases developing and being able to treat some of them successfully, at least temporarily, mortality so decreased that in 1961, only 20 babies under one year and 140 from one to four years died from tuberculosis. Of those from one to four years, 40 died from respiratory tract lesions and the remainder from other forms of the disease.

**Five to Fourteen Years**

In the entire span of human life, the lowest tuberculosis mortality rates have been reported among children from five to 14 years (Fig. 1 and 2). Numerous theories have been propounded to explain the “high resistance” of the human body to tubercle bacilli during this age period. Probably the chief explanation is to be found in the fact that they defend themselves against fondling and kissing of the elderly, including grandparents, in their homes and communities. Moreover, the elderly do not have as strong a tendency to lavish their affection on those in this period of life as they do on infants and younger children. Besides resentment of fondling and kissing by the elderly, girls and boys engage in separate activities such as games, parties, etc. Wherever they are assembled, including school, rarely do girls and boys become infected from others of their age.

In 1925, Krause estimated that among children in this age period, one death occurs for every 800 infected. Between 12 and 14 years, chronic pulmonary disease begins to appear among tuberculin reactors, but usually is not fatal until later.

In 1944, it was reported observations on 2,979 children who between 1921 and 1941 reacted to tuberculin at the ages of six to 14 years. On first examination or during our immediate period of observation, 66 (2.2 per cent) had or developed reinfection type of tuberculosis. Of this number, 36 had tuberculosis of bones and joints. Thirty had chronic pulmonary lesions on first examination, of whom the majority were 12 years or older and most of the lesions were small. As of 1941, 71 others had developed chronic pulmonary disease at the average age of 17 years.

**The Teen-age Period**

Much has been written about the destructiveness of tuberculosis during the teen-age period and numerous theories have been advanced as to the cause of chronic clinical pulmonary disease becoming relatively prevalent during this time. There has been racking of brains everywhere to explain the “low resistance.” An important cause is so simple that it was long overlooked—namely, marked increase in infection rate. In the early part of this century, large numbers of children entered the teen-age period who had already been infected. This is the age when girls and boys emerge into the most social period of life—it is mating time. It is when girls and boys assemble in large and small groups with numerous intimate contacts when one with contagious disease may disseminate tubercle bacilli to many. They are on the move more than in any other period of life. They frequent homes of many other people; therefore, chances of contact with contagious cases are greatly increased. Downes found that approximately 66 per cent of persons who developed tuberculosis in the community under her observation had contracted the disease from sources outside their homes. Although much has been said about the tuberculosis mortality rate, it has never reached its height during the teen-age period. In 1900, among persons from 15 to 24 years, the mortality rate was 205.7. However, the highest rate that year was 294.3 which occurred among persons from
25 to 34 years and was higher than the 15 to 24 year rate in each of the succeeding decades of life. The mortality rate was 152.0, 136.0, 77.3, 38.2 and 0.3 in 1910, 1920, 1930, 1940, 1950 and 1961, respectively. In 1961, the rate was six times higher for those from 25 to 34 and also higher for all succeeding decades of life than in the 15 to 24 year group.

Here again, the tremendous decline in mortality occurred with the corresponding decrease of infection resulting from preventive measures. However, unlike the situation among infants, methods of treatment were in vogue beginning shortly before 1920 which materially changed prognosis. There is no doubt but that artificial pneumothorax, which was then so extensively used, and sanatorium care prevented large numbers of persons with pulmonary tuberculosis from dying during this period of life. With the advent of antituberculosis drugs which were in quite general use by 1947, immediate prognosis was still further influenced. Thus, by 1961 there were only 80 deaths among persons from 15 to 24 years in the United States, of which 70 were due to respiratory and 10 to other forms of tuberculosis. In Minnesota (Fig. 3), among those of 15 to 24 years, the tuberculosis mortality rate was 119.8 in 1918. By 1940, it was 14.7 and it was 0 in 1961. Since 1952, 14 deaths have occurred among persons in this age period.

**Status of Antituberculosis Drugs**

It is lamentable that children still become invaded by tubercle bacilli. However, for
those who do, the most pressing problem is to find a method by which endogenous reinfections can be prevented. Many physicians are now administering antituberculosis drugs to reactor children up to three years and to older children who have recently become tuberculin converters as a prophylactic measure. It is believed that by suppressing the bacilli that may be released from primary complex lesions, one lessens the likelihood of the acute forms of reinfection type of disease which occasionally appear soon after the tissues become highly sensitized. In fact, there is evidence that the presence of drugs in the bloodstream if and when bacilli escape from lesions of primary complexes may prevent the development of some reinfection type of lesions.47

On the other hand, physicians are asking why so many tubercle bacilli should possibly be made drug-resistant since clinical lesions promptly occur in such a small percentage of recent converters and since most of the few clinical lesions which do evolve may now be satisfactorily treated with drugs. To administer antituberculosis drugs to such reactors may result in later elimination of tremendous numbers of drug-resistant bacilli to produce endogenous reinfections and to invade the bodies of other people.

Some physicians are administering antituberculosis drugs to uninfected children who may have contact with contagious adults with the hope of preventing tubercle bacilli that may pass one or more portals from gaining foothold.

It is rapidly becoming recognized everywhere that present antituberculosis drugs leave much to be desired. It is this fact that recently caused the World Health Organization to start a search in 19 nations for "a new, cheap, non-toxic, easily administered drug that will not induce drug resistance in the bacillus."48

Figures 1, 2 and 3 show that most of the reduction in tuberculosis mortality among people from birth to 24 years occurred before the antituberculosis drug era. Although from 1947 on, drugs played a considerable role, and there is no doubt that methods so effective prior to the advent of drugs also contributed significantly to the continuous decline in the mortality rate. Indeed, there is good reason to believe these methods would have accomplished the same end, but a little later if drugs had not been used. Therefore, emphasis should continue on the fundamental preventive measures which deserve most of the credit for the present tuberculosis status among children in this country. Antituberculosis drugs and resectional surgery are excellent adjuncts for the few children who can be benefitted by them. However, complete reliance on drugs as now used could lead to disaster.

Already there is considerable evidence that enthusiasm for use of antituberculosis drugs may have outrun judgment. With our present knowledge, it appears that limiting them to persons with progressive clinical disease for whom there is hope of recovery should be highly recommended.

The mortality rates presented in this manuscript apply only to persons in those age groups who have been most benefitted by the fundamental tuberculosis eradication procedures. They should not be interpreted to mean that the tuberculosis problem is solved. Just beyond this age group are more than 110 million people of whom some had moderate protection against tubercle bacilli, but many were born before any shield was afforded children. The percentage of persons now harboring tubercle bacilli in the 110 million increases with each decade of life to from 50 to 75 per cent among the aged.49,50 In this group, clinical contagious disease is continuously evolving. This tremendous tuberculosis seed bed is a threat to all that has been accomplished by attempts to eradicate the tubercle bacilli. Tuberculosis is only wounded. It should not be forgotten that a wounded wild animal is the most dangerous animal.

Summary

1. Our observations on tuberculous children have been continuous since 1921.
They have confirmed the fact that the primary type of tuberculosis is an exceedingly benign disease and differs from the reinfection type almost as though it were caused by a different etiologic agent.

2. Prognosis of primary tuberculosis per se is excellent. No method of treatment yet employed, including antituberculosis drugs and resection, has changed the course of primary tuberculosis in the human body.

3. Although primary tuberculosis per se is extremely benign, it sets the stage for all reinfection (clinical) forms of the disease by producing sensitivity of tissues to tuberculoprotein and providing tubercle bacilli for endogenous reinfections.

4. In infancy and early childhood, between 2 and 3 per cent of those who become infected develop endogenous reinfections resulting in meningitis and miliary dissemination which are usually fatal and in pneumonia which is often so. Beginning about 1947, antituberculosis drugs changed immediate prognosis in a considerable number of cases.

5. With the approach of adolescence, chronic pulmonary tuberculosis enters and thereafter is the predominating clinical form of the disease. Starting about 1920, methods of treatment, including pulmonary collapse, greatly improved prognosis and since 1947, antituberculosis drugs and resectional surgery have served as excellent adjuncts.

6. Emphasis must be placed upon the fact that the lion's share of the work responsible for the phenomenal decrease of tuberculosis among children was done before antituberculosis drugs became available. Although drugs have been valuable in the treatment of clinical cases, methods designed and used so effectively in prevention of initial infection remain the sheet anchor. Because antituberculosis drugs by present methods of administration have some undesirable qualities, it is recommended that among children they be limited to those with progressive clinical lesions.

7. The tuberculosis eradication accomplishments here discussed among persons in the first 25 years of life are phenomenal. The same methods continued with extension and increased intensity are capable of eliminating tubercle bacilli so none of the persons existing and continuing through this age period will be invaded by tubercle bacilli. Therefore, they will require no treatment. In order to attain this goal, a tremendous problem must be solved. This consists of finding all persons harboring tubercle bacilli, variously estimated between 30 and 50 million, and acting accordingly. They constitute the tuberculosis seed bed of the United States. It will require more time and effort to solve this problem and thus attain eradication than have been necessary for all previous accomplishments.

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Resumen

1. Nuestras observaciones sobre tuberculosis en niños se han continuado desde 1921. Ellas han confirmado que la forma primaria de tuberculosis es una enfermedad extraordinariamente benigna y difiere de la tuberculosis de reinfección tanto como si fuera de diferente etiología.

2. El pronóstico de la tuberculosis primaria por sí es excelente. Ningún método de tratamiento empleado hasta ahora, incluyendo las drogas antituberculosas y la resección, ha cambiado la evolución de la tuberculosis en el cuerpo humano.

3. Aunque la tuberculosis primaria por sí sea extremadamente benigna establece el campo para toda reinfección (clínica) de la enfermedad, produciendo sensibilidad de los tejidos a la tuberculoproteína y proporcionando bacilos para la reinfección endógena.

4. En la primera y el inicio de la segunda infancia de 2 a 3 por ciento de los infectados desarrollan reinfección endógena resultando la meningitis y la diseminación miliar que son habitualmente fatales y la neumonía que a menudo lo es.

Desde 1947 las drogas antituberculosas cambiaron el pronóstico inmediato y un número considerable de casos.
5. Al acercarse la adolescencia, entra la tuberculosis pulmonar crónica y es desde entonces la forma predominante de la enfermedad. A partir de 1920 los métodos de tratamiento, incluyendo el colapso, mejoraron grandemente el pronóstico y desde 1947 las drogas antituberculosas y la cirugía de resección han servido como excelentes agregados.

6. Debe recalces que la parte del león en el trabajo al que debe atribuirse el descenso fenomenal de la tuberculosis entre los niños ya se realizó antes de que aparecieran las drogas antituberculosas.

Aunque las drogas han sido valiosas en el tratamiento de los casos clínicos los métodos ideados y usados tan efectivamente para la prevención de la infección inicial permanecen los básicos.

A causa de que las drogas antituberculosas de acuerdo con los métodos actuales de administración tienen algunas características indeseables se recomienda que se limite a su uso a los niños con lesiones clínicas progresivas.

7. Lo que se ha logrado acerca de la erradicación de la tuberculosis como aquí se relata, en las personas en los primeros 25 años de la vida es fenomenal. Los mismos métodos continuados con mayor extensión son capaces de eliminar los bacilos tuberculosos de modo que ninguna de las personas existentes y pasando de esta época de la vida sean invadidas por el bacilo de la tuberculosis. Por tanto, no requerirán tratamiento. Para obtener este objetivo ha de resolverse un problema enorme. Consiste en encontrar todas las personas que alojan en su cuerpo bacilos, las cuales se estiman de 30 a 50 millones y actuar de acuerdo con eso. Éstas personas constituyen la simiente de la tuberculosis en los Estados Unidos. Se necesitará más tiempo y mayor esfuerzo para resolver este problema y así obtener la erradicación que el que ha sido necesario para todo lo hasta aquí obtenido.

ZUSAMMENFASSUNG


3. Obwohl die Primärtuberkulose als solche extrem gutartig ist, bildet sie die Grundlage für alle Reinfektions—(klinischen) Formen der Erkrankung, indem sie zu einer Sensibilisierung der Gewebe gegenüber Tuberkuloprotein führt und die Tuberkelbazillen für die endogenen Reinfektionen stellt.

4. Im Säuglings—und Kleinkindesalter kam es bei etwa 2 bis 3% von denen, die sich infiziert hatten, zu einer endogenen Reinfektion mit nachfolgender Meningitis und miliarer Aussaat, die gewöhnlich letal verlaufen, und zu einer Pneumonie, die dies oft gleichfalls tut. Mit dem Beginn der Zeitspanne ab ungefähr 1947 haben die antituberkulösen Medikamente unmittelbar die Prognose in einer beträchtlichen Zahl von Fällen verbessert.


References will appear in the reprints.